Universitat de Lleida

Adherencia a la Dieta Mediterránea y resultados percibidos por el paciente en la diabetes autoinmune

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TESI DOCTORAL

Adherencia a la Dieta Mediterránea y resultados percibidos por el paciente en la diabetes autoinmune

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Memòria presentada per optar al grau de Doctor per la Universitat de Lleida
Programa de Doctorat en Salut

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Diseño de la cubierta: Xavier Piqué i Xavier Rodriguez, Servicio de Audiovisuales de la Universitat de Lleida.

"Los sueños sin metas, son sólo sueños;

y te llevarán a desilusiones.

Las metas, son el camino hacia tus sueños;

pero no se pueden lograr sin disciplina y consistencia"

Denzel Washington

Esta tesis doctoral va dedicada a mi marido,

mis padres y hermanas,

Damià, Paquita,

y, especialmente, se la dedico a mi hijo Izan,

que se ha gestado junto con esta tesis.

Agradecimientos

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A los pacientes que participaron en este estudio, y que, sin ellos, no hubiera sido posible realizar esta tesis. Muchas gracias por vuestro tiempo y colaboración.

Y finalmente, agradecer a mi familia por todo el esfuerzo, en todos los aspectos, para que esta tesis doctoral se haya podido realizar y llegar a su fin. En especial a ti Joan, que me has acompañado durante todos estos años en este largo camino, y me has animado a seguir adelante y hasta el final; además, tú fuiste el que me animó a emprender este camino.

A todos vosotros, muchas gracias.

Contenido

Listado de abreviaturas

ACD	Asociación Catalana de Diabetes
ADA	American Diabetes Association
ADDQoL-19	Audit of Diabetes-Dependent Quality of Life
AI	Anticuerpos anti-insulina
aHEI	alternate Healthy Eating Index
aMED	alternate Mediterranean Diet Score
CVRS	Calidad de vida relacionada con la salud
DCCT	Diabetes Control and Complications Trial
DM1	Diabetes mellitus tipo 1
DM2	Diabetes mellitus tipo 2
DNCT	Diabetes Nutrition and Complications Trial
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EASD	Asociación Europea para el Estudio de la Diabetes
FID	Federación Internacional de Diabetes
GADA	Anticuerpos anti-decarboxilasa del ácido glutámico
HbA1c	Hemoglobina glucosilada
HDL	Lipoproteína de alta densidad
IA-2	Anti-tirosina fosfatasa
IC	Intervalo de confianza
IG	Índice glucémico
LADA	Latent autoimmune diabetes in adults
LDL	Lipoproteína de baja densidad
MUFA	Ácidos grasos monoinsaturados

OR	Odds ratio
OMS	Organización Mundial de la Salud
PREDIMED	Estudio de Prevención con Dieta Mediterránea
PUFA	Ácidos grasos poliinsaturados
RD	Retinopatía diabética
SFA	Ácidos grasos saturados
ZnT8	Anti-transportador de zinc 5

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Resumen

Objetivos: Evaluar los hábitos alimentarios y el grado de adherencia a la Dieta Mediterránea de los pacientes adultos con diabetes mellitus tipo 1 (DM1); evaluar las diferencias en la ingesta dietética entre pacientes con DM1 con retinopatía diabética (RD) y sin ésta; comparar los resultados percibidos por el paciente (calidad de vida y satisfacción con el tratamiento) entre los pacientes con diabetes autoinmune latente del adulto (*latent autoimmune diabetes in adults*, LADA) y los pacientes con DM1 y diabetes mellitus tipo 2 (DM2); estudiar la asociación entre los resultados percibidos por el paciente y la RD en pacientes con DM1; determinar la relación entre el patrón dietético (Dieta Mediterránea y alimentación saludable) y los resultados percibidos por el paciente en pacientes con DM1.

Métodos: El diseño del estudio fue transversal y multicéntrico. Se reclutó una muestra de 262 participantes con DM1 y 254 sujetos sin diabetes comparables en edad y sexo, seleccionados de las poblaciones de referencia. Además, se reclutaron 48 pacientes con LADA y 297 pacientes con DM2. Se administraron el cuestionario de frecuencia de consumo de alimentos diseñado por Willet et al., el *Audit of Diabetes-Dependent Quality of Life* (ADDQoL-19) y el *Diabetes Treatment Satisfaction Questionnaire* (DTSQ) mediante entrevista personal.

Resultados: Los pacientes con DM1 tuvieron mayor adherencia a la Dieta Mediterránea y una alimentación más saludable que los participantes sin diabetes. Los pacientes con RD tuvieron una ingesta total de grasas menor que los pacientes sin RD. La elevada ingesta de ácidos grasos monoinsaturados (MUFA), ácido oleico y vitamina E se asoció con una menor presencia de RD en pacientes con DM1. La ingesta de carbohidratos se relacionó con mayor presencia de RD. Los pacientes con LADA con RD y tratados con insulina mostraron una peor percepción de su calidad de vida y una mayor frecuencia de hiperglucemias percibidas. La RD se asoció con una peor calidad de vida y una mayor frecuencia de hipoglucemias percibidas. La adherencia a la Dieta Mediterránea moderada y alta se relacionó con una mejor calidad de vida en la DM1.

Conclusiones: Los pacientes adultos con DM1 mostraron una mayor adherencia a la Dieta Mediterránea y un patrón de alimentación más saludable que los participantes sin diabetes. Los pacientes con DM1 y RD tuvieron una ingesta de grasas más desfavorable que los pacientes sin RD. Los pacientes con LADA mostraron una peor calidad de vida y satisfacción con el tratamiento en comparación con los pacientes con DM1 y DM2. La RD se relacionó con una peor percepción de la calidad de vida y satisfacción con el tratamiento en pacientes con DM1. La Dieta Mediterránea se asoció positivamente con la calidad de vida en pacientes con DM1.

Resum

Objectius: Avaluar els hàbits alimentaris i el grau d'adherència a la Dieta Mediterrània dels pacients adults amb DM1; avaluar les diferències en la ingesta dietètica entre els pacients amb DM1 i RD i sense aquesta; comparar els resultats percebuts pel pacient (qualitat de vida i satisfacció amb el tractament) entre els pacients amb diabetis autoimmune latent de l'adult (LADA) i els pacients amb DM1 i DM2; estudiar l'associació entre els resultats percebuts pel pacient i la RD en pacients amb DM1; determinar la relació entre el patró dietètic (Dieta Mediterrània i alimentació saludable) i els resultats percebuts pel pacient en pacients amb DM1.

Mètodes: El disseny de l'estudi va ser transversal i multicèntric. Es va reclutar una mostra de 262 participants amb DM1 i 254 subjectes sense diabetis comparables amb edat i sexe, seleccionats de les poblacions de referència. A més, es van reclutar 48 pacients amb LADA i 297 pacients amb DM2. Es van administrar, mitjançant entrevista personal, el qüestionari de freqüència de consum d'aliments dissenyat per Willet et al., l'*Audit of Diabetes-Dependent Quality of Life* (ADDQoL-19) i el *Diabetes Treatment Satisfaction Questionnaire* (DTSQ).

Resultats: Els pacients amb DM1 van tenir una major adherència a la Dieta Mediterrània i una alimentació més saludable. Els pacients amb RD van tenir una ingesta total de greixos menor que els pacients sense RD. L'elevada ingesta d'àcids grassos mono-insaturats (MUFA), àcid oleic i vitamina E es va associar amb una menor presència de RD en pacients amb DM1. La ingesta de carbohidrats es va relacionar amb una major presència de RD. Els pacients amb LADA i RD tractats amb insulina van mostrar una pitjor percepció de la seva qualitat de vida i una major freqüència d'hiperglucèmies percebudes. La RD es va associar amb una pitjor qualitat de vida i una major freqüència d'hipoglucèmies percebudes. L'adherència a la Dieta Mediterrània moderada i alta es va relacionar amb una qualitat de vida millor.

Conclusions: Els pacients adults amb DM1 van mostrar una major adherència a la Dieta Mediterrània i un patró d'alimentació més saludable que els participants sense diabetis. Els pacients amb RD van tenir una ingesta de greixos més desfavorable que els pacients sense RD. Els pacients amb LADA van mostrar una qualitat de vida i satisfacció amb el tractament pitjor en comparació amb els pacients amb DM1 i DM2. La RD es va relacionar amb una percepció de la qualitat de vida i satisfacció amb el tractament pitjor en els pacients amb DM1. La Dieta Mediterrània es va associar positivament amb la qualitat de vida en els pacients amb DM1.

Abstract

Objectives: The aims of the study were to assess dietary habits and the adherence to the Mediterranean Diet in adult patients with type 1 diabetes (DM1); to assess the differences in terms of dietary intake between patients with DM1 with diabetic retinopathy (RD) and without this; to compare patient-reported outcomes (i.e. quality of life and treatment satisfaction) between patients with latent autoimmune diabetes in adults (LADA) and patients with DM1 and type 2 diabetes (DM2); to study the association between patient-reported outcomes in patients with DM1 and RD; to determine the relationship between dietary pattern (such as the Mediterranean Diet and healthy eating) with patient-reported outcomes in patients with DM1.

Methods: This was a cross-sectional and multicentre study design. A sample of 262 participants with DM1 and age- and sex-matched 254 subjects without diabetes of the reference populations were recruited. Furthermore, 48 patients with LADA and 297 patients with DM2 were also recruited. The food frequency questionnaire designed by Willet et al., the Audit of Diabetes-Dependent Quality of Life questionnaire (ADDQoL-19) and Diabetes Treatment Satisfaction Questionnaire (DTSQ) were administered by personal interview.

Results: Patients with DM1 had a higher adherence to the Mediterranean Diet and a healthier eating. Patients with DR had a lower total fat intake than non-DR patients. A higher monounsaturated fatty acid (MUFA), oleic acid and vitamin E intake was associated with a lower presence of DR in patients with DM1. Carbohydrate intake was related with more presence of DR. Patients with LADA with DR and insulin-treated showed a poorer quality of life perception and a higher frequency of perceived hyperglycemia. DR was associated with a poorer quality of life and a higher perception of hypoglycemia's frequency. A moderate and high Mediterranean Diet adherence was related with better quality of life.

Conclusions: Adult patients with DM1 showed a higher adherence to the Mediterranean Diet and a healthier eating in comparison with non-diabetic subjects. Patients with DR had an unfavorable fat intake compared with non-DR patients. Patients with LADA showed a poorer quality of life and treatment satisfaction in comparison with DM1 and DM2 patients. DR was related with a poorer perception of quality of life and treatment satisfaction in patients with DM1. The Mediterranean Diet was positively associated with quality of life in patients with DM1.

Presentación

Presentación

Esta tesis doctoral está organizada según las directrices de la normativa aprobada por el acuerdo número 67/2014 del Consejo de Gobierno de 10/04/2014 de la Universidad de Lleida para la presentación de tesis doctorales en formato artículos.

Los estudios realizados en la presente Tesis Doctoral inician una línea de investigación centrada en evaluar las diferencias existentes en la adherencia a la Dieta Mediterránea en pacientes con diabetes mellitus tipo 1 y la población no diabética, los factores nutricionales asociados a la presencia de retinopatía diabética, y la relación de este patrón dietético con los resultados percibidos por el paciente (calidad de vida y satisfacción con el tratamiento). Además, se ha centrado en estudiar los resultados percibidos por el paciente en la diabetes autoinmune latente del adulto (*latent autoimmune diabetes in adults*, LADA). Esta Tesis Doctoral se ha realizado en dos centros hospitalarios, en Lleida y Badalona, fruto de la colaboración entre ambos centros de investigación.

La investigadora en formación ha recibido la siguiente financiación durante la realización de la presente Tesis Doctoral:

- Contrato predoctoral para la Formación de Profesorado Universitario, Ministerio de Educación, Cultura y Deporte en el Instituto de Investigación Germans Trias i Pujol de Badalona (FPU15/3005).

- Beca de colaboración en servicios y unidades de la Universidad de Lleida, en la Unidad de Formación del Profesorado Universitario, Instituto de Ciencias de la Educación (2015-2016).

- Programa de soporte al profesorado en actividades académicas dirigidas para la mejora de la docencia en los grados de la facultad de medicina de la Universitat de Lleida (FM-8, 2016).

- Ayuda a la Investigación en Educación Terapéutica en Diabetes otorgada por la Asociación Catalana de Diabetes (ACD, 2015).

Los resultados obtenidos de esta investigación están descritos en forma de 5 artículos científicos publicados en revistas de impacto internacionales.

Artículo 1

Título: Improved adherence to Mediterranean Diet in adults with type 1 diabetes mellitus.
Autores: Minerva Granado-Casas, Nuria Alcubierre, Mariona Martín, Jordi Real, Anna M. Ramírez-Morros, Maribel Cuadrado, Núria Alonso, Mireia Falguera, Marta Hernández, Eva Aguilera, Albert Lecube, Esmeralda Castelblanco, Manel Puig-Domingo, Dídac Mauricio
Revista: European Journal of Nutrition. 2019;58(6):2271-2279
Factor de impacto: 4,449
Categoría: Nutrition & Dietetics
Cuartil: Primero (JCR 2018)
DOI: https://doi.org/10.1007/s00394-018-1777-z

Artículo 2

Título: Type 1 diabetic subjects with diabetic retinopathy show an unfavorable pattern of fat intake.
Autores: Minerva Granado-Casas, Anna Ramírez-Morros, Mariona Martín, Jordi Real, Núria Alonso, Xavier Valldeperas, Alicia Traveset, Esther Rubinat, Nuria Alcubierre, Marta Hernández, Manel Puig-Domingo, Albert Lecube, Esmeralda Castelblanco, Dídac Mauricio
Revista: Nutrients. 2018; 10(9):1184
Factor de impacto: 4,171
Categoría: Nutrition & Dietetics
Cuartil: Primero (JCR 2018)
DOI: https://doi.org/10.3390/nu10091184

Artículo 3

Título: Decreased quality of life and treatment satisfaction in patients with latent autoimmune diabetes of the adult.
Autores: Minerva Granado-Casas, Montserrat Martínez-Alonso, Nuria Alcubierre, Anna Ramírez-Morros, Marta Hernández, Esmeralda Castelblanco, Joan Torres-Puiggros, Didac Mauricio

Revista: PeerJ. 2017;5:e3928
Factor de impacto: 2,118
Categoría: Multidisciplinary Sciences
Cuartil: Segundo (JCR 2017)
DOI: https://doi.org/10.7717/peerj.3928

Artículo 4

Título: Poorer quality of life and treatment satisfaction is associated with diabetic retinopathy in patients with type 1 diabetes without other advanced late complications.
Autores: Minerva Granado-Casas, Esmeralda Castelblanco, Anna Ramírez-Morros, Mariona Martín, Nuria Alcubierre, Montserrat Martínez-Alonso, Xavier Valldeperas, Alicia Traveset, Esther Rubinat, Ana Lucas-Martin, Marta Hernández, Núria Alonso, Didac Mauricio
Revista: Journal of Clinical Medicine. 2019;8(3):E377
Factor de impacto: 5,688
Categoría: Medicine, General & Internal
Cuartil: Primero (JCR 2018)
DOI: https://doi.org/10.3390/jcm8030377

Artículo 5

Título: The Mediterranean Diet is associated with an improved quality of life in adults with type 1 diabetes.
Autores: Minerva Granado-Casas, Mariona Martín, Montserrat Martínez-Alonso, Nuria Alcubierre, Marta Hernández, Núria Alonso, Esmeralda Castelblanco, Didac Mauricio
Revista: Nutrients. 2020;12:131
Factor de impacto: 4,171
Categoría: Nutrition & Dietetics
Cuartil: Primero (JCR 2018)
DOI: https://doi.org/10.3390/nu12010131

La investigadora en formación ha participado activamente y con gran implicación en el grupo de investigación, por lo que también es coautora de las siguientes publicaciones en revistas de impacto internacional:

1. **Título**: Ultrasound tissue characterization of carotid plaques differs between patients with

type 1 diabetes and subjects without diabetes.
Autores: Castelblanco E, Betriu À, Hernández M, **Granado-Casas M**, Ortega E, Soldevila B, Ramírez-Morros A, Franch-Nadal J, Puig-Domingo M, Fernández E, Avogaro A, Alonso N, Mauricio D.
Revista: Journal of Clinical Medicine. 2019; 8(4):E424.

2. **Título**: Diabetic retinopathy is associated with the presence and burden of subclinical carotid atherosclerosis in type 1 diabetes
Autores: Carbonell M, Castelblanco E, Valldeperas X, Betriu À, Traveset A, **Granado-Casas M**, Hernández M, Vázquez F, Martín M, Rubinat E, Lecube A, Franch-Nadal J, Fernández E, Puig-Domingo M, Avogaro A, Alonso N, Mauricio D.
Revista: Cardiovascular Diabetology. 2018; 17(1):66.

3. **Título**: Vitamin D deficiency is associated with poorer satisfaction with diabetes-related treatment and quality of life in patients with type 2 diabetes: a cross-sectional study.
Autores: Alcubierre N, Castelblanco E, Martínez-Alonso M, **Granado-Casas M**, Esquerda A, Traveset A, Martinez-Gonzalez D, Franch-Nadal J, Mauricio D.
Revista: Health and Quality of Life Outcomes. 2018; 16(1):44.

4. **Título:** Calcium Phosphate Product Is Associated with Subclinical Carotid Atherosclerosis in Type 2 Diabetes.
Autores: Ramírez-Morros A, **Granado-Casas M**, Alcubierre N, Martinez-Alonso M, Real J, Castelblanco E, Esquerda A, Cao G, Rubinat E, Hernández M, Alonso N, Fernández E, Mauricio D.
Revista: Journal of Diabetes Research. 2017; 2017:3498368.

5. **Título**: Preclinical carotid atherosclerosis in patients with latent autoimmune diabetes in adults (LADA), type 2 diabetes and classical type 1 diabetes.
Autores: Hernández M, López C, Real J, Valls J, Ortega-Martinez de Victoria E, Vázquez F, Rubinat E, **Granado-Casas M**, Alonso N, Molí T, Betriu A, Lecube A, Fernández E, Leslie RD, Mauricio D.
Revista: Cardiovascular Diabetology. 2017; 16(1):94.

6. **Título**: Prevalence, clinical features and risk assessment of pre-diabetes in Spain: the prospective Mollerussa cohort study.
Autores: Vilanova MB, Falguera M, Marsal JR, Rubinat E, Alcubierre N, Castelblanco E,

Granado-Casas M, Miró N, Molló À, Mata-Cases M, Franch-Nadal J, Mauricio D.
Revista: BMJ Open. 2017; 7(6):e015158.

7. **Título**: Association of low oleic acid intake with diabetic retinopathy in type 2 diabetic patients: a case-control study.
   Autores: Alcubierre N, Navarrete-Muñoz EM, Rubinat E, Falguera M, Valls J, Traveset A, Vilanova MB, Marsal JR, Hernandez M, **Granado-Casas M**, Martinez-Gonzalez D, Jurjo C, Franch-Nadal J, Vioque J, Mauricio D.
   Revista: Nutrition & Metabolism. 2016; 13:40.

8. **Título**: Relationship of the adherence to the Mediterranean diet with health-related quality of life and treatment satisfaction in patients with type 2 diabetes mellitus: a post-hoc analysis of a cross-sectional study.
   Autores: Alcubierre N, Martinez-Alonso M, Valls J, Rubinat E, Traveset A, Hernández M, Martínez-González MD, **Granado-Casas M**, Jurjo C, Vioque J, Navarrete-Muñoz EM, Mauricio D.
   Revista: Health and Quality of Life Outcomes. 2016; 14:69.

9. **Título**: Vitamin D Deficiency Is Associated with the Presence and Severity of Diabetic Retinopathy in Type 2 Diabetes Mellitus.
   Autores: Alcubierre N, Valls J, Rubinat E, Cao G, Esquerda A, Traveset A, **Granado-Casas M**, Jurjo C, Mauricio D.
   Revista: Journal of Diabetes Research. 2015; 2015:374178.

10. **Título**: Microangiopathy of common carotid vasa vasorum in type 1 diabetes mellitus.
    Autores: Rubinat E, Ortega E, Traveset A, Arcidiacono MV, Alonso N, Betriu A, **Granado-Casas M**, Hernández M, Soldevila J, Puig-Domingo M, Jurjo C, Fernández E, Mauricio D.
    Revista: Atherosclerosis. 2015; 241(2):334-8.

Además, durante el periodo como investigadora en formación ha participado como primera autora en un capítulo de libro internacional:

Granado-Casas M, Mauricio D. Oleic Acid in the Diet and What It Does: Implications for Diabetes and Its Complications. En: Bioactive Food as Dietary Interventions for Diabetes, 2nd edition (2018). Editores: Ronald Watson y Victor Preedy. Elsevier.

Introducción

1. Introducción

1.1. Diabetes mellitus tipo 1

La diabetes mellitus es una enfermedad crónica que conlleva un impacto social y de salud pública elevado, tanto por su incidencia y prevalencia como por su cronicidad y complicaciones asociadas (1). El incremento en la morbimortalidad asociada a la diabetes mellitus tipo 1 (DM1) se debe a las complicaciones agudas (cetoacidosis e hipoglucemias graves), y crónicas microvasculares (retinopatía, nefropatía y neuropatía) y macrovasculares (enfermedad vascular coronaria, cerebral y periférica) (1).

La diabetes ocupa el 6º lugar entre las causas de muerte en España y es el primer motivo de ceguera, insuficiencia renal, amputación no traumática de miembros inferiores, e impotencia sexual de causa orgánica (1).

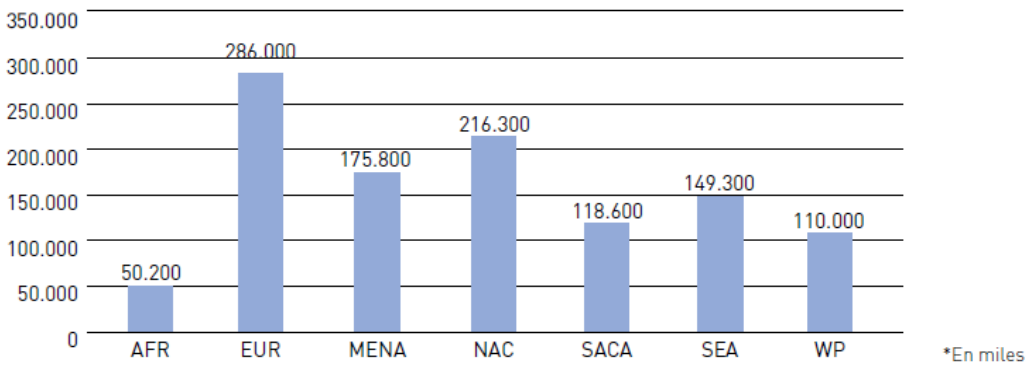
La prevención de las complicaciones es fundamental para evitar el exceso de morbimortalidad, y para ello es importante un buen control glucémico y de los factores de riesgo asociados (tabaquismo, obesidad, hipertensión arterial y dislipemia). Sin embargo, son numerosos los pacientes con diabetes mellitus que presentan un mal control glucémico o de los factores de riesgo vascular asociados (1).

Hay varios tipos de diabetes mellitus, los principales son el tipo 1 y el tipo 2. La DM1 se trata de una enfermedad en la que tiene lugar una destrucción autoinmune de las células beta pancreáticas, siendo necesaria la administración de insulinoterapia para su tratamiento (1).

La prevalencia de DM1 en la población menor de 20 años en todo el mundo es de 0,03%; en cambio, en los países desarrollados es del 0,1% (2). En 2017, Europa fue la región con mayor prevalencia de casos de DM1 en comparación con las otras regiones mundiales (Figura 1). En Cataluña, en población menor de 30 años, la incidencia es baja entre los 0 y 5 años de edad, y

máxima entre los 13-14 años (3). En adultos jóvenes (entre 15 y 29 años), la incidencia es de 10,2/ 100.000 habitantes/año, similar a la incidencia hallada en otras comunidades autónomas y otros países europeos (4–7). La elevada incidencia que se ha encontrado en España respecto a otros países de Europa justifica que se estudien los factores de riesgo que acompañan a la enfermedad, así como los posibles factores desencadenantes (8).

Figura 1. Número estimado de niños y adolescentes (menores de 20 años) con diabetes tipo 1.



Fuente: Federación Internacional de Diabetes, 2017
AFR, África; EUR, Europa; MENA, Oriente Medio y Norte de África; NAC, América del Norte y el Caribe; SACA, América del Sur y Central; SEA, Sudeste Asiático; WP, Pacífico Occidental.

La DM1 y la diabetes mellitus tipo 2 (DM2) son enfermedades heterogéneas en las cuales su presentación clínica y progresión pueden variar considerablemente. La clasificación de la diabetes es importante para determinar su tratamiento, pero en algunos pacientes no se puede clasificar claramente en el momento del diagnóstico. Antiguamente, el paradigma de que la DM2 se desarrollaba ya bien entrada la edad adulta y la DM1 en niños, adolescentes y adultos jóvenes, no es muy adecuada ya que ambas enfermedades se desarrollan actualmente en edades que están solapadas entre ambos tipos de diabetes (9). En la actualidad, la DM1 también viene definida por la presencia de uno o más autoanticuerpos circulantes dirigidos contra antígenos de la célula beta pancreática como marcadores de destrucción autoimune de estas células productoras de insulina (como anticuerpos anti-decarboxilasa del ácido glutámico (GADA), anti-tirosina fosfatasa (IA-2A), anti-insulina (AI) y anti-transportador de zinc 5 (ZnT8)). En cambio, la DM2 no presenta estos

autoanticuerpos y, además de una secreción relativamente deficiente, muestra una resistencia a la insulina con las caracteríticas que acompañan tradicionalmente este defecto fisiopatológico (9).

En la DM1, la velocidad de destrucción de las células beta pancreáticas es variable entre los individuos, siendo habitualmente más rápida en niños y más lenta en los adultos. Las causas de la destrucción autoinmune de las células beta pancreáticas se atribuye en su origen, principalmente a múltiples factores genéticos y ambientales, que están aún insuficientemente caracterizados. Aunque los pacientes con DM1 no son típicamente obesos cuando se desarrolla la enfermedad, la obesidad no excluye el diagnóstico de dicha enfermedad (9). Existen tres estadíos de la DM1 que pueden servir para realizar futuras investigaciones y que pueden condicionar su manejo (Tabla 1) (10,11).

Tabla 1. Estadíos de la diabetes mellitus tipo 1

	Estadío 1	**Estadío 2**	**Estadío 3**
Características	Autoinmunidad Normoglucemia Presintomática	Autoinmunidad Disglucemia Presintomática	Nuevo inicio hiperglucemia Sintomática
Criterios para el diagnóstico	Múltiples autoanticuerpos No intolerancia oral a la glucosa ni glucosa basal alterada aislada	Múltiples autoanticuerpos Intolerancia oral a la glucosa o glucosa basal alterada aislada Glucemia basal: 100 – 125 mg/dL Glucemia postprandial (2 horas): 140 – 199 mg/dL HbA1c 5,7% - 6,4% o incremento ≥ 10%	Síntomas clínicos Diabetes por criterios estandarizados

Adaptada de American Diabetes Association. Diabetes Care. 2018;41(Suppl. 1):S13-127.
HbA1c, hemoglobina glucosilada.

1.1.1. Latent autoimmune diabetes in adults (LADA)

En 1986, se observó que un grupo de pacientes diagnosticados clínicamente como DM2 presentaban autoanticuerpos específicos de la DM1 con una cierta preservación de la función beta pancreática (12). Se les designó como pacientes con "diabetes tipo 1 latente". Posteriormente, se acuñó el epónimo LADA para designar esta forma lenta y progresiva de diabetes autoinmune en el adulto. Inicialmente, es tratada con dieta y fármacos hipoglucemiantes orales como en la DM2, antes de que se presenten los requerimientos de insulina como en la DM1 (12).

La diabetes LADA (*latent autoinmune diabetes in adults*) es una forma más lenta y progresiva de diabetes autoinmune en comparación con la DM1. Los pacientes tienen un fenotipo variable, intermedio entre la DM1 y la DM2, y presentan por definición autoanticuerpos circulantes específicos de la DM1, principalmente autoanticuerpos GADA (13). En el momento del diagnóstico, los pacientes no requieren terapia con insulina y suelen ser clasificados como pacientes con DM2 (12,14). El perfil cardiovascular de los pacientes con LADA es intermedio entre la DM1 y la DM2. Suelen presentar un menor índice de masa corporal (IMC), perímetro de cintura, índice cintura-cadera, presión arterial, menores concentraciones circulantes de triglicéridos y colesterol LDL que los pacientes con DM2 (14–18). En cambio, en comparación con los pacientes con DM1, los pacientes LADA presentan más factores asociados al síndrome metabólico (obesidad, hipertensión y dislipemia aterogénica) (19). Además, estos pacientes muestran niveles bajos de secreción residual endógena de insulina y progresan más rápidamente al tratamiento con insulina al presentar un control glucémico pobre (15–18,20).

Hasta la realización del presente trabajo, una vez se identificaba como LADA, este tipo de diabetes no estaba aceptado como tal y se incluía estos pacientes en la categoría de DM1. Recientemente, la Organización Mundial de la Salud (OMS) ha clasificado la diabetes LADA como una forma híbrida de diabetes a la que define como *slowly evolving immune-mediated diabetes* (21). En esta tesis, hemos mantenido el epónimo LADA ya que este cambio ha sido posterior a la realización de este

trabajo, y, además, porqué así se sigue definiendo aún en los ámbitos clínico y de investigación a nivel internacional.

1.2. Retinopatía diabética

La retinopatía diabética (RD) es la complicación microangiopática más frecuente de la diabetes, y actualmente se considera una complicación neurovascular (8). Clínicamente, se define como la presencia de signos microvasculares típicos en la retina en individuos con diabetes mellitus (22). La neurodegeneración retiniana es el primer estadío en el desarrollo de la RD (23); la degeneración progresiva está caracterizada por apoptosis neuronal y gliosis reactiva, provocando alteraciones en la funcionalidad de la visión como la pérdida de contraste de los colores (23). Además, la RD es la principal causa de pérdida de visión y ceguera en adultos en edad laboral (de 20 a 65 años) (8,24). En pacientes con DM1, el riesgo de desarrollar RD está aumentado en comparación con los pacientes diagnosticados de DM2, siendo la prevalencia estimada a 10 años del inicio de la diabetes del 35,9% en este tipo de población (23,25).

Los factores de riesgo de la RD pueden ser modificables y no modificables. Los factores de riesgo modificables incluyen la hiperglucemia, la hipertensión, la dislipemia y la obesidad; los factores de riesgo no modificables son la duración de la diabetes, la etnia, el período puberal y el embarazo (22–24).

La detección temprana es la mejor estrategia para prevenir la pérdida de visión producida por la RD (23). En pacientes con DM1, se recomienda empezar con el cribado a los 5 años desde el diagnóstico en pacientes mayores de 15 años. Como prevención, las estrategias de salud pública están enfocadas a mantener un óptimo automanejo de la DM1, tratando la hiperglucemia, la hipertensión arterial y la dislipemia como los principales factores de riesgo de daño vascular (23).

La RD se clasifica en dos tipos principales: la retinopatía diabética no proliferativa (RDNP) y la retinopatía diabética proliferativa (RDP) (Tabla 2).

- La RDNP se caracteriza por presentar microaneurismas, microhemorragias, exudados formados por depósitos lipídicos, "manchas de algodón" (acumulaciones de restos axoplásmicos dentro los paquetes de células ganglionares de los axones adyacentes), dilatación venosa y capilar (22,23,26).

- La RDP se caracteriza principalmente por presentar neovascularización (22,23,26); además, se pueden observar hemorragias pre-retinianas moderadas y graves. Se puede presentar, además, con o sin edema macular.

Tabla 2. Clasificación de la retinopatía diabética

	RDNP leve	**RDNP moderada**	**RDNP grave**	**RDP**
Características clínicas	Sólo microaneurismas.	Microaneurismas y otras lesiones microvasculares no graves.	Más de 20 hemorragias intraretina en cuatro cuadrantes. Dilatación venosa en dos o más cuadrantes. Anormalidades microvasculares en uno o más cuadrantes.	Neovascularización. Hemorragia pre-retiniana. Hemorragia vítrea. Características de la RDNP moderada y grave.
Monitorización	Anualmente.	Cada 3-6 meses.	Cada 3-6 meses.	Variable.

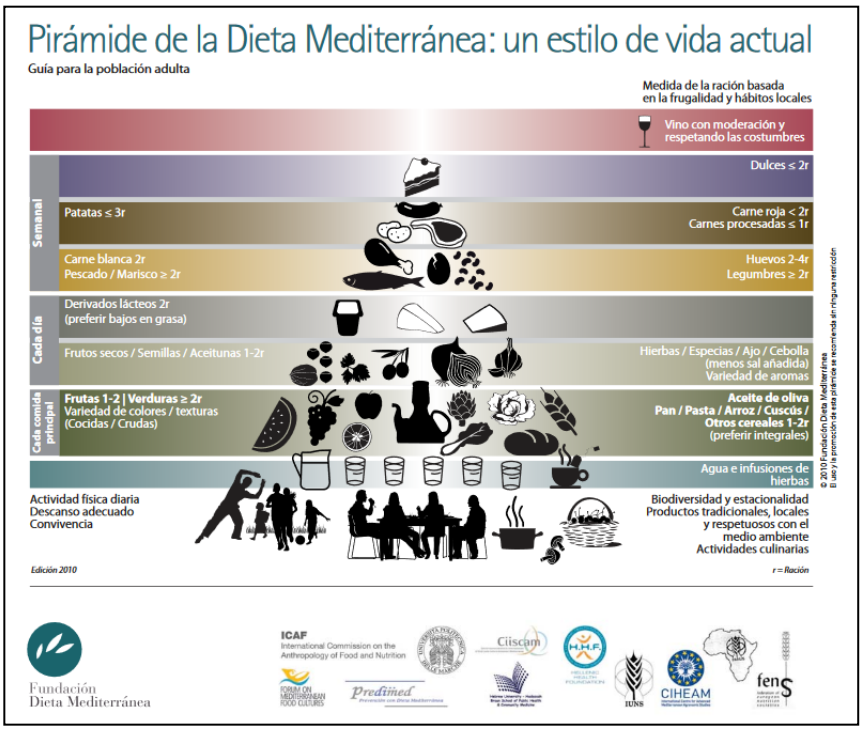
Adaptada de Cheung et al. Lancet. 2010;376:124-36.
RDNP, retinopatía diabética no proliferativa; RDP, retinopatía diabética proliferativa.

En la actualidad, existen dos tipos de tratamiento para la RD: la fotocoagulación con láser y las inyecciones de inhibidores del factor crecimiento vascular endotelial (anti-VEGF). La fotocoagulación con láser está indicada en la reducción del riesgo de pérdida de visión en pacientes con alto riesgo de desarrollar RDP, y en algunos casos, RDNP avanzada. Las inyecciones de anti-VEGF también están indicadas en los pacientes con RDP (26).

1.3. Dieta Mediterránea y diabetes mellitus tipo 1

La modificación de los hábitos dietéticos siguiendo las recomendaciones nutricionales basadas en la Dieta Mediterránea y el adecuado manejo de la ingesta de hidratos de carbono, junto con el tratamiento con insulina y la práctica de actividad física regular contribuyen a mantener un buen control de la DM1 (27–30). En los pacientes con DM1 de nuestra población, se realiza educación nutricional individual y regular incluyendo, aparte del manejo con los carbohidratos consumidos, el seguimiento de la Dieta Mediterránea (31). La Asociación Catalana de Diabetes (ACD), la Asociación Americana de Diabetes (ADA) y la Asociación Europea para el Estudio de la Diabetes (EASD) establecen recomendaciones nutricionales en las personas con DM1 basadas en la Dieta Mediterránea (31–33); estas recomendaciones son similares a los hábitos alimentarios saludables recomendados en la población general. Estas incluyen el consumo moderado de energía, ingesta baja de grasas animales, consumo elevado de frutas, vegetales, cereales integrales, legumbres, aceite de oliva, e ingesta moderada de pescado, aves, vino tinto, además de la realización de ejercicio físico durante 25-30 minutos diarios (28,29,31,34) (Figura 3).

Figura 2. Pirámide de la Dieta Mediterránea. Fundación Dieta Mediterránea.



Los estudios científicos que han investigado la relación entre los hábitos dietéticos y la DM1 en población adulta son escasos. El estudio EURODIAB Prospective Complications Study, uno de los estudios más importantes que se ha realizado en Europa con una muestra que incluyó 3.250 pacientes con DM1 de 16 países de Europa, relacionó los hábitos dietéticos como el patrón de ingesta de grasas saturadas y fibra, actividad física, consumo de alcohol e ingesta de alimentos de elevado índice glucémico (IG) con el riesgo de aparición de complicaciones cardiovasculares en pacientes con DM1 (35). Los resultados de este estudio indicaban que existe una relación inversa entre el consumo de fibra y el riesgo de mortalidad por cualquier causa (35). En relación con la hemoglobina glucosilada (HbA1c), los pacientes con DM1 que tenían una ingesta de fibra mayor presentaron menores concentraciones de HbA1c, y también menor frecuencia de complicaciones asociadas a la diabetes como la retinopatía, la nefropatía y la neuropatía (36). Una dieta baja en fibra, frutas y vegetales está asociada con un menor riesgo de morbimortalidad por enfermedades cardiovasculares en pacientes con DM1 (35,37). La ingesta moderada de alcohol, equivalente a 30-70g/semana, se describió como un factor protector de riesgo cardiovascular en pacientes con DM1. En cambio, la ingesta de más de 140g/semana de alcohol se ha descrito como un factor de riesgo en esta población (38). Los mismos autores describieron que la realización de actividad física en pacientes con DM1, así como la práctica regular y sostenida de deporte constituye un factor de protección frente a las complicaciones cardiovasculares asociadas a la diabetes (isquemia coronaria incluyendo infarto de miocardio, enfermedad cerebrovascular, y enfermedad arterial periférica) (39,40).

Un meta-análisis realizado con estudios epidemiológicos prospectivos mostró una asociación entre el grado de adherencia a la Dieta Mediterránea elevado y una reducción de la mortalidad por enfermedad cardiovascular del 9% en pacientes con cáncer y enfermedades neurodegenerativas (41,42). Diversos ensayos clínicos han demostrado que la Dieta Mediterránea como medida terapéutica en la prevención primaria y secundaria de enfermedades cardiovasculares, reduce los

niveles plasmáticos de colesterol LDL y triglicéridos, el índice de masa corporal (IMC), eleva los niveles de colesterol HDL, y mejora la glucemia, la presión arterial, la sensibilidad a la insulina y los marcadores de inflamación (42–46). Otro meta-análisis realizado con ensayos clínicos determinó que la sustitución de las grasas saturadas de la dieta por ácidos grasos poliinsaturados (PUFA) reduce el riesgo de enfermedades cardiovasculares en un 19%, acompañado de una disminución en los niveles de colesterol LDL plasmáticos (47). El Estudio de Prevención con Dieta Mediterránea (PREDIMED), un ensayo clínico multicéntrico, realizado con participantes que presentaban un riesgo cardiovascular elevado (incluidos pacientes con DM2), demostró que la Dieta Mediterránea suplementada con aceite de oliva virgen extra o frutos secos (ricos en MUFA) reduce el riesgo de enfermedad cardiovascular y mortalidad un 30% (48).

El *Diabetes Nutrition and Complications Trial* (DNCT) es un estudio observacional, prospectivo, multicéntrico realizado por el Grupo de Nutrición de la Sociedad Española de Diabetes (49,50). Se diseñó con el objetivo de estudiar los hábitos dietéticos de la población con DM1 y DM2 española, y su relación con el desarrollo de complicaciones. En aquel momento, los pacientes con DM1, al igual que los pacientes con DM2, mostraron una adherencia pobre a las recomendaciones nutricionales establecidas por la ADA, excepto en el consumo de proteínas (49). A pesar de ello, los participantes tuvieron un buen control glucémico y perfil lipídico.

Los pacientes diabéticos tienen mayor riesgo de desarrollar enfermedades cardiovasculares, y por ello, es de gran interés el seguimiento y control de una correcta alimentación con un aporte de los nutrientes fundamentales para reducir este riesgo de complicaciones. Las recomendaciones de la denominada Dieta Mediterránea tienen efectos favorables en términos de factores de riesgo cardiovascular, así como la ingesta de fibra, que puede ayudar a controlar la HbA1c y los niveles de colesterol plasmáticos, y más en concreto, los de LDL (51).

1.4. Ingesta dietética y retinopatía diabética en la diabetes mellitus tipo 1

La ADA y la EASD establecen que la terapia médico-nutricional basada en la Dieta Mediterránea juega un papel importante en la prevención de complicaciones relacionadas con el manejo y control metabólico de la enfermedad (30). Además, se ha descrito una relación positiva entre la gravedad de la RD y los factores de riesgo modificables en pacientes con DM1 (52).

En la actualidad, existen pocos estudios publicados que relacionen la ingesta dietética y la presencia de RD en pacientes con DM1 (38,53–58). Dos revisiones sistemáticas publicadas recientemente sobre la ingesta dietética y la RD describen resultados contradictorios (59,60). Un sub-análisis del estudio *Diabetes Control and Complications Trial* (DCCT) observó que aquellos participantes con una ingesta de grasas elevada presentaban un mayor riesgo en la progresión de RD, y un menor riesgo asociado con una ingesta alta de fibra dietética (53). Sin embargo, un estudio prospectivo de cohortes no encontró diferencias significativas entre los hábitos dietéticos en asociación con la RD en pacientes con DM1 (54). Sasaki et al. describieron un efecto protector sobre la retinopatía con la ingesta de ácidos grasos monoinsaturados (MUFA) y PUFA en una muestra de pacientes con DM1 y DM2 bien controlados (55). Existen solamente dos ensayos clínicos aleatorizados realizados en pacientes con DM2 que relacionan la ingesta dietética o la suplementación nutricional con la RD (61,62); Howard-Williams et al. demostraron que los pacientes con DM2 con un control glucémico deficiente que seguían una dieta con bajo contenido en ácido linoleico presentaban mayor RD (61). Además, el ensayo clínico realizado en España en pacientes con DM2 demostró una menor frecuencia de RD en aquellos pacientes que estaban suplementados con antioxidantes y PUFA (62). Sin embargo, hasta el momento de la redacción de este texto, no hemos hallado ningún ensayo clínico realizado en pacientes con DM1 (59,60).

Existen otros estudios realizados para evaluar la relación entre el consumo de alcohol y sal con la presencia de RD en pacientes con DM1 (38,56–58). El estudio EURODIAB encontró un menor riesgo de RD con un consumo de alcohol moderado (38); sin embargo, un estudio con diseño

transversal no observó ninguna asociación con el consumo de sal y la RD en los pacientes con DM1 (56). Otros estudios realizados con grandes muestras de pacientes con DM1 de carácter transversal, entre ellos el estudio FinnDiane (57), encontraron una relación inversa entre el consumo de alcohol y la presencia de RD (57,58).

1.5. Resultados percibidos por el paciente

Los resultados percibidos por el paciente representan la percepción que tiene la propia persona y las valoraciones realizadas sobre su estado de salud y el tratamiento que realiza, comunicadas por él mismo, sin la interpretación de sus respuestas por un profesional sanitario (63). En estas valoraciones, se incluye el impacto que ejerce la enfermedad y el tratamiento recibido en su capacidad de relacionarse y en su propia autonomía (63).

Debido a que la mayoría de estudios científicos publicados utilizan incorrectamente los términos referidos a la calidad de vida, es importante definir cada constructo, pues dependerá de ello la calidad de los resultados obtenidos en la investigación (64).

1.5.1. Calidad de vida relacionada con la salud

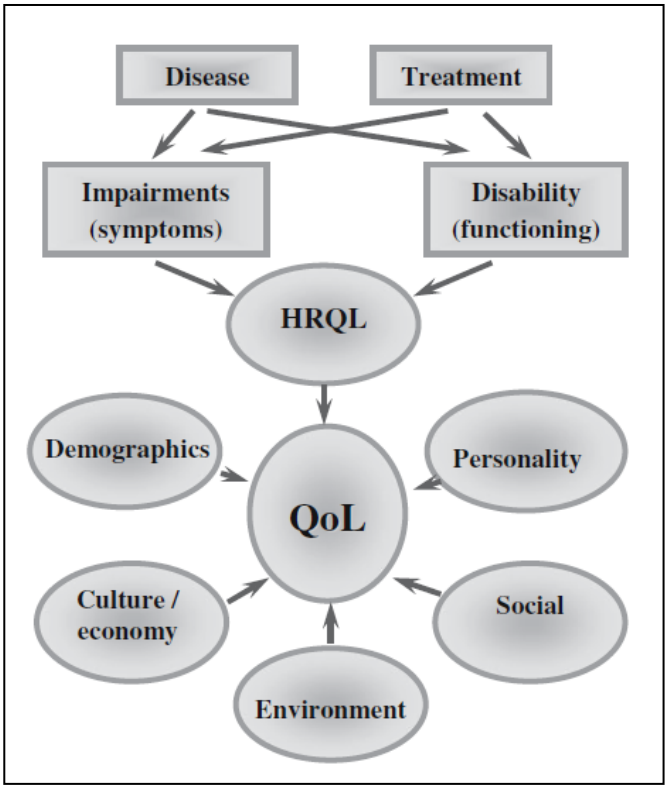
La calidad de vida relacionada con la salud (CVRS) se focaliza en aquellos aspectos de la vida que son considerados por los profesionales sanitarios como definitorios del estado de salud, ya que realmente abarca la medida de síntomas y de funcionamiento (65). Consecuentemente, el principal valor de la medida de la CVRS es la evaluación del estado de salud de los pacientes, los niveles de mejora o empeoramiento, la incapacidad funcional y la autonomía (65).

El énfasis en el funcionamiento físico de los instrumentos que miden la CVRS determina que los pacientes con incapacidad no perciban tener una buena calidad de vida (65). Por ello, es de gran importancia el instrumento utilizado para medir el constructo apropiado.

1.5.2. Calidad de vida

La calidad de vida es una medida de resultado basada en la valoración subjetiva de los pacientes respecto a su estado de salud y el bienestar emocional relacionado con la enfermedad, que abarca desde los aspectos psicosociales de los individuos hasta el funcionamiento físico, la movilidad y el cuidado personal (66) (Figura 3). Las consecuencias de la enfermedad y su tratamiento representan un grupo de factores con influencia sobre la calidad de vida. Además, se incluyen muchos otros aspectos como la personalidad, el estado económico, el ambiente, las relaciones sociales y la cultura (65).

Figura 3. Factores que influyen en la calidad de vida.



Tomado de Doward LC and McKenna SP. Value in Health, 2004;7:S4-8

Por lo tanto, para obtener una completa visión del impacto que ejerce una enfermedad y la efectividad de su tratamiento es esencial medir la calidad de vida; focalizarse solamente en la incapacidad funcional y la mejora o empeoramiento de la enfermedad es insuficiente (65).

1.5.3. Satisfacción con el tratamiento

La satisfacción con el tratamiento es la evaluación subjetiva del individuo relativa a su experiencia con el tratamiento, tanto del proceso como de los resultados, incluyendo la facilidad de uso, los efectos secundarios y la eficacia. Una elevada satisfacción no necesariamente implica que exista una mejora en la calidad de vida de las personas con diabetes por el propio impacto negativo que puede generar la diabetes mellitus en la calidad de vida (66).

1.6. Calidad de vida y satisfacción con el tratamiento en pacientes con diabetes mellitus

Una menor calidad de vida en los pacientes con DM1 respecto a los pacientes con DM2 es en parte resultado del impacto negativo que conlleva el tratamiento con insulina y la frecuencia requerida de monitorización de la glucemia a diario a lo largo de toda su vida (67). Además, el elevado riesgo de complicaciones tardías asociadas a la diabetes que tienen estos pacientes influye considerablemente en su calidad de vida, como se ha observado en diversos estudios. Los pacientes con DM1 tienen una menor calidad de vida si presentan nefropatía que aquellos sin complicaciones (68). También la edad juega un papel importante para valorar la calidad de vida y la satisfacción con el tratamiento, una mayor edad de los pacientes disminuye significativamente la calidad de vida (69). Por otro lado, un estudio demostró que el tratamiento con bomba de infusión continua de insulina intraperitoneal mejora la calidad de vida y la satisfacción con el tratamiento en pacientes con DM1 que no han logrado alcanzar un óptimo control glucémico con el tratamiento subcutáneo a pesar de la complejidad de dicho tratamiento para el paciente y los elevados costes económicos que supone el tratamiento (70).

Existen en la actualidad diversos cuestionarios genéricos que se han validado para medir la CVRS (también definida como estado de salud), así como cuestionarios específicos indicados para medir la calidad de vida en pacientes afectados por diversas enfermedades, siendo el cuestionario de calidad de vida específico para pacientes diabéticos (ADDQoL-19) y el cuestionario de satisfacción con el

tratamiento de la diabetes (DTSQ), desarrollados por el grupo liderado por Clare Bradley, como los más extendidos en la actualidad (71) (Anexo 1 y 2). Además, estos cuestionarios han sido recomendados por la OMS y la Federación Internacional de Diabetes (FID) en la evaluación de los resultados percibidos por el paciente, como la calidad de vida y la satisfacción con el tratamiento (72).

Actualmente, y hasta donde llega nuestro conocimiento, el estudio EURODIAB ha sido el único estudio multicéntrico a nivel europeo que relaciona la dieta con posibles complicaciones en pacientes con DM1 (35,38,40), pero no tiene en cuenta la calidad de vida, la satisfacción con el tratamiento o el estilo de vida (actividad física, consumo alimentario y adherencia a las recomendaciones dietéticas para la población diabética).

1.7. Calidad de vida, satisfacción con el tratamiento y retinopatía diabética en la diabetes mellitus tipo 1

La retinopatía diabética (RD) es la principal causa de pérdida de visión en la población diabética que puede afectar negativamente en la calidad de vida y satisfacción con el tratamiento de los pacientes (73). Además, la RD está relacionada con un mayor riesgo de enfermedad cardiovascular y mortalidad por todas las causas en pacientes con DM1 (74).

En pacientes con DM1, sólo existe un estudio que relaciona la calidad de vida y la RD utilizando un cuestionario específico para ello (75). Sin embargo, no encontró asociación de las mismas debido a que reclutaron una muestra conjunta de pacientes con DM2 y DM1, con una pequeña muestra de pacientes con RD (n=74). Los estudios científicos publicados hasta el momento en esta área se han realizado utilizando cuestionarios genéricos para medir la calidad de vida en pacientes diabéticos, cuando en realidad los cuestionarios genéricos son herramientas que miden la CVRS o bien el estado de salud general (76–85). Esta apreciación es importante, puesto que se ha demostrado que los pacientes pueden mostrar un estado de salud óptimo a nivel genérico, y en cambio, presentar una

calidad de vida relacionada con la diabetes pobre (64,86–88). Algunos de estos estudios no observaron relación entre la presencia de RD y la CVRS (76–78,80); en cambio, otros estudios hallaron una menor CVRS con la presencia de RD (79,83). En concreto, dos estudios recientes encontraron una menor CVRS en pacientes con DM1 que presentaban RD y, además, otras complicaciones como neuropatía, nefropatía y enfermedad cardiovascular (84,85).

Cabe destacar que los cuestionarios genéricos presentan un déficit de sensibilidad para evaluar los dominios específicos de la calidad de vida relacionados con las complicaciones específicas de la diabetes (89). Por ello, los cuestionarios específicos son considerados como los más recomendables para evaluar el impacto de las complicaciones en la calidad de vida de los pacientes con diabetes (64).

1.8. Dieta Mediterránea y resultados percibidos por el paciente en la diabetes tipo 1

Los pacientes con DM1 necesitan un régimen terapéutico que incluya el uso de insulina, la actividad física y la terapia médico-nutricional para asegurar un correcto control glucémico y metabólico de la enfermedad (28). En nuestra región, claramente Mediterránea, el recuento de carbohidratos y una alimentación saludable como la Dieta Mediterránea están incluidos en la terapia médico-nutricional de estos pacientes para prevenir la aparición de enfermedades cardiovasculares al tratarse de una población con mayor riesgo cardiovascular (28,29,31,32).

Una revisión sistemática publicada recientemente ha descrito que existe una falta de evidencia científica que relacione el patrón dietético con la calidad de vida y satisfacción con el tratamiento en pacientes adultos con diabetes (90). En la actualidad, existen pocos estudios científicos que hayan sido específicamente diseñados para evaluar la relación entre la Dieta Mediterránea y los resultados percibidos por el paciente en adultos con DM2 (91–93). Dichos estudios observaron que los pacientes que presentan una mayor adherencia a la Dieta Mediterránea mostraron una mejor calidad de vida y satisfacción con el tratamiento. Por otra parte, un estudio realizado en pacientes con

diabetes no encontró asociación entre el consumo de frutas y vegetales con la CVRS (94); sin embargo, los investigadores observaron que los pacientes con múltiples medidas de estilo de vida saludable (no fumadores, actividad física regular y una elevada ingesta de frutas y vegetales) presentaban una mayor CVRS.

En los pacientes adultos con DM1, no hay estudios diseñados para evaluar el potencial impacto del patrón dietético con la calidad de vida y satisfacción con el tratamiento. Solamente existe un estudio con diseño transversal realizado con una muestra de jóvenes y adolescentes (13 – 19 años) con DM1 que evaluó la relación entre los hábitos y estilos de vida no saludables con la calidad de vida (95); los resultados obtenidos no demostraron una asociación significativa entre la Dieta Mediterránea y la calidad de vida, debido probablemente a un tamaño de la muestra reducido. Sin embargo, encontraron que la combinación de diversos hábitos no saludables, como presentar una pobre adherencia a la Dieta Mediterránea y el sedentarismo, en conjunto, estuvieron relacionados con una menor calidad de vida en estos pacientes (95). Un estudio diseñado para auditar el manejo de la diabetes y la calidad de vida en pacientes adultos con DM1 no encontró relación con el patrón dietético (96).

Existen estudios publicados que se han llevado a cabo en pacientes adultos con DM1 y enfermedad celíaca, o para determinar la seguridad y eficacia del recuento de carbohidratos en el manejo de la enfermedad y su relación con la calidad de vida (97–99). Sin embargo, un meta-análisis publicado recientemente ha demostrado que existe una clara falta de evidencia científica en el área de la calidad de vida y el patrón dietético (99).

Justificación

2. Justificación

Los pacientes con DM1 tienen un riesgo más elevado de padecer enfermedad cardiovascular que puede aparecer por un mal control crónico de su enfermedad, aumentando y avanzado la morbimortalidad de estas personas. Unos buenos hábitos alimentarios pueden contribuir a disminuir la aparición de estas complicaciones en los pacientes diabéticos. Por tanto, resulta de interés estudiar el patrón alimentario de este tipo de pacientes y compararlo al de la población sin diabetes, así como evaluar su relación con aspectos relevantes para el paciente, como la calidad de vida y la satisfacción con el tratamiento.

En un estudio realizado por nuestro grupo (86), se demostró que la RD se asocia con peor calidad de vida en los pacientes con DM2. En la misma población, observamos que los pacientes con DM2 tenían mayor índice de adherencia a la Dieta Mediterránea que la población no diabética; además, se observó que una mejor calidad de vida y satisfacción con el tratamiento estaban asociados con un mayor grado de adherencia a la Dieta Mediterránea en pacientes con DM2 (100).

Estos hallazgos nos llevaron a pensar que también, probablemente, los pacientes con DM1 deberían presentar un patrón alimentario distinto y potencialmente más saludable que la población no diabética de edad equiparable.

Hipótesis

3. Hipótesis

Los pacientes con DM1 tienen riesgo de padecer complicaciones que pueden aparecer por un mal control crónico de su enfermedad, hecho que aumenta su morbimortalidad en relación con las personas no diabéticas. Unos buenos hábitos alimentarios pueden contribuir a reducir la aparición de estas complicaciones; por ello, es importante realizar una buena educación nutricional y terapéutica en estos pacientes. En el manejo nutricional de estos pacientes es fundamental que la persona afectada tenga un buen conocimiento de cómo realizar el recuento de hidratos de carbono, saber hacer un correcto intercambio de los mismos y la adecuación de la dosis de insulina según la ingesta. En la educación nutricional que reciben estas personas en nuestro país también se incluye el consejo sobre los hábitos dietéticos, siguiendo las recomendaciones de la Asociación Catalana de Diabetes, que son esencialmente las de una dieta saludable, es decir, para nosotros la Dieta Mediterránea. No conocemos el impacto que esta educación tiene en los hábitos que estos pacientes tienen adquiridos tiempo después de haber sido diagnosticados.

Antes de poder plantear medidas adicionales para intentar mejorar los hábitos alimentarios de los pacientes con DM1 de nuestro país, hace falta saber en qué punto nos encontramos y cuál es el impacto real de la atención a la salud de estas personas.

Por tanto, resulta de interés conocer el patrón alimentario de este tipo de pacientes y evaluar las diferencias respecto la población sin diabetes. Hasta donde llega nuestro conocimiento, ignoramos en nuestro país cuál es el punto en el que nos encontramos.

Hipótesis 1

Los pacientes con DM1 presentan unos hábitos dietéticos más saludables, y, por tanto, una mayor adherencia a la Dieta Mediterránea que aquellos sujetos de la misma población sin diabetes.

Hipótesis 2

Los pacientes con DM1 y RD tienen una menor adherencia a las recomendaciones nutricionales que

los pacientes con DM1 sin esta complicación.

Hipótesis 3

En los pacientes con LADA, específicamente, pensamos que presentan una menor calidad de vida y satisfacción con el tratamiento que los pacientes con DM1 y DM2, ya que su diagnóstico y tratamiento inicial como pacientes con DM2 conlleva un inadecuado manejo. Esto conlleva que estos pacientes presenten un peor control glucémico y un riesgo relativamente elevado de aparición de complicaciones tardías de la diabetes que pueden afectar a su calidad de vida y satisfacción con el tratamiento en comparación con los otros tipos de diabetes.

Hipótesis 4

Los pacientes con DM1 con RD presentan una peor percepción de su calidad de vida y satisfacción con el tratamiento en comparación con los pacientes con DM1 sin esta complicación.

Hipótesis 5

En los pacientes con DM1, una mayor adherencia a la Dieta Mediterránea y una alimentación saludable están relacionadas con una mejor auto-percepción de su calidad de vida y satisfacción con el tratamiento.

Objetivos

4. Objetivos

El objetivo general de esta tesis doctoral fue evaluar los hábitos alimentarios y el grado de adherencia a la Dieta Mediterránea de los pacientes adultos con DM1.

Los objetivos que se describen a continuación se corresponden con cada una de las hipótesis detalladas anteriormente.

1. Evaluar los hábitos dietéticos y el grado de adherencia a la Dieta Mediterránea en los pacientes con DM1 y su comparación con sujetos sin diabetes de la misma población. Además, estudiar los factores clínicos y sociodemográficos asociados al patrón dietético.
2. Evaluar las diferencias en la ingesta de alimentos y nutrientes entre los pacientes con DM1 que presentan RD y los que no presentan dicha complicación. Secundariamente, investigar la relación entre las características clínicas y la presencia de RD en los pacientes con DM1.
3. Determinar la calidad de vida y satisfacción con el tratamiento en los pacientes con LADA, y su comparación con aquellos con DM1 y DM2. Adicionalmente, investigar los factores relacionados con la calidad de vida y satisfacción con el tratamiento en los tres grupos de estudio.
4. Estudiar la asociación entre la calidad de vida y satisfacción con el tratamiento en los pacientes con DM1 con RD y sin RD. Además, determinar los factores clínicos relacionados con la calidad de vida y la satisfacción con el tratamiento.
5. Determinar la relación entre el patrón dietético (Dieta Mediterránea y alimentación saludable) y los resultados percibidos por el paciente (calidad de vida y satisfacción con el tratamiento) en los pacientes con DM1.

Publicaciones

5. Publicaciones

5.1. Artículo 1

Minerva Granado-Casas, Nuria Alcubierre, Mariona Martín, Jordi Real, Anna M. Ramírez-Morros, Maribel Cuadrado, Núria Alonso, Mireia Falguera, Marta Hernández, Eva Aguilera, Albert Lecube, Esmeralda Castelblanco, Manel Puig-Domingo, Dídac Mauricio. Improved adherence to Mediterranean Diet in adults with type 1 diabetes mellitus. Eur J Nutr. 2019;58(6):2271-2279.

Resumen

Objetivos

La terapia médico-nutricional basada en las recomendaciones nutricionales de la Dieta Mediterránea es importante para un óptimo auto-control de la DM1 y en la prevención de complicaciones. El objetivo principal del estudio fue comparar la ingesta dietética y la adherencia a la Dieta Mediterránea entre un grupo de pacientes con DM1 y un grupo de personas sin diabetes. Secundariamente, se evaluaron los factores relacionados con un patrón dietético más saludable.

Materiales y métodos

El diseño del estudio fue observacional, transversal y multicéntrico. Se reclutó una muestra de 513 participantes (259 pacientes con DM1 y 254 participantes sin diabetes) de dos centros (Hospital Universitari Arnau de Vilanova de Lleida y el Hospital Universitari Germans Trias i Pujol de Badalona). Ambos grupos fueron emparejados por edad y sexo. Se administró, mediante entrevista personal con cada participante, el cuestionario de frecuencia de consumo alimentario diseñado por Willet et al. basado en el Estudio de Salud de las Enfermeras Norteamericanas y validado para población española por el grupo de Epidemiología de la Nutrición de la Universidad Miguel Hernández (Anexo 3). La adherencia a la Dieta Mediterránea y la ingesta dietético-nutricional se calculó mediante dos índices: el *alternate Mediterranean Diet Score* (aMED) y el *alternate Healthy Eating Index* (aHEI). Se realizó una revisión exhaustiva de las historias clínicas y se realizaron determinación de parámetros de laboratorio en sangre y orina, y entrevistas personales en ambos centros con cada participante. El análisis estadístico incluyó comparaciones entre grupos y modelos multivariables.

Resultados

En el grupo de pacientes con DM1, se observó una mayor ingesta de lácteos, carnes procesadas, pescado graso, frutas y vegetales, frutos secos, legumbres, patatas y pan, y una menor ingesta de

marisco, dulces y bebidas alcohólicas en comparación con el grupo control. Además, los participantes con DM1 tuvieron un mayor consumo de carbohidratos complejos, fibra dietética, proteínas, PUFA, antioxidantes, vitaminas y minerales. En relación con la adherencia a la Dieta Mediterránea, los pacientes con DM1 mostraron una mayor puntuación en el aMED. En el análisis multivariable se observó asociación entre los pacientes con DM1, la práctica de actividad física regular y la edad con una mayor adherencia a la Dieta Mediterránea. En relación con el patrón de alimentación saludable (medido con el aHEI), los pacientes con DM1 tuvieron mayor puntuación en comparación con los controles. El hecho de ser un paciente con DM1, tener mayor nivel educativo, residir en una zona rural o semiurbana, la actividad física regular y una mayor edad se relacionó con mayor aHEI. En cambio, el sexo masculino estuvo asociado negativamente con el aHEI. El análisis multivariable en el grupo de participantes con DM1, mostró que residir en una zona no urbana se asocia con una mayor adherencia a la Dieta Mediterránea y una alimentación más saludable.

Conclusiones

Los pacientes adultos con DM1 tuvieron un patrón dietético más saludable y una elevada adherencia a la Dieta Mediterránea en comparación con los participantes sin diabetes. Unos hábitos dietéticos más saludables se asociaron con el hecho de residir en una zona no urbana o semiurbana.

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ORIGINAL CONTRIBUTION

Improved adherence to Mediterranean Diet in adults with type 1 diabetes mellitus

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Abstract

Purpose We aimed to assess food intake and adherence to the Mediterranean Diet in patients with T1D compared with nondiabetic individuals.

Methods This was an observational, multicenter study in 262 T1D subjects and 254 age- and sex-matched nondiabetic subjects. A validated food-frequency questionnaire was administered. The alternate Mediterranean Diet Score (aMED) and alternate Healthy Eating Index (aHEI) were assessed. The clinical variables were also collected. The analysis of data included comparisons between groups and multivariate models.

Results Compared to the controls, the patients with T1D had a higher intake of dairy products ($p<0.001$), processed meat ($p=0.001$), fatty fish ($p=0.009$), fruits and vegetables ($p<0.001$), nuts ($p=0.011$), legumes ($p<0.001$), potatoes ($p=0.045$), and bread ($p=0.045$), and a lower intake of seafood ($p=0.011$), sweets ($p<0.001$), and alcohol drinks ($p=0.025$). This intake pattern resulted in a higher consumption of complex carbohydrates ($p=0.049$), fiber ($p<0.001$), protein ($p<0.001$), polyunsaturated fatty acids (PUFA) ($p=0.007$), antioxidants ($p<0.001$), vitamins ($p<0.001$), and minerals ($p<0.001$). The frequency of patients with T1D and low aMED score (23.2%) was lower than that of the controls (35.4%; $p=0.019$). The overall multivariate analysis showed that, among other factors, being a T1D subject was associated with improved aMED and aHEI scores ($p=0.006$ and $p<0.001$). In patients with T1D, residing in a nonurban area was associated with improved aMED and aHEI scores ($p=0.001$ and $p<0.001$).

Conclusions Adult patients with T1D showed healthier dietary habits and a higher adherence to the Mediterranean Diet than nondiabetic subjects. Residing in a nonurban area is associated with an improved dietary pattern.

Keywords Type 1 diabetes mellitus · Mediterranean Diet · Dietary habits · Food intake · Intake pattern · Medical nutrition therapy

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Introduction

Medical nutrition therapy (MNT) and physical activity, in addition to insulin therapy, are cornerstones in the management of type 1 diabetes (T1D). MNT produces health benefits on glucose control, lipid profile, weight management, and maintenance of muscle mass [1–3]. Different scientific societies have issued nutritional recommendations for the medical nutrition management of T1D [2–5]. MNT is also an integral component of diabetes self-management education [2]. The handling of dietary carbohydrate content and insulin management are mainly targeted to enable the patients with T1D to self-manage the disease [2, 3]; furthermore, healthy eating recommendations are usually included in the MNT, because these patients are regarded as a high cardiovascular risk group [2, 3, 5].

In our region, the dietary habits are identified by the Mediterranean Diet (MedDiet). This dietary pattern includes moderate intake of energy, low intake of animal fat, high intake of fruits, vegetables, whole grains, legumes, olive oil and moderate intake of fish, poultry, and red wine, together with regular physical activity (25–30 min every day) [3, 6, 7]. A number of epidemiological and intervention studies have demonstrated the potential benefits of the MedDiet in preventing cardiovascular diseases [6–10]. The MedDiet has been associated with a reduction of 9% overall mortality from cardiovascular diseases and all causes [7, 10].

Several studies in T1D have assessed the comparison between the dietary habits and the American Diabetes Association (ADA) or the European Association for the Study of Diabetes (EASD) nutritional recommendations [11–15]. Higher intakes of total fat and saturated fatty acids (SFA) have been shown in European patients with T1D [11–14]. Furthermore, the intake of carbohydrates and fiber tends to be low in this population [11, 14, 15], although the protein consumption is adequate according to the established guidelines [12, 13]. The intake of micronutrients is high in children, adolescents, and adults with T1D [11, 15]. The EURODIAB Study reported a positive relationship between a higher intake of fat and SFA, and a low intake of carbohydrates and fiber with glycemic control and cardiovascular risk factors [16, 17]. Most studies have been only performed in patients with T1D, and there are very few studies that compare the dietary habits between patients with T1D and a nondiabetic group [18–20]. In addition, to the best of our knowledge, there are only two studies that assessed the adherence to the MedDiet and healthy eating pattern in a small group of Canadian patients with T1D, but without a control group [21, 22]. Furthermore, there are only two studies with a case–control design that determined the dietary habits in children and adolescents with T1D [23, 24].

Because patients with T1D receive regular nutritional education, we hypothesized that they would have healthier eating habits than nondiabetic subjects. In a Mediterranean country like ours, MNT includes recommendations for adhering to a MedDiet pattern [4]. However, there are no data on the impact of real-world MNT practices on the dietary pattern of subjects with T1D in comparison with their nondiabetic counterparts. Thus, the aim of this study was to assess the dietary habits and adherence to the MedDiet in patients with T1D and their comparison to nondiabetic counterparts. In addition, we aimed to investigate the factors related to the MedDiet and food intake pattern.

Materials and methods

Subjects

This was an observational and two-center study. A sample of 513 participants was recruited: 259 patients with T1D and 254 nondiabetic subjects matched for age and sex in each location [healthcare areas of Lleida (center 1) and Barcelona (center 2)] between January 2013 and May 2015. The location of Lleida is a mixed rural and semi-urban area, and Barcelona is a fully urban area. The cases were patients diagnosed with T1D who were regularly cared for at their reference hospital (University Hospital Arnau of Vilanova and University Hospital Germans Trias i Pujol). Participation in the study was offered to outpatients with T1D in both departments until the study sample was complete. The inclusion criteria of cases were as follows: diagnosis of T1D with a duration of more than 1 year; age > 18 years for both cases and control participants. The exclusion criteria for both groups were as follows: being a healthcare professional, participants who showed physical and cognitive deterioration as dementia, mental diseases, and known cardiovascular diseases (ischemic heart disease, cerebrovascular disease, peripheral arterial disease, and heart failure) or previous diabetic foot disease, pregnancy, and renal insufficiency (estimated glomerular filtration rate < 60 mL/min). Furthermore, for T1D, we excluded patients with a condition that requires additional MNT measures, i.e., macroalbuminuria (urine albumin/creatinine ratio > 299 mg/g). The control participants were also excluded if they had an HbA1c value ≥ 6.5% [25].

Study design

In center 1, from an initial sample of 170 patients with T1D who were contacted to participate in the study, 128 subjects accepted to participate, and 3 were excluded because of the exclusion criteria, resulting in a target sample of 125 (Supplemental Fig. 1). However, 3 additional subjects were

excluded after their inclusion because of the identification of exclusion criteria, resulting in a final sample of 122 cases. The corresponding control group was identified from a population-based study, which was performed simultaneously in that center [25]. The nondiabetic subjects were randomly selected with matching for age (in strata of 5 years) and sex with cases, resulting in a final sample of 125 controls.

In center 2, a total of 160 patients with T1D were contacted; 148 agreed to participate. From this group, 11 were excluded, because they had met the exclusion criteria. The final sample was 137 patients with T1D. The control group was recruited at the same time as the cases; from a sample of 160 controls, 151 accepted and 22 were excluded because of the exclusion criteria, resulting in a final sample of 129 controls (Supplemental Fig. 1).

The study was approved by the local Ethics Committee of both centers, and written informed consent was obtained from all the participants.

Clinical variables

The clinical variables collected for each study group are shown in Table 1. Blood and urine samples were collected, and the biochemical variables were determined using the standard methods. Cardiovascular disease was excluded based on detailed anamnesis and careful review of all clinical records. The use of any medication, including any antihypertensive or lipid-lowering agents, was also recorded. Physical activity was assessed using the validated method of Bernstein et al. [26] and Cabrera de León et al. [27]. Physical activity was classified as either regular physical activity if the subject conducted any type of physical activity that requires 4 METS (The Metabolic Equivalent) minimum, such as walking or cycling, for more than 25 min/day or sedentary if the subject spent less than 25 min/day in physical activity.

Table 1 Clinical and demographic characteristics of the study group

Characteristics	T1D ($n=259$)	Control ($n=254$)	p^a
Age (years)	43.7 ± 11.2	45.4 ± 11.2	0.10
Men (sex)	118 (45.6)	122 (48.0)	0.64
Educational level			0.05
Less than primary	15 (6.0)	6 (2.4)	
Primary	74 (29.8)	56 (22.2)	
Secondary	97 (39.1)	116 (46.0)	
Graduate or higher	62 (25.0)	74 (29.4)	
Smoking			0.43
No	130 (50.2)	112 (44.1)	
Yes	70 (27.0)	78 (30.7)	
Former smoker	59 (22.8)	64 (25.2)	
Regular physical activity	186 (71.8)	130 (51.2)	< 0.001
Diabetes duration (years)	21.5 ± 10.5	–	–
BMI (kg/m^2)	25.6 ± 4.1	25.9 ± 4.0	0.44
Waist circumference (cm)	88.3 ± 12.7	92.5 ± 11.8	< 0.001
Systolic blood pressure (mmHg)	126.6 ± 17.4	122.6 ± 15.5	0.009
Diastolic blood pressure (mmHg)	73.7 ± 9.5	77.3 ± 9.4	< 0.001
Antihypertensive treatment	64 (24.7)	18 (7.1)	< 0.001
Dyslipidemia treatment	102 (39.4)	39 (15.4)	< 0.001
HbA1c (%)	7.6 ± 0.9	5.5 ± 0.4	< 0.001
HbA1c (mmol/mol)	59.4 ± 10.4	37.0 ± 4.1	< 0.001
Total cholesterol (mg/dL)	180.6 ± 28.5	194.4 ± 37.9	< 0.001
HDLc (mg/dL)	64.7 ± 16.0	61.4 ± 16.0	0.025
LDLc (mg/dL)	101.9 ± 23.4	115.9 ± 33.5	< 0.001
Triglycerides (mg/dL)	73.7 ± 37.8	94.3 ± 53.2	< 0.001

Values are mean ± SD or *n* (%)

BMI body mass index, *HbA1c* glycated hemoglobin, *HDLc* high-density lipoprotein cholesterol, *LDLc* low-density lipoprotein cholesterol, *T1D* type 1 diabetes

[a] *p* was calculated according to the method of Benjamini and Hochberg

Assessment of food pattern intake and adherence to dietary index

The Food-Frequency Questionnaire Consumption (FFQC) was administered by personal interview by specialized and trained researchers. This is a semiquantitative questionnaire, validated and adapted for the Spanish population and based on the Nurses' Health Study [28, 29]. The questionnaire contains 101 items that ask each individual about his or her usual consumption over the previous year's visit. To assess the degree of adherence to the MedDiet, we used the alternate Mediterranean Diet Score (aMED) based on the Mediterranean Diet scale [30]. We also determined the alternate Healthy Eating Index (aHEI) based on the Dietary Guidelines for Americans and the Food Guide Pyramid [31]. The aMED includes vegetables, legumes, fruits, nuts, grains (only whole grain), red and processed meat, fish, monounsaturated fatty acids (MUFA)-to-SFA ratio, and alcohol intake. The score ranges from 0 (minimal adherence) to 9 (maximal adherence). The aHEI includes vegetables, fruit, nuts and soy, white and red meats, cereal fiber, trans fat, polyunsaturated and saturated fat, and alcohol intake. Energy and nutrient intake was obtained according to standardized measurement units. Daily nutrient intake was calculated adjusting for energy intake and expressed as units/day according to the standardized methods for the FFQC.

Sample size

The sample size was calculated to detect the differences between the study groups based on previous results from a pilot study performed to assess the potential output (60 cases and 60 controls) in which the mean and standard deviation values of aMED were estimated in both groups: T1D 4.2 ± 1.4 and controls 3.7 ± 1.4. Based on this difference, using a significance level of 5% ($\alpha = 0.05$) and a statistical power of 80% ($\beta = 0.2$), a sample of 125 cases and 125 controls was necessary to detect a statistically significant difference in the aMED score. Finally, based on the availability of a sufficient number of potential participants, we aimed to conduct the study in two different geographical areas, which also allowed us to increase the statistical power of the study.

Data analyses

An initial descriptive comparison between groups of all variables was performed. The quantitative variables were summarized using the mean and standard deviation (SD) values, and the qualitative variables were summarized using the absolute (n) and relative frequencies (%). Statistical significance was assessed using the Chi-squared test to assess the differences in the frequencies. The mean of clinical determinations, daily food and nutrient intake, and the dietary quality index were compared using Student's t test. The "BH" (aka "fdr") and "BY" methods of Benjamini, Hochberg, and Yekutieli were performed; they control the false discovery rate and the expected proportion of false discoveries among the rejected hypotheses. The false discovery rate is a less stringent condition than the family-wise error rate, so these methods are more powerful than the others. The multivariate regression models were developed to analyze the relationship between group (case and control) and dietary quality index adjusted by the potential confounders. The models were adjusted by variables that were statistically significant in the bivariate analysis or were clinically associated with diabetes. The conditional logistic regression models were designed to explain low aMED adherence (aMED low: 0–2) and adjusting linear regression models were performed for aHEI. The goodness-of-fit assumption using the Hosmer–Lemeshow test for logistic models was assessed, and for the linear regression model, the Kolmogorov–Smirnov test was performed. The estimate measures were the odds ratio (OR) with 95% confidence interval (95% CI) and with logistic regression models, and the effect (β) and standard error ($\pm$SE) with linear regression. In all the tests, a $p < 0.05$ was considered to be statistically significant.

Results

The clinical and demographic characteristics of the study groups are shown in Table 1. The patients with T1D showed lower waist circumference ($p < 0.001$) than the control group. However, the patients with T1D performed regular physical activity more frequently ($p < 0.001$), and had a high frequency of treatment for hypertension ($p < 0.001$) and dyslipidemia ($p < 0.001$). Furthermore, the patients with T1D showed a better lipid profile.

Dietary habits

The patients with T1D had a healthier food intake pattern than the control group, as shown in Table 2. Compared to the controls, the subjects with T1D had a higher intake of dairy products ($p < 0.001$), processed meat ($p = 0.001$), fatty fish ($p = 0.009$), fruits and vegetables ($p < 0.001$), nuts ($p = 0.011$), legumes ($p < 0.001$), potatoes ($p = 0.045$) and bread ($p = 0.045$), and a lower intake of seafood ($p = 0.011$), sweets ($p < 0.001$) and alcohol drinks ($p = 0.025$).

Consistent with this food pattern, there was also a differential intake of nutrients (Supplemental Table 1). The patients with T1D showed a higher intake of complex carbohydrates ($p = 0.049$), soluble and insoluble fiber ($p < 0.001$), protein ($p < 0.001$), and PUFA ($p = 0.007$); the latter included intake of omega 3 ($p < 0.001$), omega 6 ($p = 0.016$), linoleic acid ($p = 0.016$), α-linolenic acid ($p < 0.001$),

Table 2 Dietary quality index and daily food intake of the study groups

Items	T1D ($n=259$)	Control ($n=254$)	p^a
Dietary quality index			
aMED	3.7 ± 1.6	3.2 ± 1.8	0.009
aMED			0.019
Low (0–2)	60 (23.2)	90 (35.4)	
Moderate (3–5)	167 (64.5)	139 (54.7)	
High (6–9)	32 (12.4)	25 (9.8)	
aHEI	40.7 ± 6.5	37.6 ± 6.2	< 0.001
aHEI			0.011
Low (< 45)	196 (75.7)	218 (85.8)	
High (≥ 45)	63 (24.3)	36 (14.2)	
Daily food intake (g/day)			
Dairy products	401.6 ± 240.8	309.6 ± 195.0	< 0.001
Eggs	20.3 ± 11.9	20.6 ± 11.0	0.82
White meat	36.1 ± 22.0	35.9 ± 21.1	0.93
Red meat	51.9 ± 38.7	55.7 ± 37.9	0.35
Processed meat	43.6 ± 32.2	34.5 ± 25.3	0.001
Meat	129.1 ± 55.1	125.0 ± 52.7	0.48
Lean fish	31.4 ± 36.5	30.2 ± 21.2	0.72
Fatty fish	36.2 ± 29.3	29.2 ± 23.2	0.009
Seafood	9.6 ± 8.5	12.3 ± 12.2	0.011
Fish	77.5 ± 48.9	70.6 ± 37.8	0.13
Fruits and vegetables	490.1 ± 233.9	372.0 ± 163.4	< 0.001
Nuts	14.7 ± 29.3	9.0 ± 14.0	0.011
Legumes	34.2 ± 25.1	25.9 ± 19.7	< 0.001
Cereals and pasta	82.8 ± 44.5	77.7 ± 42.6	0.29
Potatoes	55.7 ± 39.6	48.1 ± 37.4	0.045
Bread	104.5 ± 52.6	93.8 ± 56.1	0.045
Sweets	17.4 ± 20.9	38.5 ± 35.1	< 0.001
Vegetable fats	40.0 ± 16.7	38.8 ± 19.6	0.52
Animal fats	0.2 ± 1.0	0.2 ± 0.7	0.72
Alcohol drinks	92.5 ± 168.8	139.0 ± 244.5	0.025
Non-alcoholic beverages	1504.1 ± 549.8	1447.8 ± 467.4	0.29
Coffee and tea	421.7 ± 280.4	448.0 ± 312.3	0.40
Prepared meals	69.2 ± 83.8	61.3 ± 54.7	0.29
Salt	1.1 ± 1.8	0.9 ± 1.1	0.19

Values are mean ± SD or *n* (%)

T1D type 1 diabetes, *aMED* alternate Mediterranean Diet index, *aHEI* alternate Healthy Eating Index

[a]*p* was calculated according to the method of Benjamini and Hochberg

eicosapentaenoic acid (EPA) ($p=0.049$), and docosahexaenoic acid (DHA) ($p=0.016$). Furthermore, subjects with T1D also showed a higher consumption of all vitamins ($p<0.001$; except vitamin B12), carotenoids ($p<0.001$), and minerals ($p<0.001$; except for iron intake). In contrast, the control group showed a higher intake of energy ($p=0.011$), sugar ($p<0.001$), stearic acid ($p=0.021$), and alcohol ($p=0.002$); they also had a higher dietary glycemic index ($p=0.002$).

Alternate Mediterranean Diet Score

The dietary quality index of each of the study groups is shown in Table 2. Compared to the control group, the participants with T1D showed a higher aMED score ($p=0.009$). Furthermore, the frequency of patients with T1D with poor adherence to a MedDiet (low aMED score) was lower ($p=0.019$). However, both groups had a moderate mean aMED score (3.7 ± 1.6, T1D; 3.2 ± 1.8, control). The multivariate logistic analysis showed that being a subject with T1D ($p=0.006$), increased physical activity ($p=0.017$) and increasing age ($p=0.008$) were negatively related to a low aMED score; thus, all these variables were associated with a higher adherence to a MedDiet (Fig. 1a, Supplemental Table 2).

Alternate Healthy Eating Index

Patients with T1D also showed a higher aHEI score than the controls ($p<0.001$) (Table 2). In addition, consistent with the results of aMED score, the frequency of patients with T1D and with a low aHEI score (defined as aHEI < 45 points) was lower (75.7%, T1D vs. 85.8%, controls; $p=0.011$). Moreover, the mean of aHEI was relatively low in both groups (40.7 ± 6.5, T1D; 37.6 ± 6.2, controls). The multivariate linear analysis revealed that the factors associated with higher aHEI scores were the T1D group ($p<0.001$), high educational level ($p=0.016$), residing in the region of Lleida ($p<0.001$), increased physical activity ($p=0.033$), and increasing age ($p=0.006$) (Fig. 1b, Supplemental Table 2). However, the male sex showed a negative association with this index ($p=0.001$).

Factors associated with the dietary pattern in T1D

The multivariate analyses within the T1D group showed that the factor related to a high adherence to the MedDiet was residence in the region of Lleida (rural/semi-urban area) ($p=0.001$) (Fig. 2a, Supplemental Table 3). The factors related to aHEI score were residence in Lleida ($p<0.001$), high educational level ($p=0.025$), and age ($p=0.006$). The male sex was negatively associated with aHEI ($p=0.008$) (Fig. 2b, Supplemental Table 3).

Discussion

In this study, we observed healthier dietary habits in patients with T1D in comparison with their nondiabetic counterparts. This finding resulted in a higher adherence to the MedDiet

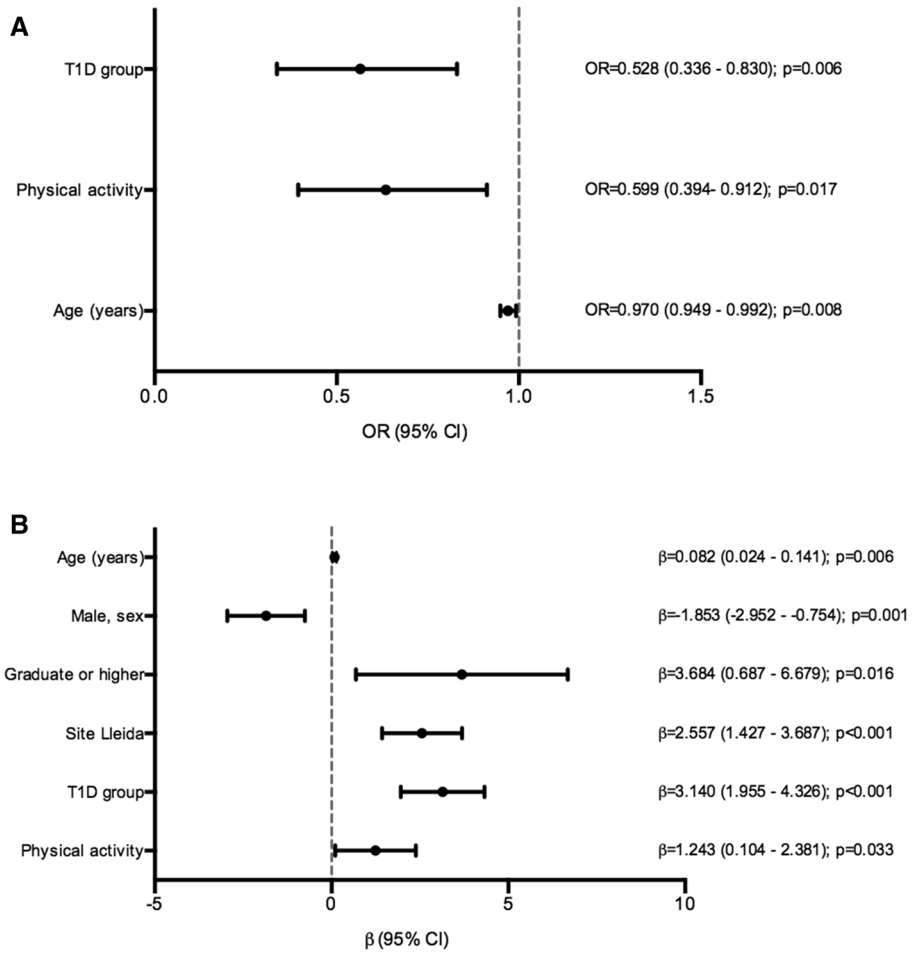

Fig. 1 Multivariate analysis for the alternate Mediterranean Diet Score (aMED) and alternate Healthy Eating Index (aHEI) of the study groups. **a** Multivariate logistic regression for the aMED low group (0–2 points). Hosmer–Lemeshow test *p* value: 0.08. **b** Multivariate linear regression for the aHEI. Multiple R^2: 0.16; adjusted R^2: 0.14. T1D, type 1 diabetes

and healthier eating patterns, with higher aMED and aHEI scores in patients with T1D. In addition, we found a positive relationship between T1D, physical activity, and age with both dietary scores. The participants who were residing in the rural/semi-urban area and had a high educational level showed an increased aHEI score, whereas the male sex was negatively related to it. This is the first study that assesses food and nutrient intake, adherence to the MedDiet, and a healthy eating pattern in adult patients with T1D. Moreover, this study was specifically designed to address this question. To the best of our knowledge, no study has addressed the issue of the adherence to the MedDiet between adult subjects with T1D and a nondiabetic group.

Consistent with the previous findings [11–15], despite patients with T1D showing a moderate aMED and healthier dietary pattern, the adherence to the nutritional recommendations cannot be regarded as optimal in terms of the recommendations [2–5]. There are only three studies that compared the dietary habits between patients with T1D and nondiabetic subjects [18–20]. Snell-Bergeon et al. [18] and Jaacks et al. [19] observed a lower energy intake and higher intakes of protein and vegetables in patients with T1D; this observation is concordant with the current findings. However, they showed a low intake of carbohydrates, high intake of fat derived from SFAs, and similar glycemic index, which is in contrast with our results. In addition, an audit of dietary management in adults with T1D found no differences in terms of macronutrient intake between the patients with T1D and a control group, although there was a potential selection bias, and both groups were not matched for age and sex [20]. Actually, there are only two studies using a case–control design that showed healthier dietary habits in children and adolescents with T1D [23, 24]. However, it is conceivable that the dietary patterns of children and adolescents with T1D are mainly determined by the parental dietary habits [23, 24]. Therefore, ours is the first study showing healthier dietary patterns in adult patients with T1D and a matched nondiabetic group.

In the current study, patients with T1D had more frequently higher aMED and aHEI scores in comparison with a control group. Nevertheless, the mean of aHEI was low in both groups according to the index classification. To date, there is no study that has assessed the adherence to the MedDiet and healthy eating using this study design. Only a Canadian study has shown a moderate adherence to the MedDiet with less than half of the patients with T1D (49%) showing

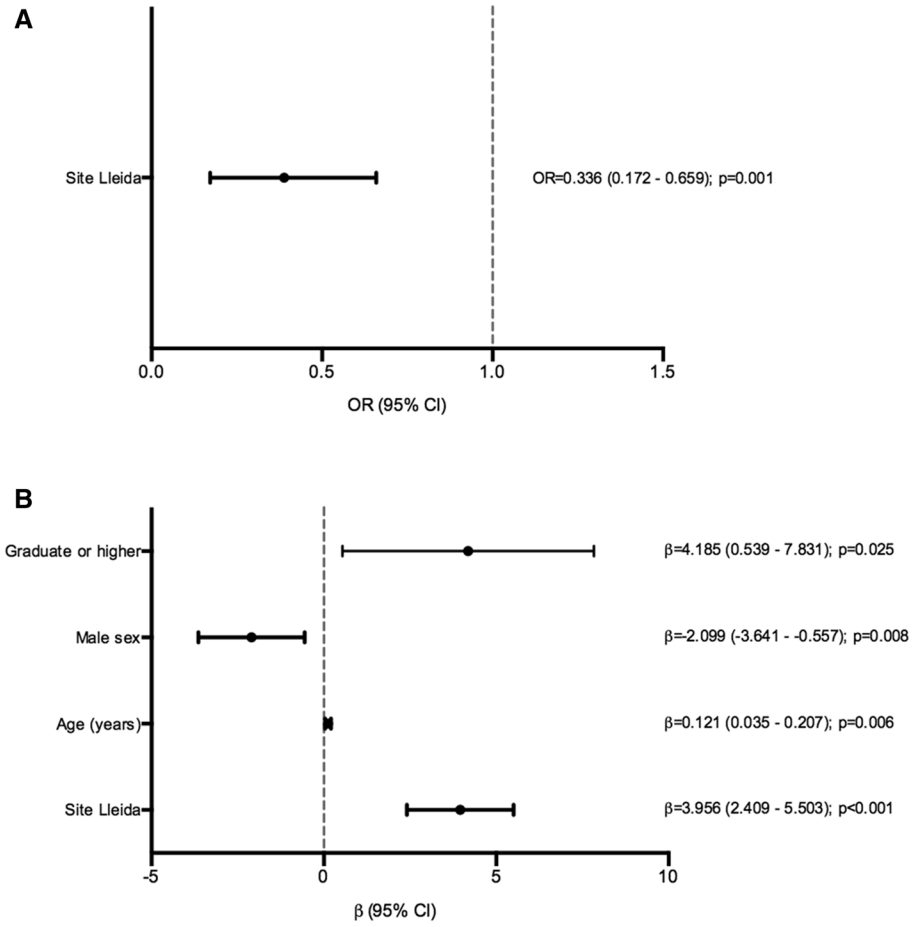

Fig. 2 Multivariate analysis for the alternate Mediterranean Diet Score (aMED) and alternate Healthy Eating Index (aHEI) of the type 1 diabetes group. **a** Multivariate logistic regression for the aMED low group (0–2 points). Hosmer–Lemeshow test *p* value: 0.163. **b** Multivariate linear regression for the aHEI. Multiple R^2: 0.20; adjusted R^2: 0.15

a high Canadian Healthy Eating Index (C-HEI); this finding is similar to our results [21, 22]. However, that study was performed using a small sample without a nondiabetic control group.

We must underscore that the fact of not residing in an urban area was the factor that was closely and consistently associated with improved dietary quality indexes in patients with T1D. This points to a relevant influence of the sociogeographical context in determining the dietary pattern of any given subject. In addition, discordant results found by different studies in T1D may, in part, be attributed to this factor. This is also an important finding for future studies, as the control group should be carefully selected.

In our study, the subjects with a high educational level, regular physical activity, and older age showed an improved healthy lifestyle behavior independent of the disease duration. It is reasonable to think that a healthy lifestyle is more likely to be adopted in older patients and that it is maintained over time [32]. In addition, as in other studies, men show an unhealthier dietary pattern than women [22, 33]. We did not find a relationship between aMED and aHEI with the presence of dyslipidemia or hypertension, although an inverse association between lipid profile, blood pressure, and a healthy lifestyle has been reported in patients with T1D [22]. Therefore, in our population, dyslipidemia and hypertension do not seem to be potential factors that enhance the adherence to a healthier dietary pattern.

The current study has several limitations. No relationship of direct causality can be established between the different variables associated with the MedDiet, because the changes in lifestyle habits produced over time cannot be addressed with a study like the current one. Although the current results point to the probable influence on the better dietary habits of T1D patients of the educational dietary intervention (usually mainly focused on carbohydrate counting) that they receive from the treating healthcare professionals, we cannot conclude that this is the case. Unfortunately, we did not assess the knowledge of patients about the dietary management of diabetes. This study has several strengths. The large number of participants, the multicenter design, and a well-characterized sample allow us to establish the variability of different populations and lifestyles associated with them. Furthermore, we could study the different pattern in two different areas of the same region, North-Eastern Spain, that differed by their urban and rural/semi-urban locations. Moreover, this is the first study that assessed the adherence

to the MedDiet between adults with T1D and a nondiabetic control group.

In conclusion, in our Mediterranean region, adults with T1D showed a healthier food intake pattern and, specifically, an improved adherence to the MedDiet than their nondiabetic counterparts. However, additional research is warranted in this field and in the identification of the educational strategies that need to be adopted to enhance the adherence of patients with T1D to a healthy diet.

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Author contributions The authors' responsibilities were as follows: MG-C, NA, and DM designed the research; MG-C, AR-M, NA, MM, EC, MF, MH, MC, and EA conducted research; MG-C, JR, and DM analyzed the data; MG-C, NA, JR, and DM wrote the paper; AL and MP-D coordinated the research; DM was the principal investigator and had the primary responsibility for the final content. All the authors read and approved the final manuscript. MG-C and NA contributed equally to this work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Mann JI (1997) The role of nutritional modifications in the prevention of macrovascular complications of diabetes. Diabetes 46(Suppl 2):S125–S130. https://doi.org/10.2337/diab.46.2.S125
2. Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, Franz MJ, Hoogwerf BJ, Lichtenstein AH, Mayer-Davis E, Mooradian AD, Wheeler ML (2008) Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. Diabetes Care 31:S61–S78. https://doi.org/10.2337/dc08-S061
3. Mann J, Lean M, Toeller M (2000) Recommendations for the nutritional management of patients with diabetes mellitus. Eur J Clin Nutr 54:353–355
4. Catalan Association of Diabetes (2013) Documento de consenso sobre "Recomendaciones nutricionales y de educación alimentaria en la diabetes. ACD, Barcelona
5. American Diabetes Association (2017) Lifestyle management. Section 4. In Standards of Medical Care in Diabetes—2017. Diabetes Care 40:S33–S43. https://doi.org/10.2337/dc17-S007
6. Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Martínez-González MA (2013) Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 368:1279–1290. https://doi.org/10.1056/NEJMoa1200303
7. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A (2008) Adherence to Mediterranean diet and health status: meta-analysis. BMJ 337:a1344. https://doi.org/10.1136/bmj.a1344
8. Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Ruiz-Gutiérrez V, Covas MI, Fiol M, Gómez-Gracia E, López-Sabater MC, Vinyoles E, Arós F, Conde M, Lahoz C, Lapetra J, Sáez G, Ros E (2006) Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Ann Intern Med 145:1–11. https://doi.org/10.7326/0003-4819-145-1-200607040-00004
9. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, D'Armiento M, D'Andrea F, Giugliano D (2004) Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA 292:1440–1446. https://doi.org/10.1016/j.accreview.2004.11.073
10. Lairon D (2007) Intervention studies on Mediterranean diet and cardiovascular risk. Mol Nutr Food Res 51:1209–1214. https://doi.org/10.1002/mnfr.200700097
11. Ahola AJ, Mikkilä V, Mäkimattila S, Forsblom C, Freese R, Groop P-H, FinnDiane Study Group (2012) Energy and nutrient intakes and adherence to dietary guidelines among Finnish adults with type 1 diabetes. Ann Med 44:73–81. https://doi.org/10.3109/07853890.2010.530682
12. Soedamah-Muthu SS, Chaturvedi N, Fuller JH, Toeller M (2013) Do European people with type 1 diabetes consume a high atherogenic diet? 7-year follow-up of the EURODIAB Prospective Complications Study. Eur J Nutr 52:1701–1710. https://doi.org/10.1007/s00394-012-0473-7
13. The Diabetes and Nutrition Study Group of the Spanish Diabetes Association (2006) Diabetes Nutrition and Complications Trial: adherence to the ADA nutritional recommendations, targets of metabolic control, and onset of diabetes complications. A 7-year, prospective, population-based, observational multicenter study. J Diabetes Complicat 20:361–366. https://doi.org/10.1016/j.jdiacomp.2005.09.003
14. The Diabetes and Nutrition Study Group of the Spanish Association (2004) Diabetes Nutrition and Complications Trial. Trends in nutritional pattern between 1993 and 2000 and targets of diabetes treatment in a sample of Spanish people with diabetes. Diabetes Care 27:2000–2003
15. Mayer-Davis EJ, Nichols M, Liese AD, Bell RA, Dabelea DM, Johansen JM, Pihoker C, Rodriguez BL, Thomas J, Williams D (2006) Dietary intake among youth with diabetes: the SEARCH for diabetes in Youth Study. J Am Diet Assoc 106:689–697. https://doi.org/10.1016/j.jada.2006.02.002
16. Balk S, Schoenaker D, Mishra G, Toeller M, Chaturvedi N, Fuller J, Soedamah-Muthu S (2015) Association of diet and lifestyle with glycated haemoglobin in type 1 diabetes participants in the EURODIAB prospective complications study. Eur J Clin Nutr 70:229–236. https://doi.org/10.1038/ejcn.2015.110
17. Toeller M, Buyken a E, Heitkamp G, Cathelineau G, Ferriss B, Michel G (2001) Nutrient intakes as predictors of body weight in European people with type 1 diabetes. Int J Obes Relat Metab Disord 25:1815–1822. https://doi.org/10.1038/sj.ijo.0801816

18. Snell-Bergeon JK, Chartier-Logan C, Maahs DM, Ogden LG, Hokanson JE, Kinney GL, Eckel RH, Ehrlich J, Rewers M (2009) Adults with type 1 diabetes eat a high-fat atherogenic diet that is associated with coronary artery calcium. Diabetologia 52:801–809. https://doi.org/10.1007/s00125-009-1280-4
19. Jaacks LM, Du S, Mendez MA, Crandell J, Liu W, Ji L, Rosamond W, Popkin BM, Mayer-Davis EJ (2015) Comparison of the dietary intakes of individuals with and without type 1 diabetes in China. Asia Pac J Clin Nutr 24:639–649. https://doi.org/10.6133/apjcn.2015.24.4.03
20. Tahbaz F, Kreis I, Calvert D (2006) An audit of diabetes control, dietary management and quality of life in adults with type 1 diabetes mellitus, and a comparison with nondiabetic subjects. J Hum Nutr Diet 19:3–11. https://doi.org/10.1111/j.1365-277X.2006.00668.x
21. Gingras V, Leroux C, Desjardins K, Savard V, Lemieux S, Rabasa-Lhoret R, Strychar I (2015) Association between cardiometabolic profile and dietary characteristics among adults with type 1 diabetes mellitus. J Acad Nutr Diet 115:1965–1974. https://doi.org/10.1016/j.jand.2015.04.012
22. Leroux C, Gingras V, Desjardins K, Brazeau AS, Ott-Braschi S, Strychar I, Rabasa-Lhoret R (2015) In adult patients with type 1 diabetes healthy lifestyle associates with a better cardiometabolic profile. Nutr Metab Cardiovasc Dis 25:444–451. https://doi.org/10.1016/j.numecd.2015.01.004
23. Maffeis C, Morandi A, Ventura E, Sabbion A, Contreas G, Tomasselli F, Tommasi M, Fasan I, Costantini S, Pinelli L (2012) Diet, physical, and biochemical characteristics of children and adolescents with type 1 diabetes: relationship between dietary fat and glucose control. Pediatr Diabetes 13:137–146. https://doi.org/10.1111/j.1399-5448.2011.00781.x
24. Lodefalk M, Aman J (2006) Food habits, energy and nutrient intake in adolescents with type 1 diabetes mellitus. Diabet Med 23:1225–1232. https://doi.org/10.1111/j.1464-5491.2006.01971.x
25. Vilanova MB, Falguera M, Marsal JR, Rubinat E, Alcubierre N, Catelblanco E, Granado-Casas M, Miró N, Molló À, Mata-Cases M, Franch-Nadal J, Mauricio D (2017) Prevalence, clinical features and risk assessment of pre-diabetes in Spain: the prospective Mollerussa cohort study. BMJ Open 7:e015158. https://doi.org/10.1136/bmjopen-2016-015158
26. Bernstein MS, Morabia A, Sloutskis D (1999) Definition and prevalence of sedentarism in an urban population. Am J Public Health 89:862–867. https://doi.org/10.2105/AJPH.89.6.862
27. Cabrera de León A, Rodríguez-Pérez MDC, Rodríguez-Benjumeda LM, Anía-Lafuente B, Brito-Díaz B, Muros de Fuentes M, Almeida-González D, Batista-Medina M, Aguirre-Jaime A (2007) Sedentary lifestyle: physical activity duration versus percentage of energy expenditure. Rev Esp Cardiol 60:244–250. https://doi.org/10.1016/S1885-5857(07)60148-0
28. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE (1985) Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 122:51–65. https://doi.org/10.1093/acprof
29. Vioque J, Navarrete-Muñoz E-M, Gimenez-Monzó D, García-de-la-Hera M, Granado F, Young IS, Ramón R, Ballester F, Murcia M, Rebagliato M, Iñiguez C (2013) Reproducibility and validity of a food frequency questionnaire among pregnant women in a Mediterranean area. Nutr J 12:26. https://doi.org/10.1186/1475-2891-12-26
30. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D (2003) Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med 348:2599. https://doi.org/10.1056/NEJMoa1005372
31. Fung TT, McCullough ML, Newby PK, Manson JE, Meigs JB, Rifai N, Willett WC, Hu FB (2005) Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr 82:163–173
32. Zamora-Ros R, Knaze V, Luján-Barroso L, Romieu I, Scalbert A, Slimani N, Hjartåker A, Engeset D, Skeie G, Overvad K, Bredsdorff L, Tjønneland A, Halkjær J, Key TJ, Khaw K-T, Mulligan AA, Winkvist A, …González CA (2013) Differences in dietary intakes, food sources and determinants of total flavonoids between Mediterranean and non-Mediterranean countries participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Br J Nutr 109:1498–1507. https://doi.org/10.1017/S0007114512003273
33. Bondia-Pons I, Serra-Majem L, Castellote AI, Lopez-Sabater MC (2007) Identification of foods contributing to the dietary lipid profile of a Mediterranean population. Br J Nutr 98:583–592. https://doi.org/10.1017/S0007114507727435

5.2. Artículo 2

Minerva Granado-Casas, Anna Ramírez-Morros, Mariona Martín, Jordi Real, Núria Alonso, Xavier Valldeperas, Alicia Traveset, Esther Rubinat, Nuria Alcubierre, Marta Hernández, Manel Puig-Domingo, Albert Lecube, Esmeralda Castelblanco, Dídac Mauricio. Type 1 diabetic subjects with diabetic retinopathy show an unfavorable pattern of fat intake. Nutrients. 2018; 10:1184

Resumen

Objetivos

Nuestro grupo de investigación publicó un estudio previo en el que observamos que una ingesta elevada de MUFA y ácido oleico estaba relacionada con una menor frecuencia de RD en pacientes con DM2. Por ello, decidimos realizar el presente estudio cuyo objetivo principal fue evaluar las diferencias en la ingesta de alimentos y nutrientes en los pacientes adultos con DM1 con presencia de RD y sin ésta.

Materiales y métodos

El diseño del estudio observacional fue transversal y multicéntrico, llevado a cabo en el Hospital Universitari Arnau de Vilanova de Lleida y el Hospital Universitari Germans Trias i Pujol de Badalona. Los participantes fueron pacientes con DM1 diagnosticados de RD y pacientes con DM1 sin RD. De los 259 pacientes con DM1 reclutados en un estudio previo, seleccionamos una muestra de 103 pacientes con RD y 140 pacientes sin RD, sin presencia de otras complicaciones tardías de la diabetes ni condiciones que requiriesen una terapia médico-nutricional específica. Se administró el cuestionario de frecuencia de consumo alimentario validado para población española mediante entrevista personal. El consumo de nutrientes se calculó mediante tablas de composición de alimentos del Departamento de Agricultura de Estados Unidos y otras fuentes españolas e inglesas. Las variables clínicas fueron recogidas mediante una revisión exhaustiva de las historias clínicas, una anamnesis y una exploración física de cada paciente. Se recogieron muestras de sangre y orina para determinar los parámetros bioquímicos. La RD se evaluó mediante exploración física por parte del Servicio de Oftalmología de ambos centros. El análisis de datos se realizó mediante modelos bivariables y multivariables.

Resultados

Los pacientes con RD mostraron una menor ingesta de grasas totales en comparación con el grupo sin RD. No se observaron diferencias estadísticamente significativas en el consumo de otros nutrientes y fuentes alimentarias entre ambos grupos; sin embargo, se encontró una tendencia entre

una ingesta elevada de pan y una menor ingesta de grasas vegetales en el grupo de pacientes con RD. La RD se asoció a mayor edad, presencia de hipertensión y mayor duración de la diabetes; sin embargo, se observó una asociación negativa con un mayor nivel educativo. El análisis multivariable ajustado por las variables confusoras (edad, sexo, nivel educativo, tabaquismo, centro, actividad física, IMC, hipertensión, dislipemia, duración de la diabetes y HbA1c) mostró que la ingesta de carbohidratos complejos estaba positivamente relacionada con la presencia de RD. Por otra parte, la ingesta de grasas totales, MUFA, ácido oleico y vitamina E estuvieron relacionadas con la ausencia de RD en este grupo de pacientes.

Conclusiones

La ingesta de grasas totales, MUFA, ácido oleico y vitamina E se relacionó con una menor presencia de RD en pacientes adultos con DM1. Por tanto, estos resultados sugieren que la ingesta de estos nutrientes podría tener un potente efecto protector en relación con el desarrollo de la RD.

nutrients

MDPI

Article

Type 1 Diabetic Subjects with Diabetic Retinopathy Show an Unfavorable Pattern of Fat Intake

Minerva Granado-Casas [1,2], Anna Ramírez-Morros [1], Mariona Martín [3], Jordi Real [4,5,6], Núria Alonso [1,2,6], Xavier Valldeperas [7], Alicia Traveset [2,8], Esther Rubinat [6,9], Nuria Alcubierre [2], Marta Hernández [2,10], Manel Puig-Domingo [1,6], Albert Lecube [2,10], Esmeralda Castelblanco [1,6,*] and Didac Mauricio [2,6,11,*]

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Abstract: Medical nutrition therapy is an important part of the management of type 1 diabetes mellitus (T1DM). Proper adherence to a healthy diet may have a favorable impact on diabetes management and its diabetic complications. Our aim was to assess differences in food and nutrient intake of type 1 diabetic patients with and without diabetic retinopathy (DR). This was a two-center, cross-sectional study in patients with T1DM, with and without DR. Subjects were recruited from the outpatient clinic of the two participating centers. A validated food frequency questionnaire was administered. A total of 103 T1DM patients with DR and 140 T1DM patient without DR were recruited. Subjects with DR showed a lower intake of total fat ($p = 0.036$) than that of their non-DR counterparts. DR was associated with increasing age ($p = 0.004$), hypertension ($p < 0.001$), and diabetes duration ($p < 0.001$), however there was a negative association with high educational level ($p = 0.018$). The multivariate-adjusted analysis showed that the intake of complex carbohydrates was positively related to the presence of DR ($p = 0.031$). In contrast, the intakes of total fat ($p = 0.009$), monounsaturated fatty acids (MUFAs) ($p = 0.012$), oleic acid ($p = 0.012$), and vitamin E ($p = 0.006$) were associated with the absence of DR. As conclusions, the intake of total MUFAs, oleic acid, and vitamin E is associated with a lower frequency of DR in patients with T1DM. These results suggest a potential protective effect of these lipid components for DR.

Keywords: type 1 diabetes; diabetic retinopathy; dietary pattern; oleic acid; fatty acids; carbohydrates

1. Introduction

Diabetic retinopathy (DR) is an important cause of visual impairment in patients with type 1 diabetes mellitus (T1DM) [1]. According to a previous study in a cohort of patients with T1DM, the 10-year incidence of DR was 35.9% [2]. The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) establish that medical nutrition therapy (MNT) plays an important role in preventing complications related to the management and metabolic control of the disease [3]. These nutritional recommendations are based on the Mediterranean Diet, which has benefits to prevent cardiovascular diseases in the diabetic population. Additionally, a positive relationship between severity of DR and modifiable risk factors such as hypertension, dyslipidemia, and smoking has been described in T1DM [1].

Currently, a controversy exists with the few published studies, regarding the relationship between the dietary intake and the presence of DR in patients with diabetes, describing controversial results between them [4,5]. The relationship between dietary intake and DR development in patients with T1DM has only been described in few studies [6–12]; specifically, there are only seven studies that have assessed the relationship between dietary intake and the prevalence of DR in patients with T1DM [6–12]. Of these, four studies related alcohol consumption and/or salt intake with the frequency of DR in a cross-sectional study design [9–12]. Results of the Diabetes Control and Complications Trial (DCCT) study cohort pointed to higher risk of DR progression in those subjects with higher intake of fatty acids, and a lower-risk association among those with higher dietary fiber intake [6]; however, another study did not find any differences [7]. A study with a cross-sectional design and a sample of 379 patients with diabetes mellitus (of whom only 52 had T1DM) observed a protective effect of MUFA and polyunsaturated fatty acid (PUFA) intake for DR in well-controlled patients [8]. The EURODIAB Study only examined the relationship between alcohol consumption and salt intake with the risk of DR in T1DM patients [9,10]. They found a lower risk of DR with a moderate alcohol consumption [9]; nevertheless, no association was observed with an increased salt intake with DR in this diabetic population [10]. On the other hand, the FinnDiane Study [11] and Moss et al. [12] found an inverse association between alcohol consumption and the presence of DR in these patients. According to two recently published systematic reviews about the relationship between dietary intake and DR, no study has assessed the relationship between the whole food and nutrient intake and DR in patients with T1DM [4,5].

In our region, apart from receiving specific education on carbohydrate counting learning, medical nutritional therapy for diabetic subjects includes recommendations to adopt a Mediterranean Diet pattern [13,14]. To our knowledge, there are no studies designed to compare the relationship between the food and nutrient intake in T1DM patients with the presence or absence of DR. In addition, our group described a positive association between the higher intake of MUFAs and oleic acid and a lower frequency of DR in patients with T2DM [15]. For this reason, we hypothesized that patients with T1DM and DR have a lower adherence to the nutritional recommendations than that of their counterparts without DR. Therefore, the aim of the current study was to assess differences in the food and nutrient intake of patients with T1DM, with and without DR.

2. Materials and Methods

This was a cross-sectional, two-center study. The participants were regularly cared for at their reference hospital (University Hospital Arnau de Vilanova and University Hospital Germans Trias i Pujol, both in Northeastern Spain). The study participants were recruited from the health care districts of Lleida (Center 1) and Badalona (Center 2). Lleida is a rural and semi-urban region, while Badalona is an urban location in the metropolitan area of Barcelona. This was a post hoc analysis from a previously

published study [14]; from a sample of 259 patients with T1DM, 16 patients were excluded because they did not have a full assessment of DR status. A final sample of 103 T1DM patients with DR and 140 T1DM without DR was included. More details of the original study are available in [14]. The recruitment was performed between January 2013 and May 2015. As inclusion criteria, we used the following: T1DM with a duration of at least one year and age over 18 years. The exclusion criteria were as follows: patients who were healthcare professionals; patients who showed physical or cognitive deterioration (e.g., dementia, mental diseases); history of clinical cardiovascular disease or diabetic foot disease, pregnancy, renal insufficiency (estimated glomerular filtration rate <60 mL/min); and patients with a condition that required additional MNT measures (i.e., macroalbuminuria defined as urine albumin/creatinine ratio >299 mg/g).

The ethics committees of the two participating centers approved the study, and written informed consent forms were obtained from all participants (PI-13-095 and PI-15-147).

2.1. Clinical Variables

Clinical variables were collected through detailed anamnesis, physical exam, and careful review of the clinical records. Hypertension and dyslipidemia were defined by the use of any specific medication for the given conditions. Blood and urine chemistry variables were determined by standardized methods. Physical activity was assessed by the validated method of Bernstein et al. [16] and Cabrera de León et al. [17]. A subject was classified as having regular physical activity if she/he performed more than 25 min/day of any type of physical activity that requires 4 METS (the metabolic equivalent) minimum. Participants were classified as sedentary if they did less than 25 min/day of any physical activity.

2.2. Dietary and Nutritional Assessment

A food frequency questionnaire (FFQ) was administered to all participants of the study during personal interviews by specialized and trained researchers. This was a semi-quantitative questionnaire, validated and adapted for the Spanish population, based on the Nurses' Health Study (available at: http://epinut.edu.umh.es/wp-content/uploads/sites/1365/2011/07/CFA101.pdf) [18,19]. The questionnaire contained 101 items, in which it asked for their usual consumption since the previous year's visit. Serving sizes were detailed for each food item in the FFQ. The questionnaire had nine possible answers, ranging from "never or less than once per month" to "six or more per day". Nutrient values were primarily obtained from the food composition tables of the US Department of Agriculture and other published sources for Spanish and English foods and portion sizes [20–22]. We used the Spanish food composition tables to avoid an overestimation of nutrient intake from the fortified dairy products of the US.

2.3. Assessment of Diabetic Retinopathy

Retinopathy was assessed and classified by an ophthalmologist according to the international clinical classification system [23]. The ophthalmologist performed a complete eye evaluation and defined DR in five stages: (1) no apparent retinopathy, (2) mild non-proliferative retinopathy, (3) moderate non-proliferative retinopathy, (4) severe non-proliferative retinopathy, and (5) proliferative diabetic retinopathy.

2.4. Statistical Analysis

Descriptive comparison between groups of all variables was performed to evaluate the differences. Statistical significance was assessed by the chi-square test, where the frequencies of comorbidities and demographic variables were compared among groups. The mean differences between groups were compared by Student's *t*-test. Methods of Benjamini, Hochberg, and Yekutieli were performed to control the false discovery rate and expected proportion of false discoveries among the rejected hypotheses. Conditional logistic regression models were developed to analyze the relationship

between the presence of diabetic retinopathy (DR), its clinical characteristics, and daily nutrient intake. Crude and adjusted odds ratios (ORs) were estimated by univariable and multivariable conditional logistic regression models, respectively. Adjusted odds ratios were fitted by age, sex, educational level, smoking, center, physical activity, body mass index, dyslipidemia, hypertension, and diabetes duration. In all models, the goodness-of-fit assumption was tested by the Hosmer–Lemeshow test. Estimates of odds ratios were reported with corresponding 95% confidence intervals and statistical significance was established as a p-value < 0.05. Data management and analyses were performed with the free software environment R version 3.3.2 and SPSS software (version 20, SPSS, Chicago, IL, USA).

3. Results

Clinical characteristics of the participants are shown in Table 1. Patients with DR demonstrated the following: were older ($p = 0.010$), had higher systolic blood pressure ($p = 0.005$) and frequency of hypertension ($p < 0.001$), had longer duration of diabetes ($p < 0.001$) and showed worse glycemic control ($p < 0.001$) and lipid profile, and had lower HDL ($p = 0.045$) and higher triglycerides ($p = 0.045$).

Table 1. Clinical characteristics of participants according to diabetic retinopathy status.

Characteristics	DR (n = 103)	No DR (n = 140)	p [1]
Age (years)	46.2 ± 10.8	42.1 ± 10.3	0.010
Sex (male)	48 (46.6)	62 (44.3)	0.867
Educational level			0.107
Not even primary	4 (4.1)	8 (5.9)	
Completed primary	36 (36.0)	34 (25.2)	
Secondary high school	39 (40.2)	49 (36.3)	
Graduate or higher	18 (18.6)	44 (32.6)	
Smoking			0.602
No	48 (46.6)	73 (52.1)	
Yes	32 (31.1)	34 (24.3)	
Former smoker	23 (22.3)	33 (23.6)	
Regular physical activity	77 (74.8)	98 (70.0)	0.602
Waist circumference (cm)	90.7 ± 13.4	87.0 ± 12.1	0.075
Systolic blood pressure (mmHg)	131.0 ± 18.4	123.2 ± 16.1	0.005
Diastolic blood pressure (mmHg)	73.8 ± 9.3	74.2 ± 9.6	0.846
BMI (kg/m^2)	26.2 ± 4.3	25.3 ± 4.0	0.111
Hypertension	40 (38.8)	20 (14.3)	<0.001
Dyslipidemia	49 (47.6)	49 (35.0)	0.107
Diabetes duration (years)	26.5 ± 9.9	17.9 ± 9.1	<0.001
HbA1c (%)	7.9 ± 1.1	7.4 ± 0.8	<0.001
HbA1c (mmol/mol)	63.0 ± 11.9	56.9 ± 8.3	<0.001
Total cholesterol (mg/dL)	179.0 ± 30.8	182.3 ± 27.1	0.602
HDL cholesterol (mg/dL)	61.9 ± 16.8	66.8 ± 14.9	0.045
LDL cholesterol (mg/dL)	102.7 ± 25.5	102.2 ± 22.7	0.993
TG (mg/dL)	81.4 ± 49.9	68.7 ± 26.7	0.045

Data are means ± SD or n (%). [1] p was calculated by method of Benjamini and Hochberg. DR, diabetic retinopathy; HbA1c, glycated hemoglobin; BMI, body mass index; HDL cholesterol, high density lipoprotein cholesterol; LDL cholesterol, low density lipoprotein cholesterol; TG, triglycerides.

Concerning daily nutrient intake, patients with DR had a lower fat intake than those without DR did ($p = 0.036$) (Table 2). Although not significantly different, the intake of MUFAs, oleic acid, and vitamin E was lower in patients with DR than in those without ($p = 0.050$). In terms of daily food intake, no statistical differences were found between patients with and without DR (Table S1). However, a tendency to eat more bread ($p = 0.072$) and less vegetable fat ($p = 0.072$) was observed in patients with DR.

Table 2. Daily nutrient intake of participants according to diabetic retinopathy status.

Daily Nutrient Intake [1]	DR (n = 103)	No DR (n = 140)	p [2]
Energy intake (kcal)	2047.0 ± 556.0	2077.7 ± 482.3	0.796
Carbohydrate (g)	198.0 ± 36.3	186.6 ± 31.2	0.075
Complex carbohydrate (g)	91.6 ± 18.6	85.8 ± 18.1	0.096
Sugar (g)	82.0 ± 24.3	78.9 ± 23.1	0.604
Fiber (g)	23.4 ± 5.8	22.4 ± 6.2	0.545
Soluble fiber (g)	3.6 ± 1.3	3.5 ± 1.2	0.604
Insoluble fiber (g)	13.6 ± 4.4	12.9 ± 4.1	0.545
Glycemic index (%)	87.0 ± 18.1	81.1 ± 15.8	0.075
Protein (g)	98.7 ± 16.0	97.0 ± 14.0	0.604
Total fat (g)	98.9 ± 16.3	105.8 ± 13.9	0.036
SFAs (g)	25.4 ± 5.1	26.8 ± 4.4	0.193
MUFAs (g)	50.2 ± 11.2	54.3 ± 9.9	0.050
PUFAs (g)	16.5 ± 4.1	17.8 ± 5.7	0.193
Omega 3 (g)	1.6 ± 0.4	1.7 ± 0.4	0.263
Omega 6 (g)	14.8 ± 4.1	16.0 ± 5.8	0.214
Trans fat (g)	1.0 ± 0.5	1.0 ± 0.5	0.864
Cholesterol (mg)	290.0 ± 75.4	287.7 ± 66.6	0.834
Palmitic acid (g)	15.7 ± 2.7	16.5 ± 2.2	0.090
Stearic acid (g)	5.9 ± 1.2	6.1 ± 1.1	0.545
Oleic acid (g)	47.7 ± 11.0	51.7 ± 9.7	0.050
Linoleic acid (g)	14.7 ± 4.1	15.9 ± 5.8	0.214
α-Linolenic acid (g)	1.1 ± 0.2	1.2 ± 0.2	0.214
Arachidonic acid (g)	0.2 ± 0.1	0.2 ± 0.0	0.604
EPA (g)	0.2 ± 0.1	0.2 ± 0.1	0.604
DHA (g)	0.3 ± 0.2	0.3 ± 0.2	0.604
Alcohol (g)	6.5 ± 11.6	5.6 ± 9.2	0.686
Caffeine (g)	244.0 ± 196.0	275.4 ± 233.9	0.601
Water (g)	2962.0 ± 720.0	2883.5 ± 676.8	0.604
Vitamin A (μg)	1283.0 ± 671.0	1212.1 ± 705.7	0.604
Retinol (μg)	355.0 ± 464.0	346.9 ± 374.3	0.887
Carotene (μg)	900.0 ± 436.0	841.6 ± 547.1	0.604
α Carotene (μg)	703.0 ± 535.0	610.2 ± 581.2	0.545
β Carotene (μg)	4868.0 ± 2 324.0	4578.6 ± 2 957.4	0.604
B Cryptoxanthin (μg)	332.0 ± 222.0	302.0 ± 190.4	0.602
Lutein+zeoxanthin (μg)	4147.0 ± 2 479.0	3951.2 ± 360.3	0.796
Lycopene (μg)	4457.0 ± 2 096.0	4292.6 ± 2 065.8	0.658
Folate (μg)	292.0 ± 73.0	283.7 ± 81.7	0.604
Vitamin B_{12} (mg)	8.3 ± 3.8	8.5 ± 3.5	0.796
Vitamin B_6 (mg)	1.9 ± 0.5	1.9 ± 0.5	0.802
Vitamin C (mg)	116.0 ± 62.4	112.3 ± 55.6	0.796
Vitamin D (mg)	4.3 ± 1.7	4.4 ± 1.6	0.828
Vitamin E (mg)	13.9 ± 2.9	15.2 ± 3.6	0.050
Thiamine (mg)	1.6 ± 0.2	1.5 ± 0.3	0.075
Riboflavin (mg)	2.3 ± 0.5	2.2 ± 0.5	0.796
Niacin (mg)	27.9 ± 6.0	27.8 ± 6.3	0.860
Niacin equivalents (mg)	44.0 ± 8.0	43.6 ± 7.8	0.796
Calcium (mg)	1115.0 ± 329.0	1108.2 ± 317.7	0.887
Iron (mg)	13.1 ± 2.2	13.0 ± 2.8	0.796
Sodium (mg)	3381.0 ± 520.0	3449.8 ± 579.7	0.604
Potassium (mg)	3491.0 ± 695.0	3332.5 ± 652.4	0.262
Magnesium (mg)	415.0 ± 77.4	405.4 ± 84.4	0.604
Zinc (mg)	11.7 ± 1.7	11.4 ± 1.5	0.561
Selenium (μg)	145.0 ± 26.6	142.1 ± 24.0	0.604

[1] Adjusted by energy intake. Data are means ± SD. [2] p was calculated by method of Benjamini and Hochberg. DR, diabetic retinopathy; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

In the bivariate analysis, including the clinical characteristics (Table 3), higher educational level was associated with the absence of DR (OR: 0.47; 95% CI: 0.25–0.88; $p = 0.018$). In contrast, DR was associated with increasing age (OR: 1.04; 95% CI: 1.01–1.06; $p = 0.004$), hypertension (OR: 3.77; 95% CI: 2.05–7.13; $p < 0.001$), diabetes duration (OR: 1.10; 95% CI: 1.07–1.14; $p < 0.001$), and glycemic control (OR: 1.97, 95% CI: 1.44–2.69; $p = 0.001$).

Table 3. Bivariate analysis for the relationship between the presence of diabetic retinopathy and clinical characteristics.

Characteristics	DR (n = 103)	No DR (n = 140)	OR [95% CI] [1]	p
Sex (male)	48 (46.6)	62 (44.3)	1.10 [0.66;1.83]	0.722
Completed primary	36 (36.0)	34 (25.2)	1.75 [1.00; 3.09]	0.052
Secondary high school	39 (40.2)	49 (36.3)	1.17 [0.69; 1.99]	0.545
Graduate or higher	18 (18.6)	44 (32.6)	0.47 [0.25; 0.88]	0.018
Smoker, current	32 (31.1)	34 (24.3)	1.35 [0.76; 2.38]	0.241
Smoker, former	23 (22.3)	33 (23.6)	0.95 [0.52; 1.73]	0.820
Site Lleida	51 (49.5)	55 (39.3)	1.60 [0.96; 2.67]	0.113
Physical activity	77 (74.8)	98 (70.0)	1.27 [0.72; 2.27]	0.420
Age (years)	46.2 ± 10.8	42.1 ± 10.3	1.04 [1.01; 1.06]	0.004
BMI (kg/m^2)	26.2 ± 4.3	25.3 ± 4.0	1.06 [0.99; 1.13]	0.073
Dyslipidemia	49 (47.6)	49 (35.0)	1.68 [1.00; 2.84]	0.050
Hypertension	40 (38.8)	20 (14.3)	3.77 [2.05; 7.13]	<0.001
Diabetes duration (years)	26.5 ± 9.9	17.9 ± 9.1	1.10 [1.07; 1.14]	<0.001
HbA1c (%)	7.9 ± 1.1	7.4 ± 0.8	1.97 [1.44; 2.69]	0.001

Data are mean ± SD or n (%). [1] Odds ratio and 95% confidence interval of diabetic retinopathy by clinical characteristics. DR, diabetic retinopathy; BMI, body mass index; HbA1c, glycated hemoglobin.

In the crude multivariate analysis for nutrient intake, a high intake of complex carbohydrates ($p = 0.031$) was associated with the presence of DR (Table 4). On the other hand, the absence of retinopathy was associated with a higher intake of total fat ($p = 0.009$), MUFAs ($p = 0.012$), oleic acid ($p = 0.012$), and vitamin E ($p = 0.006$). In the multivariate adjusted model, only the intake of complex carbohydrates ($p = 0.031$) remained associated with the presence of DR, whereas the intake of total fat ($p = 0.009$), MUFAs ($p = 0.012$), oleic acid ($p = 0.012$), and vitamin E ($p = 0.006$) were still associated with the absence of DR.

Table 4. Crude and adjusted multivariate analysis for the presence of diabetic retinopathy and daily nutrient intake.

Nutrients	DR (n = 103)	No DR (n = 140)	Crude OR [95% CI]	Crude p	Adjusted OR [95% CI] [1]	Adjusted p [1]
Carbohydrate (g)	198.0 ± 36.3	186.6 ± 31.2	1.01 [1.00; 1.02]	0.127	1.01 [0.99; 1.01]	0.127
Complex carbohydrate (g)	91.6 ± 18.6	85.8 ± 18.1	1.02 [1.00; 1.04]	0.031	1.02 [1.00; 1.04]	0.031
Glycemic index (%)	87.0 ± 18.1	81.1 ± 15.8	1.02 [1.00; 1.04]	0.087	1.02 [0.99; 1.04]	0.087
Total fat (g)	98.9 ± 16.3	105.8 ± 13.9	0.97 [0.94; 0.99]	0.009	0.96 [0.94; 0.98]	0.009
SFAs (g)	25.4 ± 5.1	26.8 ± 4.4	0.96 [0.90; 1.03]	0.290	0.97 [0.91; 1.03]	0.290
MUFAs (g)	50.2 ± 11.2	54.3 ± 9.9	0.96 [0.92; 0.99]	0.012	0.95 [0.92; 0.99]	0.012
Palmitic acid (g)	15.7 ± 2.7	16.5 ± 2.2	0.90 [0.78; 1.03]	0.126	0.89 [0.78; 1.02]	0.126
Oleic acid (g)	47.7 ± 11.0	51.7 ± 9.7	0.96 [0.92; 0.99]	0.012	0.95 [0.92; 0.99]	0.012
α-Linolenic acid (g)	1.1 ± 0.2	1.2 ± 0.2	0.16 [0.02; 1.23]	0.077	0.16 [0.02; 1.23]	0.077
Vitamin E (mg)	13.9 ± 2.9	15.2 ± 3.6	0.86 [0.77; 0.96]	0.006	0.85 [0.77; 0.95]	0.006
Thiamine (mg)	1.6 ± 0.2	1.5 ± 0.3	3.70 [0.86; 15.84]	0.078	3.70 [0.86; 15.84]	0.078

Crude and adjusted odds ratios and corresponding 95% confidence interval of diabetic retinopathy. Data are mean ± SD. [1] Adjusted by age, sex, educational level, smoking, center, physical activity, body mass index, dyslipidemia, hypertension, diabetes duration, and glycated hemoglobin. DR, diabetic retinopathy; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids.

4. Discussion

Our results suggest that the intake of total fat, MUFAs, oleic acid, and vitamin E is associated with the absence of DR in subjects with T1DM. In contrast, the intake of complex carbohydrates is related to the presence of DR. To our knowledge, this is the first study that has so far assessed the overall food and nutrient intake in patients with T1DM with DR.

In terms of total fat and MUFA intake, the present results are discordant with the results of a sub-study of the DCCT trial, which found an association between the increased intake of fat, SFAs and MUFAs and the presence of DR [6]; however, these researchers did not adjust for potential confounders [5], i.e., age, sex, smoking, diabetes duration, glycated hemoglobin (HbA1c), body mass index (BMI), and the presence of hypertension or dyslipidemia. In addition, Roy et al. [7] did not find any association between the intake of fatty acids and the risk of 6-year progression of DR in a large cohort of T1DM subjects who consumed a high amount of SFAs, PUFAs, and dietary cholesterol. This result was in line with the results of a cross-sectional study, including well-controlled patients with T1DM and T2DM [8]. On the other hand, a protective association with higher intake of MUFAs and oleic acid was observed in a previous study in patients with T2DM performed by our group, a finding that was similar with the current results [15]. The PREDIMED trial showed that a Mediterranean diet supplemented with extra virgin olive oil (a MUFA-rich diet) and a PUFA-rich diet were related with a lower incidence of DR at follow-up in patients with T2DM [24,25]. Moreover, a cross-sectional study observed that the intake of PUFAs was a protective factor of DR in well-controlled diabetic patients [8]. However, the DCCT study found that an intake of PUFAs was related with a high risk of DR [6]; no such association was shown in another prospective study in patients with T1DM [7], a finding that is similar to our results. These two prospective studies are contrary with our results. Two meta-analyses of randomized clinical trials showed that a high-MUFA diet improves glycated hemoglobin and fasting blood glucose in patients with diabetes when compared with that of a low-MUFA diet or high-carbohydrate diet [26,27]; furthermore, MUFAs have potential benefits in the lipid profile, i.e., increasing high-density lipoprotein (HDL) serum levels in diabetic patients [27]. This result has great importance because a MUFA-rich diet may have the potential to prevent diabetic complications long-term. A recent review on the role of omega-3 in the development of DR described that α-linolenic acid improves the progression of DR by means of various antioxidant and anti-inflammatory mechanisms in animal and human studies [28].

Interestingly, our results showed that a higher intake of carbohydrates was positively related with the presence of DR in patients with T1DM. This finding is in contrast with those of the DCCT study, which found a lower presence of DR with a high intake of carbohydrates and dietary fiber in adolescents and young adult patients with T1DM [6]. However, the other few studies that have assessed the possible association between dietary carbohydrates and DR did not find such association [7,8,15,29]. In line with our results, the EURODIAB study described that a rich-carbohydrate diet derived from complex carbohydrates (not dietary fiber) produces negative effects in glycemic control and consequently a high risk of diabetic complications [30].

Our findings indicate that a higher intake of vitamin E is associated with a lower presence of DR; this result is due to a high intake of vegetable fats. Although a risk association between the intake of vitamin E and DR was found in a cross-sectional study including a large sample of patients with T2DM [31], some prospective and other cross-sectional studies did not confirm this association [8,32,33]. This finding should be further investigated due to controversy in the scientific studies.

In terms of alcohol consumption, we did not find any difference between the two groups; however, two cross-sectional studies performed in patients with T1DM found a positive relationship between alcohol consumption and the presence of DR [9,11]; and another cross-sectional study showed that an increased alcohol consumption was related to a lower prevalence of DR in younger-onset diabetes [12]. Therefore, we must gain more insight into this potential dietary contributing factor.

Moreover, the current study showed that a higher educational level was related with a lower presence of DR; this result is similar to the those of the EPIC study, which associated a high educational level with better dietary habits in Mediterranean countries [34]. This result points to the possible link between a healthier dietary intake and a lower prevalence of DR in diabetic subjects.

This study has some limitations. First, the association of causality between the intake of nutrients and the presence of DR cannot be established because of the cross-sectional study design. For this reason, no specific nutritional recommendations to the patients can be derived from our results.

Furthermore, the changes in dietary habits over time cannot be determined with this study. Another limitation of our study is that we did not assess the specific knowledge of each study participant on the dietary management of diabetes and its relationship with the individual food intake. Therefore, we could not evaluate whether patients with DR had a less favorable dietary fat intake as a result of poorer adherence and/or lower knowledge of dietary measures. Moreover, this is a sub-study of a previous study designed to assess differences in the Mediterranean diet between patients with T1DM and the non-diabetic population [14]. However, this study has several strengths. This is the first study that assessed the relationship between the overall dietary intake and the prevalence of DR in patients diagnosed with T1DM. Additionally, we included a large number of participants in this multicenter study with a very well-defined sample that allowed us to establish the variability of different populations and regions. The use of the FFQ allowed us to define the proper estimation of nutrients and food intake of patients. Patients with T1DM receive nutritional education for the management of the disease over the time. In our region, the MNT is based on the nutritional recommendations of the Mediterranean diet. Therefore, we can assume that the patients had maintained the dietary habits over a long period of time; among other factors, a higher adherence to a healthy dietary pattern may help to prevent diabetes-related complications. In addition, this FFQ has been shown to be representative of the previous five-year period of the subject's food intake [35]. However, the cross-sectional design does not allow us to draw a final conclusion. Finally, we can consider that the present results could be potentially important for future research because there has been no other study that specifically assesses food and nutrient intake with the prevalence of DR in patients with T1DM.

5. Conclusions

In conclusion, a lower intake of total fat, MUFAs, oleic acid, and vitamin E was shown to be associated with the presence of DR. However, a lower intake of complex carbohydrates was associated with DR absence. Further research is necessary to establish associations and causality between dietary patterns and the presence of DR in this population.

Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6643/10/9/1184/s1, Table S1: Daily food intake of participants according to diabetic retinopathy status.

Author Contributions: The authors' contributions were as follows: M.G.-C. and D.M. designed the research. M.G.-C., A.R.-M., M.M., N.A., X.V., A.T., E.R., N.A., and M.H. conducted the study and collected the data. M.G-C., J.R., and D.M. analyzed and interpreted the data. M.P-D., A.L., E.C., and D.M. coordinated the study. M.G.-C., J.R., and D.M wrote the paper. D.M. was the principal investigator and had the primary responsibility for the final content. All the authors read and approved the final manuscript.

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References

1. Klein, R.; Lee, K.E.; Gangnon, R.E.; Klein, B.E.K. The 25-Year Incidence of Visual Impairment in Type 1 Diabetes Mellitus. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Ophthalmology* **2010**, *117*, 63–70. [CrossRef] [PubMed]
2. Romero-Aroca, P.; Baget-Bernaldiz, M.; Fernandez-Ballart, J.; Plana-Gil, N.; Soler-Lluis, N.; Mendez-Marin, I.; Bautista-Perez, A. Ten-year incidence of diabetic retinopathy and macular edema. Risk factors in a sample of people with type 1 diabetes. *Diabetes Res. Clin. Pract.* **2011**, *94*, 126–132. [CrossRef] [PubMed]

3. American Diabetes Association. Lifestyle management. Sec. 4. In Standards of Medical Care in Diabetes-2017. *Diabetes Care* **2017**, *40*, S33–S43. [CrossRef]
4. Dow, C.; Mancini, F.; Rajaobelina, K.; Boutron-Ruault, M.-C.; Balkau, B.; Bonnet, F.; Fagherazzi, G. Diet and risk of diabetic retinopathy: A systematic review. *Eur. J. Epidemiol.* **2017**. [CrossRef] [PubMed]
5. Wong, M.Y.Z.; Man, R.E.K.; Fenwick, E.K.; Gupta, P.; Li, L.-J.; van Dam, R.M.; Chong, M.F.; Lamoureux, E.L. Dietary intake and diabetic retinopathy: A systematic review. *PLoS ONE* **2018**, *13*, e0186582. [CrossRef] [PubMed]
6. Cundiff, D.K.; Nigg, C.R. Diet and diabetic retinopathy: Insights from the Diabetes Control and Complications Trial (DCCT). *Med. Gen. Med.* **2005**, *7*, 3.
7. Roy, M.S.; Janal, M.N. High caloric and sodium intakes as risk factors for progression of retinopathy in type 1 diabetes mellitus. *Arch. Ophthalmol.* **2010**, *128*, 33–39. [CrossRef] [PubMed]
8. Sasaki, M.; Kawasaki, R.; Rogers, S.; Man, R.E.K.; Itakura, K.; Xie, J.; Flood, V.; Tsubota, K.; Lamoureux, E.; Wang, J.J. The associations of dietary intake of polyunsaturated fatty acids with diabetic retinopathy in well-controlled diabetes. *Investig. Ophthalmol. Vis. Sci.* **2015**, *56*, 7473–7479. [CrossRef] [PubMed]
9. Beulens, J.; Kruidhof, J.; Grobbee, D. Alcohol consumption and risk of microvascular complications in type 1 diabetes patients: The EURODIAB Prospective Complications Study. *Diabetologia* **2008**, *51*, 1631–1638. [CrossRef] [PubMed]
10. Engelen, L.; Soedamah-Muthu, S.S.; Geleijnse, J.M.; Toeller, M.; Chaturvedi, N.; Fuller, J.H.; Schalkwijk, C.G.; Stehouwer, C.D.A. Higher dietary salt intake is associated with microalbuminuria, but not with retinopathy in individuals with type 1 diabetes: The EURODIAB Prospective Complications Study. *Diabetologia* **2014**, *57*, 2315–2323. [CrossRef] [PubMed]
11. Harjutsalo, V.; Feodoroff, M.; Forsblom, C.; Groop, P.H. Patients with Type 1 diabetes consuming alcoholic spirits have an increased risk of microvascular complications. *Diabet. Med.* **2014**, *31*, 156–164. [CrossRef] [PubMed]
12. Moss, S.E.; Klein, R.; Klein, B.E. Alcohol consumption and the prevalence of diabetic retinopathy. *Ophthalmology* **1992**, *99*, 926–932. [CrossRef]
13. *Recomendaciones Nutricionales y de Educación Alimentaria en la Diabetes*; ACD: Barcelona, Spain, 2013; Available online: http://www.acdiabetis.org/d_avui/docs/Document_de_consens_pdf (accessed on 8 July 2018).
14. Granado-Casas, M.; Alcubierre, N.; Martín, M.; Real, J.; Ramírez-Morros, A.M.; Cuadrado, M.; Alonso, N.; Falguera, M.; Hernández, M.; Aguilera, E.; et al. Improved adherence to Mediterranean Diet in adults with type 1 diabetes mellitus. *Eur. J. Nutr.* **2018**. [CrossRef] [PubMed]
15. Alcubierre, N.; Navarrete-Muñoz, E.M.; Rubinat, E.; Falguera, M.; Valls, J.; Traveset, A.; Vilanova, M.-B.; Marsal, J.R.; Hernandez, M.; Granado-Casas, M.; et al. Association of low oleic acid intake with diabetic retinopathy in type 2 diabetic patients: A case-control study. *Nutr. Metab.* **2016**, *13*, 40. [CrossRef] [PubMed]
16. Bernstein, M.S.; Morabia, A.; Sloutskis, D. Definition and prevalence of sedentarism in an urban population. *Am. J. Public Health* **1999**, *89*, 862–867. [CrossRef] [PubMed]
17. Cabrera de León, A.; Rodríguez-Pérez, M.D.C.; Rodríguez-Benjumeda, L.M.; Anía-Lafuente, B.; Brito-Díaz, B.; Muros de Fuentes, M.; Almeida-González, D.; Batista-Medina, M.; Aguirre-Jaime, A. Sedentary lifestyle: Physical activity duration versus percentage of energy expenditure. *Rev. Esp. Cardiol.* **2007**, *60*, 244–250. [CrossRef] [PubMed]
18. Willett, W.C.; Sampson, L.; Stampfer, M.J.; Rosner, B.; Bain, C.; Witschi, J.; Hennekens, C.H.; Speizer, F.E. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am. J. Epidemiol.* **1985**, *122*, 51–65. [CrossRef] [PubMed]
19. Vioque, J.; Navarrete-Muñoz, E.-M.; Gimenez-Monzó, D.; García-de-la-Hera, M.; Granado, F.; Young, I.S.; Ramón, R.; Ballester, F.; Murcia, M.; Rebagliato, M.; et al. Reproducibility and validity of a food frequency questionnaire among pregnant women in a Mediterranean area. *Nutr. J.* **2013**, *12*, 26. [CrossRef] [PubMed]
20. US Department of Agriculture Agricultural Research Service. USDA National Nutrient Database for Standard Reference. Available online: https://www.ars.usda.gov/ (accessed on 1 July 2018).
21. Palma, I.; Farran, P.; Cervera, P. *Tablas de Composición de Alimentos por Medidas Caseras de Consumo Habitual en España*; Mc Graw Hill Interamericana: Barcelona, Spain, 2008.
22. Food Standards Agency. *McCance and Widdowson´s The Composition of Foods*, 6th ed.; Royal Society of Chemistry: Cambridge, UK, 2002.

23. Wilkinson, C.P.; Ferris, F.L.; Klein, R.E.; Lee, P.P.; Agardh, C.D.; Davis, M.; Dills, D.; Kampik, A.; Pararajasegaram, R.; Verdaguer, J.T.; et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology* **2003**, *110*, 1677–1682. [CrossRef]
24. Díaz-López, A.; Babio, N.; Martínez-González, M.A.; Corella, D.; Amor, A.J.; Fitó, M.; Estruch, R.; Arós, F.; Gómez-Gracia, E.; Fiol, M.; et al. Mediterranean Diet, Retinopathy, Nephropathy, and Microvascular Diabetes Complications: A Post Hoc Analysis of a Randomized Trial. *Diabetes Care* **2015**, *38*, 2134–2141. [CrossRef] [PubMed]
25. Sala-Vila, A.; Díaz-López, A.; Valls-Pedret, C.; Cofán, M.; García-Layana, A.; Lamuela-Raventós, R.-M.; Castañer, O.; Zanon-Moreno, V.; Martinez-Gonzalez, M.A.; Toledo, E.; et al. Dietary Marine ω-3 Fatty Acids and Incident Sight-Threatening Retinopathy in Middle-Aged and Older Individuals with Type 2 Diabetes: Prospective Investigation from the PREDIMED Trial. *JAMA Ophthalmol.* **2016**, *134*, 1142. [CrossRef] [PubMed]
26. Schwingshackl, L.; Strasser, B.; Hoffmann, G. Effects of Monounsaturated Fatty Acids on Cardiovascular Risk Factors: A Systematic Review and Meta-Analysis. *Ann. Nutr. Metab.* **2011**, *59*, 176–186. [CrossRef] [PubMed]
27. Schwingshackl, L.; Hoffmann, G. Monounsaturated fatty acids and risk of cardiovascular disease: Synopsis of the evidence available from systematic reviews and meta-analyses. *Nutrients* **2012**, *4*, 1989–2007. [CrossRef] [PubMed]
28. Behl, T.; Kotwani, A. Omega-3 fatty acids in prevention of diabetic retinopathy. *J. Pharm. Pharmacol.* **2017**. [CrossRef] [PubMed]
29. Horikawa, C.; Yoshimura, Y.; Kamada, C.; Tanaka, S.; Tanaka, S.; Matsunaga, S.; Hanyu, O.; Araki, A.; Ito, H.; Tanaka, A.; et al. Is the proportion of carbohydrate intake associated with the incidence of diabetes complications?—An analysis of the Japan diabetes complications study. *Nutrients* **2017**, *9*, 113. [CrossRef] [PubMed]
30. Buyken, A.E.; Toeller, M.; Heitkamp, G.; Irsigler, K.; Holler, C.; Santeusanio, F.; Stehle, P.; Fuller, J.H.; John, G.; Viberti, G.C.; et al. Carbohydrate sources and glycaemic control in type 1 diabetes mellitus. *Diabet. Med.* **2000**, *17*, 351–359. [CrossRef] [PubMed]
31. Mayer-Davis, E.J.; Bell, R.A.; Reboussin, B.A.; Rushing, J.; Marshall, J.A.; Hamman, R.F. Antioxidant nutrient intake and diabetic retinopathy. *Ophthalmology* **1998**, *105*, 2264–2270. [CrossRef]
32. Millen, A.E.; Klein, R.; Folsom, A.R.; Stevens, J.; Palta, M.; Mares, J.A. Relation between intake of vitamins C and E and risk of diabetic retinopathy in the Atherosclerosis Risk in Communities Study. *Am. J. Clin. Nutr.* **2004**, *79*, 865–873. [CrossRef] [PubMed]
33. Tanaka, S.; Yoshimura, Y.; Kawasaki, R.; Kamada, C.; Tanaka, S.; Horikawa, C.; Ohashi, Y.; Araki, A.; Ito, H.; Akanuma, Y.; et al. Japan Diabetes Complications Study Group Fruit Intake and Incident Diabetic Retinopathy with Type 2 Diabetes. *Epidemiology* **2013**, *24*, 204–211. [CrossRef] [PubMed]
34. Zamora-Ros, R.; Knaze, V.; Luján-Barroso, L.; Romieu, I.; Scalbert, A.; Slimani, N.; Hjartåker, A.; Engeset, D.; Skeie, G.; Overvad, K.; et al. Differences in dietary intakes, food sources and determinants of total flavonoids between Mediterranean and non-Mediterranean countries participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Br. J. Nutr.* **2013**, *109*, 1498–1507. [CrossRef] [PubMed]
35. Vioque, J.; Gonzalez, L. Validez de la evaluación de la ingesta dietética. In *Nutrición y Salud Pública. Métodos, Bases Científicas y Aplicaciones*; Serra Majem, L., Aranceta Bartrina, J., Eds.; Masson-Elsevier: Barcelona, Spain, 2006; pp. 199–210. ISBN 84-458-1528-8.

5.3. Artículo 3

Minerva Granado-Casas, Montserrat Martínez-Alonso, Nuria Alcubierre, Anna Ramírez-Morros, Marta Hernández, Esmeralda Castelblanco, Joan Torres-Puiggros, Didac Mauricio. Decreased quality of life and treatment satisfaction in patients with latent autoimmune diabetes of the adult. PeerJ. 2017;5:e3928.

Resumen

Objetivos

El objetivo principal del estudio fue evaluar la calidad de vida y la satisfacción con el tratamiento de los pacientes con LADA y las diferencias existentes entre este grupo de pacientes y aquellos con DM1 y DM2.

Materiales y métodos

Se diseñó un estudio observacional y transversal. Se reclutó una muestra total de 48 pacientes con LADA, 297 pacientes con DM2 y 124 DM1 de las consultas externas del Servicio de Endocrinología del Hospital Universitari Arnau de Vilanova de Lleida. Los criterios de inclusión de los pacientes fueron el diagnóstico de diabetes mellitus con una duración de la enfermedad superior a un año, edad superior a 18 años, ausencia de incapacidad por complicaciones macrovasculares y ausencia de macroalbuminuria o enfermedad renal. Los criterios de exclusión fueron las condiciones que podían influir en los resultados, como demencia, enfermedades mentales, problemas auditivos y lingüísticos, embarazo e incapacidad por enfermedad cardiovascular. Se administraron, mediante entrevista personal, los cuestionarios *Audit of Diabetes-Dependent Quality of Life* (ADDQoL-19) y *Diabetes Treatment Satisfaction Questionnaire* (DTSQ) validados en población diabética española. Las variables clínicas fueron recogidas mediante anamnesis, exploración física, revisión exhaustiva de las historias clínicas de cada paciente. El análisis de datos incluyó la comparación entre grupos y modelos multivariables.

Resultados

Los pacientes con LADA presentaron una menor calidad de vida relacionada con la diabetes que los pacientes con DM2. Sin embargo, no encontramos diferencias en los ítems de calidad de vida del cuestionario ADDQoL-19 entre los pacientes LADA y los pacientes con DM1. El subgrupo de pacientes LADA con RD que estaban siendo tratados con insulina tuvieron un menor impacto promedio ponderado en el ADDQoL en comparación con los otros grupos de pacientes con diabetes (DM1 con RD, DM2 con RD tratados con y sin insulina). Además, la presencia de RD, una mayor duración de la diabetes, un nivel educativo más bajo y el ser exfumador tuvieron un impacto

negativo en el impacto promedio ponderado del cuestionario de calidad de vida. Aunque la satisfacción con el tratamiento global no fue distinta entre los pacientes LADA y los pacientes con DM1 y DM2, los pacientes con LADA tuvieron una peor autopercepción en la frecuencia de hiperglucemias que los pacientes con DM2, y una mejor percepción en la frecuencia de hipoglucemias que los pacientes con DM1.

Conclusiones

Estos resultados sugieren que los pacientes con diabetes LADA tienen una peor calidad de vida, especialmente en relación con la RD y el tratamiento insulínico, comparados con los pacientes con DM1 y DM2. La percepción en la frecuencia de hiperglucemias fue más pobre en los pacientes LADA en comparación con los pacientes con DM1 y DM2. Es necesario realizar más estudios con un diseño prospectivo y con mayor tamaño muestral para obtener resultados concluyentes.

Decreased quality of life and treatment satisfaction in patients with latent autoimmune diabetes of the adult

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ABSTRACT

Objectives. Our main aim was to assess the quality of life (QoL) and treatment satisfaction (TS) of subjects with LADA (latent autoimmune diabetes of the adult) and compare these measures with those of patients with other diabetes types, i.e., type 1 (T1DM) and type 2 diabetes mellitus (T2DM).

Methods. This was a cross-sectional study with a total of 48 patients with LADA, 297 patients with T2DM and 124 with T1DM. The Audit of Diabetes-Dependent Quality of Life (ADDQoL-19) questionnaire and the Diabetes Treatment Satisfaction Questionnaire (DTSQ) were administered. Relevant clinical variables were also assessed. The data analysis included comparisons between groups and multivariate linear models.

Results. The LADA patients presented lower diabetes-specific QoL ($p = 0.045$) and average weighted impact scores ($p = 0.007$) than the T2DM patients. The subgroup of LADA patients with diabetic retinopathy (DR) who were treated with insulin had a lower ADDQoL average weighted impact score than the other diabetic groups. Although the overall measure of TS was not different between the LADA and T2DM ($p = 0.389$) and T1DM ($p = 0.091$) groups, the patients with LADA showed a poorer hyperglycemic frequency perception than the T2DM patients ($p < 0.001$) and an improved frequency of hypoglycemic perception compared with the T1DM patients ($p = 0.021$).

Conclusions. The current findings suggest a poorer quality of life, especially in terms of DR and insulin treatment, among patients with LADA compared with those with T1DM and T2DM. Hyperglycemia frequency perception was also poorer in the LADA patients than in the T1DM and T2DM patients. Further research with prospective studies and a large number of patients is necessary.

Subjects Diabetes and Endocrinology, Nursing, Public Health

Keywords Treatment satisfaction, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Quality of life, Autoimmune diabetes

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INTRODUCTION

Latent autoimmune diabetes in adults (LADA) is a slowly progressive form of autoimmune diabetes that presents an initial type 2 diabetes mellitus (T2DM) phenotype combined with diabetes-related autoantibodies (*Leslie et al., 2016*). At diagnosis, patients do not require insulin therapy and are often classified as T2DM patients (*Hawa et al., 2013*; *Stenstrom et al., 2005*). Patients with LADA are younger and leaner that T2DM patients (*Hawa et al., 2013*; *Stenstrom et al., 2005*). They usually have a lower body mass index (BMI), serum triglycerides (TG), waist circumference (WC), waist-to-hip ratio, and blood pressure (BP) and higher HDL cholesterol levels than the T2DM population (*Fourlanos et al., 2005*; *Hawa et al., 2009*; *Hawa et al., 2013*; *Isomaa et al., 1999*; *Mollo et al., 2013*). The cardiovascular risk profile of LADA is intermediate, falling between that of type 1 and type 2 diabetes. Additionally, these patients show lower residual endogenous insulin secretion and progress more rapidly to insulin treatment with worse glycemic control (*Fourlanos et al., 2005*; *Hawa et al., 2009*; *Isomaa et al., 1999*; *Mollo et al., 2013*; *Hernandez et al., 2015*).

Quality of life (QoL) is a subjective measure of health and well-being related to disease. It includes psychosocial features, physical functioning, mobility and personal care (*Esteban y Peña et al., 2010*). The aim of measuring QoL is to provide a more comprehensive, integral, precise and valid evaluation of patients' health status (*Speight, Reaney & Barnard, 2009*). Treatment satisfaction (TS) is an individual subjective measure that assesses the patients' experience of treatment processes and results, including ease of use, side effects and efficacy (*Hervás et al., 2002*). TS can be influenced by demographic characteristics such as age, educational level and salary (*Villar-López et al., 2009*). The development of the disease, information regarding treatment, therapy availability and costs are also associated with TS (*Villar-López et al., 2009*). Furthermore, diabetes mellitus reportedly has a negative impact QoL, but TS is optimal in this population (*Speight, Reaney & Barnard, 2009*).

Previous studies have investigated the QoL and TS of patients with type 1 diabetes mellitus (T1DM) and T2DM, but not those with LADA (*Ahola et al., 2010*; *Bradley et al., 2011*; *Depablos-Velasco et al., 2014*; *Nicolucci et al., 2009*; *Oliva, Fernandez-Bolanos & Hidalgo, 2012*). The PANORAMA study found that T2DM patients with poor glycemic control, complex treatments and severe hypoglycemic episodes showed poorer QoL compared with patients without these factors (*Bradley et al., 2011*; *Depablos-Velasco et al., 2014*). Other studies observed that QoL and treatment satisfaction were lower with increasing age, female sex, lower education level, insulin treatment and obesity, the presence of diabetic comorbidities, poorer glycemic control and lower socioeconomic status (*Ahola et al., 2010*; *Nicolucci et al., 2009*; *Oliva, Fernandez-Bolanos & Hidalgo, 2012*).

As the diagnosis of LADA among subjects with type 2 diabetes is usually delayed, which may increase the disease burden, we hypothesized that LADA patients might have a lower QoL and TS than their counterparts with T2DM; however, LADA is an autoimmune form of diabetes that usually evolves into a phenotype closely related to that of classical type 1 diabetes. Furthermore, the identification of LADA subjects may be relevant from the clinical point of view.

To our knowledge, no studies have evaluated QoL and TS in subjects with LADA. Therefore, the primary objective of this study was to assess QoL and TS in patients with LADA and to compare these measures with those of T2DM and T1DM patients. We also evaluated the factors related to both QoL and TS in the study subjects.

MATERIALS AND METHODS

The study design was observational and cross-sectional. LADA was defined as diabetes diagnosed in individuals over 30 years of age with a positive test for glutamic acid decarboxylase (GAD) antibodies and without the need for insulin treatment during the first six months after diagnosis (*Leslie et al., 2008*; *Mollo et al., 2013*). Patients with T1DM and T2DM were diagnosed according to the current standard diagnostic criteria, as described previously (*Mollo et al., 2013*). The inclusion criteria for the three groups of patients were as follows: a diagnosis of diabetes mellitus with a disease duration of more than one year; age greater than 18 years; absence of disability due to macrovascular complications (including a history of diabetic foot disease); and absence of macroalbuminuria (defined as urine albumin-to-creatinine ratio >300 mg/g) or renal failure (estimated glomerular filtration rate <60 ml/min/1.73 m^2). The exclusion criteria were as follows: conditions that could affect the results, such as dementia, mental diseases, hearing and languages problems, pregnancy and disability due to cardiovascular diseases. Dementia and mental diseases had to be diagnosed by a physician and could be determined using the registered clinical records of the patient's general practitioner. No screening tools for detecting initial cognitive impairment were used. All included patients had an estimated glomerular filtration rate >60 ml/min, except for two LADA participants who had a glomerular filtration rate between 30 and 59 ml/min. Two patients in the T1DM group had previous cerebrovascular events, and one patient had bilateral femoral stenosis; none of the patients had any disability. The study was approved by the Ethics Committee of Hospital Arnau de Vilanova (Ethical Application Ref: CEIC 1079 and Ref: PI-13-095). Written informed consent was obtained from all of the subjects.

Clinical variables

Trained researchers (MG-C and NA) conducted personal interviews with each of the patients and reviewed the medical records to collect the data regarding the variables of interest. Anthropometric measures were determined according to standard criteria. Laboratory tests and blood pressure were measured using standard procedures as previously described (*Alcubierre et al., 2014*). Hypertension and dyslipidemia were defined if the participant was undergoing pharmacological treatment for these conditions. Microalbuminuria was defined as an albumin creatinine ratio >30 mg/g. Physical activity was assessed using a validated method by *Bernstein, Morabia & Sloutskis (1999)*; participants were classified as engaging in regular exercise if they performed any physical activity that required at least ≥4 METS (The Metabolic Equivalent) of brisk walking for 30 min or more and as sedentary if they did not perform any daily physical activity or if they engaged less than 30 min of physical activity per day (*Bernstein, Morabia & Sloutskis, 1999*; *Cabrera de León et al., 2007*).

Quality of life

QoL was assessed through the Audit of Diabetes-Dependent Quality of Life (ADDQoL-19), a disease-specific QoL questionnaire designed and validated in diabetic Spanish subjects (*Bradley et al., 2011*; *Bradley et al., 1999*; *Depablos-Velasco et al., 2014*) (File S1). This questionnaire consists of 21 items, of which 19 are related to specific life domains and are scored on a 5-point scale. The impact of diabetes on each domain is weighted according to the importance of the domain to the patient's QoL and is reported as the average weighted impact score. These scores can range from +9 (maximum positive impact) to −3 (maximum negative impact). The first two items are general and are scored separately. The first item measures current QoL and is scored from +3 (excellent) to −3 (very bad). The second item measures diabetes-specific QoL and ranges from −3 (maximum negative impact) to +1 (maximum positive impact). Moreover, five of the 19 items that may not have importance for some patients are included in a preliminary question that can be ignored if not applicable. All the questionnaires were administered individually by two trained interviewers (MG-C and NA.).

Treatment satisfaction

TS was determined by a diabetes-specific questionnaire, the Diabetes Treatment Satisfaction Questionnaire status-version (DTSQ-s) (*Bradley, 1994*), that has been validated for the Spanish diabetic population (*Gomis et al., 2006*) (File S2). This questionnaire consists of eight items scored on a 6-point scale. The final score is weighted according to six items with total scores ranging from 36 (very satisfied) to 0 (very unsatisfied). The two remaining items measure the frequency of hyperglycemia and hypoglycemia, respectively, and are scored on a scale from 0 (never) to 6 (always).

Sample size

To our knowledge, no previous studies have reported QoL and TS in patients with LADA. Additionally, the number of subjects with LADA is limited at the local level, and we aimed to recruit all available patients.

Statistical analysis

The statistical analysis included the comparability among the groups of subjects with diabetes (LADA, T2DM and T1DM) and multivariate linear regression models' estimation of the variability of the overall mean score for QoL and the present QoL and diabetes-specific QoL items provided by the ADDQoL questionnaire. The TS score and the hyperglycemia and hypoglycemia frequencies were also fitted in multivariate linear regression models to identify differences between the types of diabetes after adjustment for significantly related patient characteristics. The comparison of QoL and TS between the diabetic groups was stratified by the median of the two groups. In the multivariate linear regression models, LADA patients undergoing insulin treatment were used as the reference group in all of the analyses. The comparability analysis included Pearson's chi-squared test (or Fisher's exact test in the case of any expected frequency lower than 5) to compare the distribution of qualitative characteristics. The Kruskal-Wallis test was performed to compare the distribution of quantitative characteristics, including pairwise comparisons to adjust for

multiple testing according to the Benjamini & Hochberg method; furthermore, these characteristics were described by median and interquartile intervals for each diabetic group. The significance level was set at 0.05. The statistical software R version 3.3.2 (*R Core Team, 2016*) was used for the analyses.

RESULTS

We had previously identified a total of 106 LADA patients in the local cohort of the only reference hospital in Lleida (North-Eastern Spain). This hospital is the public reference center for specialized diabetes care for the health care district of Lleida. From this sample, 20 participants were excluded after the initial screening based on the exclusion criteria. From a sample of 86 LADA patients who were contacted to participate in the study, 51 participants initially accepted, and an additional three patients were excluded. Thus, 48 LADA patients were included in the study. From a sample of 170 T1DM patients who were contacted to participate in the study, a total of 127 agreed to participate, and 3 were excluded for pregnancy, yielding a final sample of 124 patients. As a comparison with T2DM, we used the entire group of 297 patients with T2DM who had been included in a previous study of QoL conducted at the same center (*Alcubierre et al., 2014*).

The comparison between the patients with LADA included in the study and those who refused to participate ($n = 35$) revealed no differences in clinical characteristics except for a lower frequency of insulin treatment in the non-participant group (72%; $p = 0.049$ for the comparison with the LADA patients included in the current study).

The clinical and demographic characteristics of the study groups are shown in Table 1. The LADA patients had an intermediate cardiovascular risk profile in terms of adiposity, lipids and blood pressure compared with the T2DM and T1DM groups. The patients with LADA were older than those with T1DM ($p < 0.001$). The duration of diabetes in the LADA group was longer (10.7 years) than that of the T2DM group (8 years) and shorter than that of the T1DM group (20.5 years; $p < 0.001$). The frequency of diabetic retinopathy (DR) was 22.9% in the LADA group, 49.8% in the T2DM group and 40.3% in the T1DM group ($p = 0.001$). There were no differences in glycated hemoglobin (HbA1c) among the 3 groups ($p = 0.689$).

Quality of life

The scores for current QoL did not differ among the 3 study groups ($p = 0.503$; Table 2); however, there was a higher proportion of patients with negative diabetes-specific QoL in the LADA group (70.8%) than in the T2DM group (52.9%; $p = 0.045$). Furthermore, more subjects with LADA had a negative average weighted impact score (60.4%) compared with the T2DM patients (37.7%; $p = 0.007$). Concerning these QoL measures, we could not find differences between the LADA and T1DM patients.

The multivariate linear model of the diabetes-specific QoL score revealed a significant interaction with insulin treatment, as indicated in Table 3. The results are expressed using the group of insulin-treated patients with LADA as the reference group. The LADA and T2DM subjects without insulin treatment showed a higher diabetes-specific QoL than the reference group ($p = 0.004$ and $p < 0.001$, respectively), whereas there were no differences

Table 1 Clinical characteristics of the study groups.

Characteristics	LADA ($N = 48$)	T2DM ($N = 297$)	T1DM ($N = 124$)	p-value*	p-LADA vs. T2DM	p-LADA vs. T1DM
Age (years)	62 [53.8;70.2]	60 [52.0;68.0]	46 [37.0;53.0]	<0.001	0.118	<0.001
Sex, male	26 (54.2)	151 (50.8)	57 (46.0)	0.543		
Education level				<0.001	0.181	0.012
<Primary	3 (6.3)	38 (12.8)	17 (13.7)			
Primary	24 (50.0)	169 (56.9)	31 (25.0)			
Secondary	18 (37.5)	69 (23.2)	54 (43.5)			
Graduate or higher	3 (6.3)	21 (7.1)	22 (17.7)			
Smoking				0.891		
Non-smoker	24 (50.0)	139 (47.3)	57 (46.0)			
Smoker, current	11 (22.9)	62 (21.1)	31 (25.0)			
Smoker, former	13 (27.1)	93 (31.6)	36 (29.0)			
Physical activity				0.052		
Sedentary	13 (27.1)	114 (38.4)	34 (27.4)			
Regular physical activity	35 (72.9)	183 (61.6)	90 (72.6)			
Diabetes duration (years)	10.7 [6.5;16.7]	8 [4.0;15.0]	20.5 [14.0;30.2]	<0.001	0.035	<0.001
BMI (kg/m^2)	27.1 [24.1;30.4]	30.6 [28.1;34.7]	24.6 [22.5;27.2]	<0.001	<0.001	0.001
Waist (centimeters)	96.7 ± 15.5	106 ± 11.8	87.7 ± 12.8	<0.001	<0.001	<0.001
Hypertension	26 (54.2)	168 (56.6)	41 (33.1)	<0.001	0.878	0.027
Systolic blood pressure (mmHg)	134 [124.0;148.0]	139 [127.0;150.0]	127 [113.0;139.0]	<0.001	0.220	0.017
Diastolic blood pressure (mmHg)	73 [69.0;79.0]	77 [70.0;84.0]	73 [65.0;78.2]	<0.001	0.126	0.235
Dyslipidemia	34 (70.8)	131 (44.1)	55 (44.4)	0.002	0.003	0.005
Diabetic retinopathy	11 (22.9)	148 (49.8)	50 (40.3)	0.001	0.003	0.075
Microalbuminuria	11 (23.4)	43 (14.5)	11 (9.1)	0.051		
Insulin treatment	43 (89.6)	97 (32.7)	124 (100.0)	<0.001	<0.001	0.001
HbA1c (%)	7.5 [6.9;8.2]	7.6 [6.8;8.5]	7.6 [7.0;8.1]	0.689		
Total cholesterol (mg/dL)	176 [155.0;202.0]	181 [163.0;205.0]	182 [165.0;202.0]	0.553		
HDL-c (mg/dL)	58.5 [40.8;70.2]	48 [41.8;59.0]	63 [53.9;74.0]	<0.001	0.040	0.011
LDL-c (mg/dL)	101 [84.0;123.0]	106 [87.2;128.0]	102 [89.6;116.0]	0.391		
Triglycerides (mg/dL)	91.5 [66.8;134.0]	117 [83.0;167.0]	65.5 [53.8;81.2]	<0.001	0.003	<0.001

Notes.

*p-value for comparison between groups.

LADA, latent autoimmune diabetes of adult; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; BMI, body mass index; HbA1c, glycated haemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.

Data are median [interquartile], n (%) or means ± SD.

between the patients with T1DM and insulin-treated T2DM patients. Additionally, the presence of hypertension, longer disease duration and a larger waist circumference had a negative impact on diabetes-specific QoL.

Concerning the ADDQoL average weighted impact score, we found a significant interaction between DR, the study group (i.e., type of diabetes) and insulin treatment (Table 4). Insulin-treated LADA subjects showed a poorer average weighted impact score than their corresponding type 2 non-insulin-treated counterparts ($p < 0.001$). Additionally, T2DM patients with DR and with ($p = 0.01$) or without ($p = 0.03$) concomitant insulin

Table 2 Descriptive analysis for the Audit of Diabetes Dependent Quality of Life (ADDQoL) results of the study groups.

Items	LADA ($N = 48$) *n* (%)	T2DM ($N = 297$) *n* (%)	T1DM ($N = 124$) *n* (%)	*p*-value*	*p*-LADA vs. T2DM	*p*-LADA vs. T1DM
Present QoL				0.503		
[−3,2)	42 (87.5)	242 (81.5)	99 (79.8)			
[2,3]	6 (12.5)	55 (18.5)	25 (20.2)			
Diabetes-specific QoL				<0.001	0.045	0.634
[−3,0)	34 (70.8)	157 (52.9)	94 (75.8)			
[0,2]	14 (29.2)	140 (47.1)	30 (24.2)			
Average weighted impact score				<0.001	0.007	0.069
[−6.526,−0.842)	29 (60.4)	112 (37.7)	94 (75.8)			
[−0.842,0.316]	19 (39.6)	185 (62.3)	30 (24.2)			

Notes.
The groups are stratified by medians.
*p-value for comparison between groups.
QoL, quality of life; LADA, latent autoimmune diabetes of adult; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus.

Table 3 Multivariate linear regression for the Audit of Diabetes Dependent Quality of Life (ADDQoL) diabetes-specific QoL score.

Coefficients	Estimate	Standard error	*p* value
Intercept	0.278998	0.407968	0.490
T2DM* without insulin	0.815249	0.154823	<0.001
LADA* without insulin	1.187429	0.415424	0.004
T2DM* insulin	0.238438	0.168811	0.160
T1DM	0.024457	0.164031	0.880
Hypertension	−0.310550	0.089091	0.001
HbA1c	−0.070135	0.035407	0.050
Disease duration	−0.010606	0.004989	0.030
Waist circumference	−0.008147	0.003458	0.020

Notes.
Multiple R-squared: 0.2284 (27 cases with missing information for any variable in the model).
Reference group: LADA patients receiving insulin treatment.
*Indicates the existence of interactions between variables.
LADA, latent autoimmune diabetes of adult; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; HbA1c, glycated haemoglobin.

treatment and T1DM patients with DR ($p = 0.03$) had a better average weighted impact score than LADA patients undergoing insulin treatment. The presence of DR, longer disease duration, lower education level (less than a primary education) and former smoking had a negative impact on the average weighted impact score. Nevertheless, physical activity was positively related to this measure of QoL ($p = 0.010$). Furthermore, using the LADA patients undergoing insulin treatment with or without DR as reference groups, we could estimate the combined coefficients using the same model (Table S1). These analyses showed that LADA subjects with DR who were treated with insulin showed a lower QoL than any other combination of diabetes type, insulin treatment and DR. Furthermore, the LADA patients undergoing insulin treatment without DR had a lower QoL than the T2DM patients without insulin treatment either with ($p = 0.006$) or without DR ($p < 0.001$).

Table 4 Multivariate linear regression for the Audit of Diabetes Dependent Quality of Life (ADDQoL) average weighted impact score.

Coefficients	Estimate	Standard error	*p* value
Intercept	−1.29375	0.21782	<0.001
T2DM* without insulin	0.95200	0.20699	<0.001
LADA* without insulin	1.06176	0.64037	0.100
T2DM* insulin	0.10006	0.31884	0.750
T1DM	−0.04103	0.22328	0.850
DR	−1.25952	0.40942	0.002
Disease duration	−0.01674	0.00663	0.010
No education**	−0.45008	0.15383	0.004
Physical activity	0.27361	0.10539	0.010
Smoker, current	−0.21031	0.12937	0.100
Smoker, former	−0.30882	0.11674	0.008
T2DM* without insulin* DR	0.92912	0.43927	0.030
LADA* without insulin* DR	1.10620	1.05301	0.290
T2DM* insulin* DR	1.23910	0.49206	0.010
T1DM* DR	0.98320	0.44443	0.030

Notes.

Multiple R-squared: 0.2895 (six cases with missing information for any variable in the model).

Reference group: LADA patients receiving insulin treatment.

*Indicates the existence of interactions between variables.

**"No education" identifies patients who did not complete compulsory education.

LADA, latent autoimmune diabetes of adult; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; DR, diabetic retinopathy.

Treatment satisfaction

The proportion of subjects with a lower DTSQ final score differed among the study groups: LADA, 60.4%; T2DM, 52.5%; and T1DM, 41.9% ($p = 0.049$). However, individual paired comparisons between the groups did not yield statistically significant differences (Table 5). The multivariate linear regression analysis of the DTSQ final score revealed no differences between the different combinations of groups according to diabetes type and insulin-treatment (Table S2). Physical activity had a positive impact ($p = 0.001$) and former smoking had a negative impact on the DTSQ final score ($p = 0.01$).

Concerning another measure of TS, the proportion of patients with a perception of increased hyperglycemia frequency was higher in the LADA group (87.5%) than in the T2DM (53.9%) and T1DM groups (71%; $p < 0.001$ and $p = 0.039$, respectively). The multivariate linear regression analysis found an interaction between the type of diabetes and insulin treatment (Table S3). The insulin-treated LADA patients had a higher hyperglycemia frequency perception than the T1DM ($p = 0.04$) and insulin-treated T2DM subjects ($p = 0.05$). Physical activity was associated with a lower hyperglycemia perception frequency ($p = 0.002$). Additionally, DR and higher HbA1c were associated with higher hyperglycemia frequency perception ($p = 0.05$ and $p < 0.001$, respectively).

Finally, the proportion of patients with higher hypoglycemia frequency perception differed among the groups ($p < 0.001$; Table 5). A higher proportion of patients with T1DM (55.6%) than patients with LADA (33.3%) reported a high frequency of perceived

Table 5 Results of the variables corresponding to the Diabetes Treatment Satisfaction Questionnaire (DTSQ) in the different study groups.

Items	LADA ($N = 48$) *n* (%)	T2DM ($N = 297$) *n* (%)	T1DM ($N = 124$) *n* (%)	*p*-value*	*p*-LADA vs. T2DM	*p*-LADA vs. T1DM
Hyperglycemia frequency perception				<0.001	<0.001	0.039
0–2	6 (12.5)	137 (46.1)	36 (29)			
3–6	42 (87.5)	160 (53.9)	88 (71)			
Hypoglycemia frequency perception				<0.001	0.095	0.021
0–2	32 (66.7)	234 (78.8)	55 (44.4)			
3–6	16 (33.3)	63 (21.2)	69 (55.6)			
Final score				0.049	0.389	0.091
[4,28)	29 (60.4)	156 (52.5)	52 (41.9)			
[28,36)	19 (39.6)	141 (47.5)	72 (58.1)			

Notes.
The groups are stratified by medians.
*p-value for comparisons between groups.
LADA, latent autoimmune diabetes of adult; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus.

hypoglycemia ($p = 0.021$). In the multivariate linear regression analysis (Table S4), T2DM patients without insulin treatment showed a significantly lower hypoglycemia frequency perception compared with insulin-treated LADA subjects ($p = 0.006$). Additionally, the following conditions increased this measure: T1DM ($p = 0.02$), female sex ($p = 0.001$) and disease duration ($p = 0.006$).

DISCUSSION

In the current study, we demonstrated that LADA patients presented with lower diabetes-associated specific and average weighted impact QoL scores than patients with T2DM; however, we found no differences in terms of present QoL. Insulin treatment had a negative impact on diabetes-specific QoL, and the subgroup of insulin-treated patients with LADA did not differ from other insulin-treated groups (T2DM and T1DM) in this regard; however, the average weighted impact score was poorer in insulin-treated LADA subjects than in their corresponding T2DM counterparts. The group with the worst values for this impact score was the subgroup of LADA patients with DR and insulin treatment.

Although there was a significant difference in the DTSQ final score among the groups, paired comparisons between groups did not reach significant differences; however, there were differences concerning the hyperglycemia and hypoglycemia frequency perception among the groups. The LADA patients showed an increased hyperglycemia frequency perception compared with the T2DM and T1DM groups, which was mainly at the expense of the insulin-treated LADA group. In contrast, the LADA patients had an improved hypoglycemia perception frequency compared with the T1DM patients.

To our knowledge, there are no previous studies on QoL and TS in subjects with LADA. Concerning quality of life, previous studies revealed a lower QoL in patients with type 1 diabetes or insulin-treated type 2 diabetes and in subjects with one or more late diabetic

complications (*Collins et al., 2009*). In a previous study by our group, we also found that patients with T2DM and DR had a lower QoL than those without this complication (*Alcubierre et al., 2014*), which is in line with the current findings in patients with LADA. Our results are also in line with other previous studies that reported that insulin therapy and diabetic complications were associated with a poorer QoL in patients with T2DM (*Bradley & Speight, 2002*; *Collins et al., 2009*; *Depablos-Velasco et al., 2014*; *Shim et al., 2012*; *Speight & Bradley, 2000*; *Sundaram et al., 2007*); however, in a longitudinal study of patients with T2DM starting insulin therapy, QoL improved six months after the commencement of insulin therapy (*Wilson, Moore & Lunt, 2004*). The negative impact of insulin treatment on LADA patients is associated with a poorer QoL perception, which may be linked to impaired metabolic control and the delayed initiation of insulin treatment. Furthermore, *Depablos-Velasco et al. (2014)* observed that diabetic patients with poor metabolic control had a low QoL; however, we found no significant differences in terms of glycemic control.

Shim et al. (2012) described that the ADDQoL average weighted impact score was lower in association with male gender, higher education level and longer disease duration. Other studies have related lower QoL to advanced age, female sex, lower educational level, obesity, the presence of diabetic comorbidities, poorer glycemic control and lower socioeconomic status in the type 1 and type 2 diabetic populations (*Ahola et al., 2010*; *Bradley & Speight, 2002*; *Collins et al., 2009*; *Imayama et al., 2011*; *Nicolucci et al., 2009*; *Oliva, Fernandez-Bolanos & Hidalgo, 2012*; *Shim et al., 2012*; *Speight & Bradley, 2000*; *Sundaram et al., 2007*). These findings are similar to our results concerning the presence of complications (i.e., DR), longer disease duration and waist circumference, all of which were related to a lower QoL.

However, we found a positive relationship between QoL and physical activity in patients with diabetes. Physical activity is an important component of the lifestyle measures used to treat patients living with diabetes. *Imayama et al. (2011)* performed a longitudinal study of 490 T1DM and 1,147 T2DM patients to investigate the determinants of health-related QoL (HRQoL). The authors also found a higher HRQoL in patients with a high physical activity level.

Concerning TS, the results showed a relatively high score despite the negative impact of diabetes on QoL, which has been reported in previous studies (*Bradley & Speight, 2002*; *Speight & Bradley, 2000*; *Speight, Reaney & Barnard, 2009*). We could not detect any difference between the LADA patients and the other groups in the DTSQ final score. Nevertheless, the hyperglycemia frequency perception was worse in the insulin-treated LADA patients, although glycemic control was not different between the groups. The increased hyperglycemia frequency perception in the subjects with LADA may be attributable to previous poorer glycemic control compared with type 1 diabetic patients under stable control. It is worth noting that the LADA subjects were recruited from a specialized hospital clinic, where patients are usually referred from primary care because of poor glycemic control. In contrast, the frequency of hypoglycemia perception was similar between the LADA and T2DM patients and was clearly increased in T1DM patients. This finding could be attributed to a higher intensity of insulin treatment in T1DM, which may be associated with a higher frequency of hypoglycemia in these patients. Unfortunately, the frequency of previous mild and severe hypoglycemia episodes was not

assessed. Additionally, as expected from the exposure to insulin treatment, the insulin-treated LADA patients had an increased frequency of hypoglycemia compared with the non-insulin treated T2DM patients.

Improved TS has been associated with optimal glycemic control (HbA1c $\leq$ 7%) in T2DM without concomitant complications or insulin treatment (*Biderman et al., 2009*; *Mancera-Romero et al., 2016*). These findings are in line with those reported here. Furthermore, we found that physical activity showed a positive association with TS, as in our previous study that involved the subgroup of T2DM patients included in our study (*Alcubierre et al., 2014*); however, we could not identify other studies addressing this specific issue in the diabetic population.

The current study has several limitations. A causal relationship between QoL, TS and related factors could not be established because of the cross-sectional study design; however, the variation in the QoL among patients was shown to be strongly influenced by the characteristics that do not vary over time (*Alva et al., 2014*). The low number of patients with LADA that were included is an important limitation. Therefore, the low number of subjects in the LADA group raises a point of caution regarding the external validity of the current results. Additionally, a significant number of potential subjects from the local LADA cohort refused to participate. However, there were no differences between the participating LADA patients and the non-participating LADA patients in the proportion of comorbidities that could affect the main study outcomes. Thus, the current study should be considered an exploratory investigation that raises awareness of the need for further studies of patient-oriented outcomes in subjects with LADA. Additionally, the current study compared the QoL and TS of LADA patients with that of patients with the two main classical types of diabetes. Another limitation arises from the potential selection bias of the current study hospital setting. Subjects with worse glycemic control are referred to specialized care for further diagnostic work-up that leads to the final diagnosis of LADA, while subjects with LADA who have better glycemic control are likely to remain unidentified at the primary care level. Therefore, the current results may not be extrapolated to the whole population of LADA subjects. The issue of poor QoL is very relevant to patients with LADA who are ultimately referred to specialized care because of unstable glycemic control and the need for insulin treatment. Finally, mental well-being may have an impact on the main outcomes evaluated in the current study. Although mood items are included in the ADDQoL-19 questionnaire, a proper evaluation of emotional or mental well-being was not performed in this study. This latter issue should be taken into consideration in future studies of patients with LADA.

CONCLUSIONS

In conclusion, in the current study we found that that LADA patients with DR who were undergoing insulin treatment had a negative QoL compared with T2DM and T1DM patients. Furthermore, the LADA patients undergoing insulin treatment perceived a greater frequency of hyperglycemia than the other diabetic groups. Further research is warranted to study the status and changes over time in the QoL and TS of patients with LADA in other settings and with a larger number of patients.

ADDITIONAL INFORMATION AND DECLARATIONS

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Competing Interests

The authors declare there are no competing interests.

Author Contributions

- Minerva Granado-Casas conceived and designed the experiments, performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, wrote the paper, prepared figures and/or tables.
- Montserrat Martínez-Alonso analyzed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables.
- Nuria Alcubierre, Anna Ramírez-Morros, Marta Hernández and Esmeralda Castelblanco performed the experiments, contributed reagents/materials/analysis tools.
- Joan Torres-Puiggros contributed reagents/materials/analysis tools, prepared figures and/or tables, reviewed drafts of the paper.
- Didac Mauricio conceived and designed the experiments, analyzed the data, contributed reagents/materials/analysis tools, wrote the paper, prepared figures and/or tables, reviewed drafts of the paper.

Human Ethics

The following information was supplied relating to ethical approvals (i.e., approving body and any reference numbers):

The study was approved by the Ethics Committee of University Hospital Arnau of Vilanova from Lleida.

Data Availability

The following information was supplied regarding data availability:

The raw data and code have been provided as a Supplemental File.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.3928#supplemental-information.

REFERENCES

Ahola AJ, Saraheimo M, Forsblom C, Hietala K, Sintonen H, Groop P-H, FinDiane Study G. 2010. Health-related quality of life in patients with type 1 diabetes-association with diabetic complications (the FinDiane Study). *Nephrology Dialysis Transplantation* **25(6)**:1903–1908 DOI 10.1093/ndt/gfp709.

Alcubierre N, Rubinat E, Traveset A, Martinez-Alonso M, Hernandez M, Jurjo C, Mauricio D. 2014. A prospective cross-sectional study on quality of life and treatment satisfaction in type 2 diabetic patients with retinopathy without other major late diabetic complications. *Health and Quality of Life Outcomes* **12**:131 DOI 10.1186/s12955-014-0131-2.

Alva M, Gray A, Mihaylova B, Clarke P. 2014. The effect of diabetes complications of health-related quality of life: the importance of longitudinal data to address patient heterogeneity. *Health Economics* **23**:487–500 DOI 10.1002/hec.2930.

Bernstein MS, Morabia A, Sloutskis D. 1999. Definition and prevalence of sedentarism in an urban population. *American Journal of Public Health* **89(6)**:862–867 DOI 10.2105/AJPH.89.6.862.

Biderman A, Noff E, Harris SB, Friedman N, Levy A. 2009. Treatment satisfaction of diabetic patients: what are the contributing factors? *Family Practice* **26(2)**:102–108 DOI 10.1093/fampra/cmp007.

Bradley C. 1994. Diabetes treatment satisfaction questionnaire (DTSQ). In: *Handbook of psychology and diabetes: a guide to psychological measurement in diabetes research and practice*. New York: Harwood Academic Publishers, 111–112.

Bradley C, De Pablos-Velasco P, Parhofer KG, Eschwge E, Gönder-Frederick L, Simon D. 2011. PANORAMA: a European study to evaluate quality of life and treatment satisfaction in patients with type 2 diabetes mellitus—Study design. *Primary Care Diabetes* **5(4)**:231–239 DOI 10.1016/j.pcd.2011.04.004.

Bradley C, Speight J. 2002. Patient perceptions of diabetes and diabetes therapy: assessing quality of life. *Diabetes/Metabolism Research and Reviews* **18(Suppl 3)**:S64–S69 DOI 10.1002/dmrr.279.

Bradley C, Todd C, Gorton T, Symonds E, Martin APR. 1999. The development of an individualised questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL. *Qual Life Research* **8**:79–81 DOI 10.1023/A:1026485130100.

Cabrera de León A, Rodríguez-Pérez MDC, Rodríguez-Benjumeda LM, Anía-Lafuente B, Brito-Díaz B, Muros de Fuentes M, Almeida-González D, Batista-Medina M, Aguirre-Jaime A. 2007. Sedentary lifestyle: physical activity duration versus percentage of energy expenditure. *Revista Española de Cardiologia* **60(3)**:244–250 DOI 10.1016/S1885-5857(07)60148-0.

Collins M, O'Sullivan T, Harkins V, Perry I. 2009. Quality of Life and Quality of Care in patients with diabetes experiencing different models of care. *Diabetes Care* **32(4)**:603–605 DOI 10.2337/dc08-1169.

Depablos-Velasco P, Salguero-Chaves E, Mata-Poyo J, Derivas-Otero B, Garcia-Sanchez R, Viguera-Ester P. 2014. Quality of life and satisfaction with treatment in subjects with type 2 diabetes: results in Spain of the PANORAMA study. *Endocrinologia y Nutricion* **61(1)**:18–26 DOI 10.1016/j.endonu.2013.05.005.

Esteban y Peña MM, Hernandez Barrera V, Fernández Cordero X, Gil de Miguel A, Rodríguez Pérez M, Lopez-de Andres A, Jiménez-García R. 2010. Self-perception of health status, mental health and quality of life among adults with diabetes residing in a metropolitan area. *Diabetes & Metabolism* **36(4)**:305–311 DOI 10.1016/j.diabet.2010.02.003.

Fourlanos S, Dotta F, Greenbaum CJ, Palmer JP, Rolandsson O, Colman PG, Harrison LC. 2005. Latent autoimmune diabetes in adults (LADA) should be less latent. *Diabetologia* **48(11)**:2206–2212 DOI 10.1007/s00125-005-1960-7.

Gomis R, Herrera-Pombo J, Calderón A, Rubio-Terrés C, Sarasa P. 2006. Validación del cuestionario "Diabetes treatment satisfaction questionnaire" (DTSQ) en la población española. *Pharmacoeconomics* **3**:7–20.

Hawa MI, Kolb H, Schloot N, Beyan H, Paschou SA, Buzzetti R, Mauricio D, De Leiva A, Yderstraede K, Beck-Neilsen H, Tuomilehto J, Sarti C, Thivolet C, Hadden D, Hunter S, Schernthaner G, Scherbaum WA, Williams R, Brophy S, Pozzilli P, Leslie RD, Action LADA Consortium. 2013. Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: action LADA 7. *Diabetes Care* **36(4)**:908–913 DOI 10.2337/dc12-0931.

Hawa MI, Thivolet C, Mauricio D, Alemanno I, Cipponeri E, Collier D, Hunter S, Buzzetti R, De Leiva A, Pozzilli P, Leslie RD, Action LADA Group. 2009. Metabolic syndrome and autoimmune diabetes: action LADA 3. *Diabetes Care* **32(1)**:160–164 DOI 10.2337/dc08-1419.

Hernandez M, Mollo A, Marsal JR, Esquerda A, Capel I, Puig-Domingo M, Pozzilli P, De Leiva A, Mauricio D, Action LADA Consortium. 2015. Insulin secretion in patients with latent autoimmune diabetes (LADA): half way between type 1 and type 2 diabetes: action LADA 9. *BMC Endocrine Disorders* **15(1)**:1 DOI 10.1186/1472-6823-15-1.

Hervás A, Zabaleta A, De Miguel G, Beldarrain ODJ. 2002. Health related quality of life in patients with diabetes mellitus type 2. *Diabetes Care* **25**:464–470 DOI 10.2337/diacare.25.3.464.

Imayama I, Plotnikoff RC, Courneya KS, Johnson JA. 2011. Determinants of quality of life in adults with type 1 and type 2 diabetes. *Health and Quality of Life Outcomes* **9(1)**:115 DOI 10.1186/1477-7525-9-115.

Isomaa B, Almgren P, Henricsson M, Taskinen MR, Tuomi T, Groop L, Sarelin L. 1999. Chronic complications in patients with slowly progressing autoimmune type 1 diabetes (LADA). *Diabetes Care* **22(8)**:1347–1353 DOI 10.2337/diacare.22.8.1347.

Leslie RD, Kolb H, Schloot NC, Buzzetti R, Mauricio D, De Leiva A, Yderstraede K, Sarti C, Thivolet C. 2008. Diabetes classification: grey zones, sound and smoke: action LADA 1. *Diabetes Metabolism Research and Reviews* **24(7)**:511–519 DOI 10.1002/dmrr.877.

Leslie RD, Palmer J, Schloot NC, Lernmark A. 2016. Diabetes at the crossroads: relevance of disease classification to pathophysiology and treatment. *Diabetologia* **59(1)**:13–20 DOI 10.1007/s00125-015-3789-z.

Mancera-Romero J, Carramiñana Barrera F, Muñoz González L, Guillén-Álvarez P, Murillo-García D, Sánchez-Pérez MR. 2016. Satisfaction of patients with type 2 diabetes mellitus after starting treatment with insulin. *Sociedad Española de Medicina Rural y Generalista* **42(5)**:298–306 DOI 10.1016/j.semerg.2015.06.002.

Mollo A, Hernandez M, Marsal JR, Esquerda A, Rius F, Blanco-Vaca F, Verdaguer J, Pozzilli P, De Leiva A, Mauricio D, Action LADA 8. 2013. Latent autoimmune diabetes in adults is perched between type 1 and type 2: evidence from adults in one region of Spain. *Diabetes Metabolism Research and Reviews* **29(6)**:446–451 DOI 10.1002/dmrr.2411.

Nicolucci A, Cucinotta D, Squatrito S, Lapolla A, Musacchio N, Leotta S, Vitali L, Bulotta A, Nicoziani P, Coronel G, QuoLITy Study Group. 2009. Clinical and socio-economic correlates of quality of life and treatment satisfaction in patients with type 2 diabetes. *Nutrition, Metabolism, and Cardiovascular Diseases* **19(1)**:45–53 DOI 10.1016/j.numecd.2007.12.005.

Oliva J, Fernandez-Bolanos A, Hidalgo A. 2012. Health-related quality of life in diabetic people with different vascular risk. *BMC Public Health* **12(1)**:812 DOI 10.1186/1471-2458-12-812.

R Core Team. 2016. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing. *Available at https://www.r-project.org*.

Shim YT, Lee J, Toh MPHS, Tang WE, Ko Y. 2012. Health-related quality of life and glycaemic control in patients with Type 2 diabetes mellitus in Singapore. *Diabetic Medicine* **29(8)**:e241-8 DOI 10.1111/j.1464-5491.2012.03689.x.

Speight J, Bradley C. 2000. ADDQoL indicates negative impact of diabetes on quality of life despite high levels of satisfaction with treatment [Abstract 225]. *Diabetologia* **43(Suppl 1)**.

Speight J, Reaney MD, Barnard KD. 2009. Not all roads lead to Rome—a review of quality of life measurement in adults with diabetes. *Diabetic Medicine* **26(4)**:315–327 DOI 10.1111/j.1464-5491.2009.02682.x.

Stenstrom G, Gottsater A, Bakhtadze E, Berger B, Sundkvist G. 2005. Latent autoimmune diabetes in adults: definition, prevalence, cell function, and treatment. *Diabetes* **54(Suppl 2)**:S68–S72 DOI 10.2337/diabetes.54.suppl_2.S68.

Sundaram M, Kavookjian J, Patrick JH, Miller L-A, Madhavan SS, Scott VG. 2007. Quality of life, health status and clinical outcomes in Type 2 diabetes patients. *Quality of Life Research* **16(2)**:165–177 DOI 10.1007/s11136-006-9105-0.

Villar-López J, Lizán-Tudela L, Soto-Alvarez J, Peiró Moreno S. 2009. Treatment satisfaction. *Atención Primaria* **41(11)**:637–645 DOI 10.1016/j.aprim.2008.10.021.

Wilson M, Moore MP, Lunt H. 2004. Treatment satisfaction after commencement of insulin in Type 2 diabetes. *Diabetes Research and Clinical Practice* **66(3)**:263–267 DOI 10.1016/j.diabres.2004.04.01.

5.4. Artículo 4

Minerva Granado-Casas, Esmeralda Castelblanco, Anna Ramírez-Morros, Mariona Martín, Nuria Alcubierre, Montserrat Martínez-Alonso, Xavier Valldeperas, Alicia Traveset, Esther Rubinat, Ana Lucas-Martin, Marta Hernández, Núria Alonso, Didac Mauricio. Poorer quality of life and treatment satisfaction is associated with diabetic retinopathy in patients with type 1 diabetes without other advanced late complications. J Clin Med. 2019;8:377.

Resumen

Objetivos

La limitada evidencia científica en el campo de la RD y los resultados percibidos por el paciente en población adulta con DM1, utilizando cuestionarios específicos, condujo a nuestro grupo a desarrollar el presente trabajo. Por tanto, el objetivo del estudio fue evaluar el impacto de la RD en la calidad de vida y satisfacción con el tratamiento de los pacientes con DM1 utilizando cuestionarios específicos. Además, estudiamos la relación con los factores clínicos que podían estar asociados con la calidad de vida y satisfacción con el tratamiento.

Materiales y métodos

El diseño del estudio fue observacional, transversal, y multicéntrico. De los 259 pacientes con DM1 reclutados en el estudio previo publicado por nuestro grupo (101), se seleccionó una muestra de 102 pacientes con RD y 140 sin RD, sin presencia de otras complicaciones tardías de la diabetes. Los criterios de inclusión fueron el diagnóstico de DM1 superior a 12 meses y una edad superior a 18 años. Los criterios de exclusión fueron: enfermedad mental o demencia, ser profesional sanitario, enfermedad cardiovascular previa, pie diabético, presencia de cualquier enfermedad visual que pudiera influir en los resultados, embarazo y presencia de otras complicaciones mayores relacionadas con la diabetes. Los cuestionarios *Audit of Diabetes-Dependent Quality of Life* (ADDQoL-19) y el *Diabetes Treatment Satisfaction Questionnaire* (DTSQ) se administraron mediante entrevista personal con cada paciente. Las variables clínicas fueron recogidas mediante anamnesis, exploración física, determinación de variables de laboratorio en sangre y orina, y una revisión exhaustiva de las historias clínicas. El análisis de los datos incluyó modelos bivariables y multivariables.

Resultados

Los pacientes con RD mostraron una peor percepción de la calidad de vida actual, y en algunos aspectos específicos de la calidad de vida como la vida laboral y dependencia en comparación con el grupo sin RD. Además, el grupo de participantes con RD tuvo un menor impacto promedio

ponderado de los ítems del cuestionario de calidad de vida (ADDQoL-19). En el análisis multivariable, la RD y el hecho de ser exfumador se asociaron con una menor calidad de vida actual, vida laboral y dependencia. Sin embargo, la RD no se asoció con el impacto promedio ponderado del cuestionario ADDQoL-19. Tampoco se observaron asociaciones entre los distintos grados de RD y la calidad de vida. Además, la edad estuvo negativamente relacionada con la calidad de vida; la actividad física y el tratamiento con insulina tuvieron una asociación positiva con ésta. En relación con la satisfacción con el tratamiento, la RD se relacionó con una mayor percepción en la frecuencia de hipoglucemias. No se observó asociación entre la RD y la satisfacción con el tratamiento global o la frecuencia de hiperglucemias percibidas. Los factores clínicos negativamente asociados con la satisfacción con el tratamiento fueron el sexo masculino y la duración de la diabetes.

Conclusiones

En los pacientes con DM1, la presencia de RD se relacionó con una peor percepción en algunos aspectos importantes de la calidad de vida, como la calidad de vida actual, la vida laboral y la dependencia. Además, en relación con la satisfacción con el tratamiento, la RD se asoció con una mayor percepción en la frecuencia de hipoglucemias.

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Article

Poorer Quality of Life and Treatment Satisfaction is Associated with Diabetic Retinopathy in Patients with Type 1 Diabetes without Other Advanced Late Complications

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Abstract: Diabetic retinopathy (DR) may potentially cause vision loss and affect the patient's quality of life (QoL) and treatment satisfaction (TS). Using specific tools, we aimed to assess the impact of DR and clinical factors on the QoL and TS in patients with type 1 diabetes. This was a cross-sectional, two-centre study. A sample of 102 patients with DR and 140 non-DR patients were compared. The Audit of Diabetes-Dependent Quality of Life (ADDQoL-19) and Diabetes Treatment Satisfaction Questionnaire (DTSQ-s) were administered. Data analysis included bivariate and multivariable analysis. Patients with DR showed a poorer perception of present QoL ($p = 0.039$), work life ($p = 0.037$), dependence ($p = 0.010$), and had a lower average weighted impact (AWI) score ($p = 0.045$). The multivariable analysis showed that DR was associated with a lower present QoL ($p = 0.040$), work life ($p = 0.036$) and dependence ($p = 0.016$). With regards to TS, DR was associated with a higher perceived frequency of hypoglycaemia ($p = 0.019$). In patients with type 1 diabetes, the presence of DR is associated with a poorer perception of their QoL. With regard to TS, these subjects also show a higher perceived frequency of hypoglycaemia.

Keywords: diabetic retinopathy; type 1 diabetes; quality of life; treatment satisfaction; patient-reported outcomes

1. Introduction

Diabetic retinopathy (DR) is a significant diabetic complication in patients with type 1 diabetes [1]. This complication is a potential cause of vision loss in the diabetic population that can negatively affect their quality of life (QoL) [2]. Moreover, DR is also associated with an increased risk for all-cause mortality and cardiovascular disease in patients with type 1 diabetes [3].

QoL is a multidimensional, subjective and dynamic construct comprising the individual's subjective perception of the physical, psychological and social well-being aspects of his or her life [4]. Treatment satisfaction (TS) is an individual's subjective appraisal of his or her experience of the treatment, including both the process and results [4]. From the patient's point of view, QoL and TS as patient-reported outcomes (PROs) are two important measures because these are often stronger determinants of medical outcomes such as hospitalization, mortality and the presence of complications [5,6]. Furthermore, an assessment of PROs has been accepted to complement visual acuity information in clinical trials, interventions or research [7]. Regarding QoL and TS, recent studies have found that having DR negatively impacts the QoL and TS in patients with type 2 diabetes [8–14].

To our knowledge, only one study with a cross-sectional design has assessed the relationship between QoL and the presence of DR in patients with type 1 diabetes using a diabetes-specific QoL questionnaire [15]. So far, all of the published scientific evidence regarding this issue used generic instruments or visual function scales to appraise the impact of DR in the QoL of patients with type 1 diabetes [16–30]. The FinnDiane study, which included a large sample of patients with type 1 diabetes, did not find any association between the presence of DR and health-related quality of life (HRQoL) using a generic instrument [16]; it should be pointed out that, in this study, DR was determined to be present if the subject had ever received treatment for DR and that 53% of the patients had also diabetic nephropathy, which could influence the results. Other cross-sectional studies with large samples of patients with type 1 diabetes did not report any association between DR and HRQoL [17,23,24]. However, other prospective cohort and cross-sectional studies observed a negative impact of DR on HRQoL in patients with type 1 diabetes using generic instruments [25,28]. Two recently published studies found a lower HRQoL in patients with type 1 diabetes and more severe DR in the presence of other diabetic complications such as neuropathy, nephropathy and cardiovascular disease [29,30]. The Wisconsin Epidemiologic Study of Diabetic Retinopathy did not find changes in the QoL with the presence of DR over time using a visual function scale [18,19]; nevertheless, researchers included a study sample of patients with other important diabetic complications that could influence the results. Furthermore, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study designed to assess the effects of intensive insulin treatment and risk factors on the patient-reported visual function in patients with type 1 diabetes did not find changes with DR [20]. Although researchers used a diabetes-specific QoL questionnaire and a visual function scale, these patients also showed other diabetic complications. Other studies performed in patients with type 1 and type 2 diabetes using a visual function scale related lower scores with DR [21,22]; however, the study subjects had also other diabetic complications and comorbidities such as cardiovascular diseases, cancer, arthritis or rheumatism and hearing problems. Regarding DR and PROs, it has been pointed out that generic instruments have a lack of sensitivity to assess specific domains of QoL that are related to diabetic complications [7]. This is an important point because the scientific evidence has shown that patients can report a good patient-reported health status, often measured with generic questionnaires, even though their diabetes-specific QoL is negative [8,9,31]. Besides, visual function scales cannot be regarded as sufficient to assess the diabetes-related QoL due to the lack of specific quality of life domains related to diabetes. For this reason, the disease-specific questionnaires, but not the generic tools, are the more adequate instruments to measure specific disease-related QoL [31].

To the best of our knowledge, there have not been any studies primarily designed to assess the impact of DR on QoL and TS in patients with type 1 diabetes. In addition, there are not any studies that have assessed the impact of DR on QoL and TS that included a well-defined sample of patients with

type 1 diabetes and that used diabetes-specific questionnaires. Therefore, we hypothesized that patients with type 1 diabetes who have been diagnosed with DR have a lower perception of their QoL and TS in comparison to their non-DR counterparts. The aim of the study was to assess the association of DR with QoL and TS in adult type 1 diabetic patients with DR as compared to a group of patients without this condition. Additionally, we also determined which clinical factors that could be related to QoL and TS.

2. Materials and Methods

This was a cross-sectional, two-centre study. Participants were patients with type 1 diabetes regularly cared for at their reference hospital from two health care regions (Lleida and Badalona). The recruitment took place between January 2013 and May 2015. From a total number of 330 patients with type 1 diabetes that were invited to participate, 276 accepted to be included in the study, while 17 could not be included because of exclusion criteria. Finally, a total sample of 259 patients with type 1 diabetes was included in the previously published study [32]. From this sample, 16 patients were excluded because they had not had their eyes assessed; furthermore, one patient was excluded because he did not answer the questionnaires. A final sample of 102 patients with DR and 140 without DR were included. A detailed description of the characteristics of the study are provided elsewhere [32]. The inclusion criteria were: having the diagnosis of type 1 diabetes, a current age greater than 18 years, and a disease duration of more than 1 year. We intended to avoid the inclusion of other advanced late diabetic complications to exclude their negative impact on top of DR. Thus, the exclusion criteria were as follows: psychological or cognitive deterioration (e.g., mental diseases or dementia); being a healthcare professional; the presence of previous clinical cardiovascular diseases (ischemic heart disease, cerebrovascular disease, peripheral arterial disease and heart failure) or diabetic foot disease; the presence of any eye disease that could influence the results (macular oedema, media opacity that hindered assessment of the retina, other concomitant retinal pathology, ophthalmological surgery in the previous year and laser treatments during the six months before the study visit); pregnancy; and the presence of other advanced diabetic late complications such as macroalbuminuria (urine albumin/creatinine ratio > 299 mg/g) and renal insufficiency (estimated glomerular filtration rate < 60 mL/min). In the DR group, three patients had glaucoma and one patient had myopia superior to 5 dioptres. In the non-DR group, three patients had myopia superior to 5 dioptres. The assessment of DR was performed and classified by an expert ophthalmologist according to the international clinical classification system [33]. Optic coherence tomography measurements were performed using spectral-domain OCT (SD-OCT) (Cirrus HD-OCT, model 4000, Carl Zeiss Meditec, Dublin, CA, USA) and deep Enhanced Imaging (EDI-OCT), with HD 5 Line Raster scan pattern. An ophthalmologist assessed and classified DR as follows: no apparent retinopathy, mild non-proliferative retinopathy, moderate non-proliferative retinopathy, severe non-proliferative retinopathy and proliferative retinopathy. The ethics committee of each of the two participating centres (Ethics Committee of the University Hospital Arnau de Vilanova, and Ethics Committee of the University Hospital Germans Trias i Pujol) approved the study. Written informed consent form was obtained from all participants.

2.1. Clinical Variables

Anthropometric measures, including waist circumference, weight, height and body mass index (BMI), blood pressure and laboratory variables were determined according to standard procedures. Cardiovascular disease was excluded based on detailed anamnesis and careful review of all clinical records. Besides, predefined questionnaires specially designed for the study were used for conduction of personal interviews and data extraction for collection of all other variables: medication use, physical activity, educational level, ethanol consumption and smoking habit. Hypertension and dyslipidaemia were defined by the use of specific medication for treatment of these two conditions. Microalbuminuria was defined as an albumin creatinine ratio above 30 mg/g. Physical activity was assessed according to two previously validated methods [34,35]. This was classified as regular physical activity (if the patients spent more than 25 min/day in any activity that requires 4 METS (the metabolic equivalent), or as sedentary if

the participants spent up to 25 min/day. Ethanol consumption (g per day) was estimated from frequency, beverage type, and average amount according to previously validated methods [32].

2.2. Quality of Life

The Audit of Diabetes-Dependent Quality of Life (ADDQoL-19) questionnaire in Spanish was used to assess the QoL of the patients. This is an instrument specifically designed for its use in subjects with diabetes, and validated in the diabetic Spanish population [36–38]. The questionnaire consists of 21 items, 19 of which are related to specific life domains and are scored multiplying the impact rating (from −3 to +1) by the importance rating (from +3 to 0); these produce scores ranging from +3 to −9 points. The overall score is the mean of 19 specific domains and is assigned as the average weighted impact score (AWI); this ranges from +3 (highest QoL) to −9 (poorest QoL). Additionally, there are two overview items that are scored separately; they measure present QoL ranging from +3 (excellent) to −3 (very bad) and diabetes-specific QoL, which is scored from −3 (maximum negative impact) to +1 (maximum positive impact). Two trained researchers (MG-C and MM) conducted individual interviews with all of the patients. All questionnaires have been recommended by the World Health Organization and the International Diabetes Federation to assess the PROs [6].

2.3. Treatment Satisfaction

The Diabetes Treatment Satisfaction Questionnaire-status version (DTSQ-s) in Spanish, a diabetes-specific questionnaire validated for Spanish diabetic subjects was administered [39,40]. This questionnaire consists of 8 items scored on a 6-point scale from 0 (very unsatisfied) to 6 (very satisfied). The final score is calculated by summing up the individual scores from six items (current treatment, convenience, flexibility, understanding, recommend to others and continue with); this final score ranges from 36 (very satisfied) to 0 (very unsatisfied). Additionally, two items are calculated separately and measure the perceived frequency of hyperglycaemia and hypoglycaemia, respectively; they are scored from 0 (never) to 6 (always).

2.4. Sample Size

The sample size was determined by using the standard deviation for the ADDQoL items from a previously published study on DR and QoL that was performed in patients with type 2 diabetes by our group in the same region [8]. Then, we assumed that the differences would be similar in patients with type 1 diabetes for present QoL, diabetes-specific QoL and AWI items. A sample of 54 patients with DR and 54 without DR was deemed necessary to detect significant differences between both groups. We used the Mann-Whitney test and a statistical power of 80% with a significance level of 5%. From our previous study, a sufficiently large number of patients with type 1 diabetes was available to fulfil the sample size [32].

2.5. Statistical Methods

The descriptive analysis of quantitative variables included mean and standard deviation for the normally distributed variables, as well as median and interquartile intervals. Qualitative variables were summarized by absolute and relative frequencies. Bivariate analysis comparing the groups of patients with and without diabetic retinopathy included the *t*-test (or the Mann–Whitney test for non-normally distributed variables) and the chi-squared test for quantitative and qualitative patient characteristics as well as QoL and TS outcomes (including overall and subscale scores), respectively. Simple linear regression analysis was performed to assess the univariate association of patients' characteristics with overall QoL and TS, as well as each of their domains. Those domains showing a significant univariate association with DR were evaluated in a linear multivariable regression analysis to assess the statistical significance of their association after having adjusted by other patients' characteristics. For this purpose, in a first step and separately for each domain associated with DR, we estimated a multivariable linear (or ordinary least squares) regression model including all variables with a p-value <0.25 according to

the likelihood ratio test (LRT). In the next step, we used the same method (LRT) to simplify the model by dropping non-significant variables, starting with the one with the highest and non-significant p-value, until obtaining a model with variables showing a significant contribution according to the LRT. Afterwards, we checked the possible additional significant contribution of any other patient characteristics. The final proposed regression models included any possible interactions involving the patient characteristics that were included in the corresponding regression model. We used a significance level of 0.05 and the open-source program R for all statistical analysis [41].

3. Results

The clinical and demographic characteristics of the participants are shown in Table 1. Patients with DR were older ($p = 0.004$), had higher systolic blood pressures ($p = 0.003$), higher glycated haemoglobin (HbA1c) ($p < 0.001$), longer diabetes duration ($p < 0.001$) and lower high density lipoprotein (HDL) concentrations ($p = 0.015$) in comparison with non-DR patients. Furthermore, the former had a higher frequency of hypertension ($p < 0.001$) and microalbuminuria ($p = 0.014$).

Table 1. Clinical and demographic characteristics of the study groups.

Characteristics	No DR (n = 140)	DR (n = 102)	p
Age (years)	42.1 ± 10.3	46.2 ± 10.8	0.004
Sex (men)	62 (44.3)	47 (46.1)	0.884
Race (Caucasian)	137 (97.9)	101 (99.0)	0.640
Study site			0.168
Badalona	85 (60.7)	52 (51.0)	
Lleida	55 (39.3)	50 (49.0)	
Educational level			0.069
Less than primary school	8 (5.9)	4 (4.1)	
Completed primary school	34 (25.2)	35 (36.5)	
Secondary/high school	49 (36.3)	39 (40.6)	
Graduate school or higher	44 (32.6)	18 (18.8)	
Smoking			0.282
Non or former smoker	106 (75.7)	70 (68.6)	
Yes	34 (24.3)	32 (31.4)	
Regular physical activity	98 (70.0)	77 (75.5)	0.425
Insulin dose (UI/kg/day)	0.57 [0.41; 0.75]	0.65 [0.45; 0.86]	0.027
Waist circumference (cm)	86.0 [79.0; 95.0]	90.0 [81.0; 100.0]	0.050
Systolic blood pressure (mmHg)	120.0 [110.0; 134.0]	130.0 [118.0; 140.0]	0.003
Diastolic blood pressure (mmHg)	74.2 ± 9.6	73.6 ± 9.3	0.666
Body mass index (kg/m^2)	24.7 [22.4; 27.3]	25.9 [23.1; 28.3]	0.091
Hypertension	20 (14.3)	40 (39.2)	<0.001
Dyslipidaemia	49 (35.0)	48 (48.0)	0.056
Microalbuminuria	5 (3.6)	13 (12.9)	0.014
Diabetes duration (years)	17.0 [11.0; 22.0]	26.5 [19.2; 33.0]	<0.001
Glaucoma	–	3 (2.9)	–
Myopia over 5 dioptres	3 (2.1)	1 (0.9)	–
HbA1c (%)	7.3 [6.8; 7.8]	7.7 [7.2; 8.5]	<0.001
HbA1c (mmol/mol)	56.3 [50.8; 61.7]	60.7 [55.2; 69.4]	<0.001
Total cholesterol (mg/dL)	177.0 [164.0; 201.0]	176 [158.0; 200.0]	0.560
HDL cholesterol (mg/dL)	65.5 [55.0; 75.0]	59.5 [51.0; 71.0]	0.015
LDL cholesterol (mg/dL)	102.0 [87.0; 115.0]	100.0 [83.2; 119.0]	0.777
Triglycerides (mg/dL)	64.0 [49.8; 80.0]	68.0 [53.0; 89.8]	0.084
Ethanol consumption (g/day)	5.6 ± 9.2	6.5 ± 11.6	0.686

Data are shown as median [interquartile], means ± SD or n (%). DR, diabetic retinopathy; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein.

3.1. Diabetes-Related Quality of Life

Patients with DR showed lower present QoL ($p = 0.039$) in comparison with their counterparts without DR (Table 2). Work life and dependence scores were also lower in patients with DR ($p = 0.037$ and $p = 0.010$, respectively). Although no differences between the groups in the diabetes-specific QoL item ($p = 0.069$) were observed, the AWI score showed a poorer QoL in patients with DR ($p = 0.045$). In the multivariable analysis, DR was associated with a low score in present QoL ($\beta = -0.25$; $p = 0.040$) and with a poorer perception of QoL items such as work life ($\beta = -0.78$; $p = 0.036$) and dependence ($\beta = -0.83$; $p = 0.016$) (Table 3). Together with smoking habit, these variables only explained a 2.0%, 2.3% and 3.8% of the variability of those scores, respectively. On the other hand, no association was found between DR and the AWI score ($p = 0.111$) after adjusting for smoking status, age, insulin dose and physical activity (Supplemental Table S1). However, there was a negative correlation between older age and the AWI score ($p = 0.015$). Conversely, physical activity and the daily insulin dose showed a positive association with a higher AWI score ($p = 0.005$ and $p = 0.028$, respectively).

Table 2. Bivariate analysis for the Audit of Diabetes Dependent Quality of Life (ADDQoL-19) and the Diabetes Treatment Satisfaction Questionnaire-status (DTSQ-s) by diabetic retinopathy status.

Items	No DR ($n = 140$)	DR ($n = 102$)	p
ADDQoL-19			
Present QoL	1.00 [1.00; 2.00]	1.00 [0.00; 1.00]	0.039
Diabetes-specific QoL	−1.00 [−2.00; −1.00]	−2.00 [−2.00; −1.00]	0.069
Leisure	−1.00 [−3.00; 0.00]	−2.00 [−3.75; 0.00]	0.198
Work life	0.00 [−3.00; 0.00]	−2.00 [−4.00; 0.00]	0.037
Travel	−2.00 [−4.00; 0.00]	−1.00 [−3.75; 0.00]	0.242
Holidays	−2.00 [−3.00; 0.00]	−2.00 [−3.00; 0.00]	0.987
Physical ability	−2.00 [−4.00; 0.00]	−2.00 [−4.00; 0.00]	0.306
Family life	0.00 [−3.00; 0.00]	0.00 [−3.00; 0.00]	0.333
Friends/social life	0.00 [0.00; 0.00]	0.00 [0.00; 0.00]	0.556
Personal relationships	0.00 [−2.00; 0.00]	0.00 [−2.00; 0.00]	0.122
Sex life	0.00 [−2.00; 0.00]	0.00 [−3.00; 0.00]	0.054
Physical appearance	0.00 [−1.00; 0.00]	0.00 [−2.00; 0.00]	0.144
Self-confidence	0.00 [−2.25; 0.00]	0.00 [−3.75; 0.00]	0.315
Motivation	0.00 [−2.00; 0.00]	0.00 [−2.00; 0.00]	0.950
Society/people's reactions	0.00 [0.00; 0.00]	0.00 [0.00; 0.00]	0.301
Future	−2.00 [−4.00; 0.00]	−2.00 [−6.00; 0.00]	0.144
Finances	0.00 [0.00; 0.00]	0.00 [0.00; 0.00]	0.070
Living conditions	0.00 [0.00; 0.00]	0.00 [0.00; 0.00]	0.853
Dependence	0.00 [−3.00; 0.00]	−2.00 [−4.00; 0.00]	0.010
Freedom to eat	−4.00 [−6.00; −2.00]	−4.00 [−9.00; −2.00]	0.447
Freedom to drink	−2.00 [−4.50; 0.00]	−2.50 [−6.00; 0.00]	0.270
AWI	−1.32 [−2.05; −0.68]	−1.61 [−2.66; −0.94]	0.045
DTSQ-s			
Hyperglycaemia frequency perception	3.00 [2.00; 4.00]	3.00 [2.00; 4.00]	0.385
Hypoglycaemia frequency perception	2.00 [2.00; 3.00]	3.00 [2.00; 4.00]	0.022
Final score	28.00 [23.00; 31.00]	28.00 [24.00; 31.80]	0.987

Data are shown as median [interquartile]. AWI, average weighted impact score; DR, diabetic retinopathy; QoL, quality of life.

To further explore the effect of advanced DR stages on QoL and TS, we analyzed differences between study groups: without DR, with mild DR (grade 1), and more than mild DR (grades 2–4) (Supplemental Table S2). The comparison among the 3 groups revealed no statistical differences. However, head to head comparison between groups yielded some differences. For instance, patients with mild DR showed a poorer perception of the present QoL ($p = 0.040$), dependence ($p = 0.005$), and an AWI score ($p = 0.038$) in comparison with non-DR patients (Supplemental Table S2). Furthermore, patients with advanced (more than mild) DR had a lower AWI score ($p = 0.032$) in

comparison with the non-DR group. No statistical differences were observed between groups with the other items (Supplemental Table S2).

Table 3. Multivariable linear regression models for present quality of life, work life and dependence as reported on the Audit of Diabetes Dependent Quality of Life (ADDQoL-19) questionnaire.

	Present QoL [1]		Work Life [2]		Dependence [3]	
	Estimate β (95% CI)	*p*	Estimate β (95% CI)	*p*	Estimate β (95% CI)	*p*
(Intercept)	1.00 (0.83; 1.17)	<0.001	−1.81 (−2.31; −1.32)	<0.001	−2.45 (−1.51; −1.73)	<0.001
Retinopathy	−0.25 (−0.49; −0.01)	0.040	−0.78 (−1.50; −0.05)	0.036	−0.83 (−1.51; −0.16)	0.016
Smoker, current	0.12 (−0.14; 0.39)	0.361	0.07 (−0.74; 0.87)	0.867	0.49 (−0.26; 1.24)	0.197

No significant contribution of the variables according to the likelihood ratio test: age, sex, race, educational level, insulin dose, physical activity, hypertension, dyslipidaemia, diabetes duration, body mass index, waist circumference, microalbuminuria, glycated haemoglobin, systolic and diastolic blood pressure, HDL and LDL cholesterol and triglycerides. Model estimates (β) refers to the overall mean (intercept) and the estimated change in the score mean between patient with and without the corresponding characteristic. [1] Coefficient of determination, r-squared: 2.0%. [2] Coefficient of determination, r-squared: 2.3%. [3] Coefficient of determination, r-squared: 3.8%. QoL, quality of life.

3.2. Treatment Satisfaction

The perception of the frequency of hypoglycaemia was higher in the DR group ($p = 0.022$) (Table 2). However, no significant differences were observed between the groups in terms of hyperglycaemia frequency perception and the DTSQ-s final score. We did not find any difference among groups defined by the status of DR in any of the DTSQ-s items (Supplemental Table S2). In the multivariable analysis for the hypoglycaemia frequency perception item of the DTSQ-s, we observed a higher hypoglycaemia frequency perception in subjects with DR (β = 0.019; $p = 0.019$) (Table 4). In addition, male sex was associated with a lower hypoglycaemia frequency perception (β = −0.60; $p = 0.001$). DR together with male sex only explained 6.3% of the variability. In Supplemental Table S3, the multivariable analysis of the DTSQ-s final score did not show any relationship with DR ($p = 0.244$). Only sex and diabetes duration were associated with the DTSQ-s final score.

Table 4. Multivariable linear regression model for hypoglycaemia frequency perception of the Diabetes Treatment Satisfaction Questionnaire-status (DTSQ-s).

	Estimate β (95% CI)	*p*
(Intercept)	2.91 (2.62; 3.20)	<0.001
Retinopathy	0.44 (0.07; 0.80)	0.019
Sex, male	−0.60 (−0.96; −0.24)	0.001

No significant contribution of the variables according to the likelihood ratio test: age, race, educational level, insulin dose, physical activity, hypertension, dyslipidaemia, diabetes duration, body mass index, waist circumference, smoking, systolic and diastolic blood pressure, triglycerides, glycated haemoglobin, microalbuminuria, HDL and LDL cholesterol. Model estimates (β) refers to the overall mean (intercept) and the estimated change in the score mean between patient with and without the corresponding characteristic. Coefficient of determination, *r*-squared: 6.3%.

4. Discussion

Our results indicate that patients with type 1 diabetes and DR had a poorer QoL than those without DR. In addition, DR is associated with poorer individual items related to QoL, i.e., present QoL, work life and dependence. Additionally, older age was also associated with a poorer QoL; however, physical activity and insulin dose were associated with a higher QoL. In terms of overall TS, although no difference between the two groups was observed, DR was associated with a higher hypoglycaemia frequency perception. In addition, a longer diabetes duration in men was associated with higher TS.

The current study showed a poorer perception of the QoL in the presence of DR; this could be due to the fact that DR is a condition that more frequently develops in those patients with poorer

management of the disease and less healthy lifestyle behaviour. This could explain, at least in part, the poorer perceived QoL of patients with DR in comparison with those without DR. However, there is only one previous cross-sectional study that has assessed the QoL in patients with type 1 diabetes using a diabetes-specific QoL instrument [15]. That study did not find any association between DR and QoL, which is in contrast with our results. Nevertheless, this could be because patients in that study had a high frequency of advanced late complications, such as diabetic foot disease, which could be potential confounders. In addition, the previous study was not specifically designed to assess the relationship between DR and QoL; the authors studied a sample of patients with type 1 and type 2 diabetes together, with a small sample of patients with DR (n = 74) [15]. Other cross-sectional studies that focused on patients with type 1 diabetes and used generic instruments to measure QoL also did not find an association between DR and QoL [16,17,24]. Fenwick et al. [23] performed a cross-sectional study to assess the impact of DR on the QoL with a sample of patients that included both type 1 and type 2 diabetes. They did not find any association between DR and QoL because they used a generic instrument; besides, these cross-sectional studies were not specifically designed to assess the relationship between the QoL and DR in this population. Nevertheless, a prospective study performed on patients with type 1 diabetes using generic instruments found a negative relationship between the presence of late diabetic complications and HRQoL [25]. However, these patients had a higher frequency of comorbidities and other complications apart from DR. Peasgood et al. [28] conducted a post hoc analysis from an interventional study and observed a decreased HRQoL in patients with type 1 diabetes who also had DR. These results are consistent with the results of the current study. Although they also used generic instruments to measure a specific condition associated with diabetes, the sample showed other diabetic complications, which were self-reported; all of these characteristics could influence the results. Furthermore, another cross-sectional study involving patients with type 1 diabetes observed a lower HRQoL in patients with severe DR; this is similar to our findings, although their results were not adjusted for other complications [29]. There are two cross-sectional studies performed with a sample of patients with type 1 and type 2 diabetes that found a lower HRQoL in the presence of DR [26,27]. These are similar findings to the current study, even though the authors used generic instruments and data from both types of diabetes were pooled. A previous study performed on patients with type 2 diabetes by our group showed the negative impact of the presence and severity of DR on the QoL [8]. Additionally, the PANORAMA study, which was conducted with a large sample of patients with type 2 diabetes, also showed that a negative perception of QoL was associated with the presence of DR [9]; this is similar to the current results in patients with type 1 diabetes, even though the two types of diabetes have remarkably different characteristics. There are other studies that yielded results that are discordant with our findings. First, the Wisconsin Epidemiologic Study for Diabetic Retinopathy did not find changes in the QoL with the presence and severity of DR [18,19]. We should point out that in that study the authors used a visual function scale to assess the diabetes-specific QoL. Furthermore, a relevant proportion of the study subjects had other diabetic complications that could significantly impact on QoL, such as nephropathy, neuropathy, cardiovascular diseases and limb amputations. Finally, the DCCT/EDIC study did not observe a relationship of QoL with DR [20]; although they used a diabetes-specific instrument and a visual function scale, again the study subjects showed other complications that could influence QoL.

The factor associated with a poorer QoL was advanced age; this is in line with our previous results in subjects with type 2 diabetes [42]. Nyanzi et al. [15] found a negative relationship between age and some aspects of QoL, which is similar to our results; moreover, in line with our study, they did not find any association between smoking status and perceived QoL. Other studies performed in patients with type 1 and type 2 diabetes also found that a reduced QoL was associated with older age [9,24,43,44]. However, a cross-sectional study of patients with type 2 diabetes did not find any association between QoL and these factors, despite using a diabetes-specific QoL instrument [14]. On the other hand, physical activity was associated with a higher QoL in patients with type 1 diabetes, which is in line with our previously published results about patients with type 2 diabetes [8,42].

However, we could not identify any study that has specifically assessed this issue in the diabetic population. The association of the daily insulin dose with a higher QoL has not been described in type 1 diabetes. We have no clear explanation for this finding. Lastly, emotional factors, such as the lack of optimism and a depressive style, contribute to impairing the QoL in women with type 1 diabetes [44]. However, in the current study we did not find any statistical difference between men and women in the emotional items of the QoL questionnaire.

In the current study, the DTSQ-s final score was neither different between the two study groups nor correlated with the presence of DR; this is similar to the results of the recent PANORAMA study and other studies performed on patients with type 2 diabetes [8,9,45]. However, no studies have assessed the relationship between DR and TS in patients with type 1 diabetes specifically. Furthermore, we found that DR was associated with a higher hypoglycaemia frequency perception. This increased perception of hypoglycaemia is probably associated with poorer glycaemic control, which is associated with a high risk for the development of diabetic complications such as DR [3]. Another factor that may influence this perception in patients with type 1 diabetes is ethanol consumption. However, there were no differences between both study groups in ethanol intake. A longer diabetes duration in men was associated with higher TS and a lower hypoglycaemia frequency perception; this is also in line with our previous results [8,42] and with other cross-sectional studies performed in patients with type 2 diabetes [9,45].

This study has several limitations. A causality association between QoL, TS and DR in patients with type 1 diabetes cannot be established due to the cross-sectional study design; additionally, changes over time in terms of QoL and TS cannot be determined by this study. In addition, hypoglycaemia unawareness and the frequency of self-blood glucose monitoring are factors that may influence the hypoglycaemia frequency perception in patients with type 1 diabetes. The absence of data on these aspects in our study is another limitation. Furthermore, it is well-known that insulin pump therapy is a treatment option for those patients with recurrent episodes of severe hypoglycaemia. Therefore, this treatment option may also have an impact on the perception of hypoglycaemia frequency; unfortunately, although the proportion of patients treated with pump therapy is low in our region, we did not collect data on this mode of therapy. Unfortunately, in the current study we did not assess the visual function of the study participants. In this regard, we should point out that the impact of DR on QoL is mainly produced by impairment of the visual function. Furthermore, although we could analyse the effect of advanced DR stages, the number of patients with advanced DR (moderate, severe and proliferative DR) was very low; for this reason, we cannot draw any conclusion as to whether patients with more severe DR are those than have poorer QoL and treatment satisfaction outcomes. This also applies to conditions known to produce visual impairment (e.g., myopia) that were present in a low number of participants. Although DR was significantly associated with specific QoL domains and overall diabetic treatment satisfaction, according to our results, there is a high percentage of variability in these patient-reported outcomes that remains unexplained. Actually, some other factors or comorbidities associated with DR, that were not assessed in the current study, could have a relevant contribution to explain our findings on QoL and TS. For instance, although we used diabetic foot disease as an exclusion criterion, we did not assess diabetic neuropathy in this sample of patients, a complication that could affect the QoL and TS of the patients. All the limitations mentioned above call for caution when interpreting the current results. Further studies are clearly needed to address all the aforementioned issues, especially those in relation to eye-related burden, i.e., the contribution of the impairment of visual function and the impact of advanced stages of DR.

On the other hand, this study has several strengths. This is the first study that has assessed the potential relationship between QoL and TS in adult patients with type 1 diabetes and DR by using diabetes-specific QoL and TS questionnaires. Many studies have used generic instruments to assess QoL. In point of fact, generic instruments cannot assess the impact of a specific condition on the aspects of patient's life due to a demonstrated lack of sensitivity of these instruments; this has been described in scientific literature [5–7]. Additionally, we recruited a relevant number of patients with type 1

diabetes without other diabetic complications and comorbid conditions in this two-centre study and included a representative sample of subjects.

5. Conclusions

In conclusion, DR was associated with poorer QoL and TS in patients with type 1 diabetes. Moreover, DR was associated with a higher hypoglycaemia frequency perception. Finally, the current results have implications for potential future research because there has been no other study that specifically assesses the impact of DR on the QoL and TS of adult patients with type 1 diabetes. Future research should lead to the identification of the individual contribution of each of the relevant factors on these patient-reported outcomes.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/8/3/377/s1, Table S1: Multivariate linear regression for the Audit of Diabetes Dependent Quality of Life (ADDQoL-19) average weighted impact score, Table S2: Multivariate linear regression for the Diabetes Treatment Satisfaction Questionnaire-status (DTSQ-s) final score.

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References

1. Cho, N.H.; Kirigia, J.; Mbanya, J.C.; Ogurstova, K.; Guariguata, L.; Rathmann, W.; Roglic, G.; Forouhi, N.G.; Dajani, R.; Esteghamati, A.; et al. IDF Diabetes Atlas. Available online: https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/134-idf-diabetes-atlas-8th-edition.html (accessed on 3 September 2018).
2. Hendrick, A.M.; Gibson, M.V.; Kulshreshtha, A. Diabetic Retinopathy. *Prim. Care* **2015**, *42*, 451–464. [CrossRef] [PubMed]
3. Van Hecke, M.V.; Dekker, J.M.; Stehouwer, C.D.A.; Polak, B.C.P.; Fuller, J.H.; Sjolie, A.K.; Kofinis, A.; Rottiers, R.; Porta, M.; Chaturvedi, N. Diabetic retinopathy is associated with mortality and cardiovascular disease incidence: The EURODIAB prospective complications study. *Diabetes Care* **2005**, *28*, 1383–1389. [CrossRef] [PubMed]
4. Speight, J.; Reaney, M.D.; Barnard, K.D. Not all roads lead to Rome—A review of quality of life measurement in adults with diabetes. *Diabet. Med.* **2009**, *26*, 315–327. [CrossRef]
5. Rubin, R.R.; Peyrot, M. Quality of life and diabetes. *Diabetes Metab. Res. Rev.* **1999**, *15*, 205–218. [CrossRef]
6. Sánchez-Lora, F.J.; Santana, T.T.; Trigueros, A.G. Instrumentos específicos de medida de la calidad de vida relacionada con la salud en la diabetes mellitus tipo 2 disponibles en España. *Med. Clin.* **2010**, *135*, 658–664. [CrossRef] [PubMed]
7. Fenwick, E.K.; Pesudovs, K.; Rees, G.; Dirani, M.; Kawasaki, R.; Wong, T.Y.; Lamoureux, E.L. The impact of diabetic retinopathy: Understanding the patient's perspective. *Br. J. Ophthalmol.* **2010**, *95*, 774–782. [CrossRef]
8. Alcubierre, N.; Rubinat, E.; Traveset, A.; Martinez-Alonso, M.; Hernandez, M.; Jurjo, C.; Mauricio, D. A prospective cross-sectional study on quality of life and treatment satisfaction in type 2 diabetic patients with retinopathy without other major late diabetic complications. *Health Qual. Life Outcomes* **2014**, *12*, 131. [CrossRef] [PubMed]

9. Bradley, C.; Eschwège, E.; de Pablos-Velasco, P.; Parhofer, K.G.; Simon, D.; Vandenberghe, H.; Gönder-Frederick, L. Predictors of quality of life and other patient-reported outcomes in the PANORAMA multinational study of people with type 2 diabetes. *Diabetes Care* **2018**, *41*, 267–276. [CrossRef]
10. Man, R.E.K.; Fenwick, E.K.; Sabanayagam, C.; Li, L.J.; Tey, C.S.; Soon, H.J.T.; Cheung, G.C.M.; Tan, G.S.W.; Wong, T.Y.; Lamoureux, E.L. Differential impact of unilateral and bilateral classifications of diabetic retinopathy and diabetic macular edema on vision-related quality of life. *Investig. Ophthalmol. Vis. Sci.* **2016**, *57*, 4655–4660. [CrossRef]
11. Pereira, D.M.; Shah, A.; D'Souza, M.; Simon, P.; George, T.; D'Souza, N.; Suresh, S.; Baliga, M.S. Quality of life in people with diabetic retinopathy: Indian study. *J. Clin. Diagnost. Res.* **2017**, *11*, NC01–NC06. [CrossRef]
12. Sepúlveda, E.; Poínhos, R.; Constante, M.; Pais-Ribeiro, J.; Freitas, P.; Carvalho, D. Relationship between chronic complications, hypertension, and health—Related quality of life in Portuguese patients with type 2 diabetes. *Diabetes Metab. Syndr. Obes.* **2015**, *8*, 535–542. [CrossRef] [PubMed]
13. Das, T.; Wallang, B.; Semwal, P.; Basu, S.; Padhi, T.R.; Ali, M.H. Changing clinical presentation, current knowledge-attitude-practice, and current vision related quality of life in self-reported type 2 diabetes patients with retinopathy in eastern India: The LVPEI eye and diabetes study. *J. Ophthalmol.* **2016**, *2016*, 1–9. [CrossRef]
14. Timar, R.; Velea, I.; Timar, B.; Lungeanu, D.; Oancea, C.; Roman, D.; Mazilu, O. Factors influencing the quality of life perception in patients with type 2 diabetes mellitus. *Patient Prefer. Adher.* **2016**, *10*, 2471–2477. [CrossRef]
15. Nyanzi, R.; Wamala, R.; Atuhaire, L.K. Diabetes and quality of life: A Ugandan perspective. *J. Diabetes Res.* **2014**, *2014*, 1–9. [CrossRef]
16. Ahola, A.J.; Saraheimo, M.; Forsblom, C.; Hietala, K.; Sintonen, H.; Groop, P.-H.; FinDiane Study, G. Health-related quality of life in patients with type 1 diabetes-association with diabetic complications (the FinDiane Study). *Nephrol. Dial. Transplant.* **2010**, *25*, 1903–1908. [CrossRef] [PubMed]
17. Alva, M.; Gray, A.; Mihaylova, B.; Clarke, P. The effect of diabetes complications of health-related quality of life: The importance of longitudinal data to address patient heterogeneity. *Health Econ.* **2014**, *23*, 487–500. [CrossRef] [PubMed]
18. Hirai, F.E.; Tielsch, J.M.; Klein, B.E.K.; Klein, R. Ten-year change in vision-related quality of life in type 1 diabetes: Wisconsin epidemiologic study of diabetic retinopathy. *Ophthalmology* **2011**, *118*, 353–358. [CrossRef] [PubMed]
19. Hirai, F.E.; Tielsch, J.M.; Klein, B.E.K.; Klein, R. Ten-year change in self-rated quality of life in a type 1 diabetes population: Wisconsin epidemiologic study of diabetic retinopathy. *Qual. Life Res.* **2013**, *22*, 1245–1253. [CrossRef]
20. Gubitosi-Klug, R.A.; Sun, W.; Cleary, P.A.; Braffett, B.H.; Aiello, L.P.; Das, A.; Tamborlane, W.; Klein, R. Effects of prior intensive insulin therapy and risk factors on patient-reported visual function outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort. *JAMA Ophthalmol.* **2016**, *134*, 137–145.
21. Matza, L.S.; Rousculp, M.D.; Malley, K.; Boye, K.S.; Oglesby, A. The longitudinal link between visual acuity and health-related quality of life in patients with diabetic retinopathy. *Health Qual. Life Outcomes* **2008**, *6*, 1–10. [CrossRef]
22. Cusick, M.; SanGiovanni, J.P.; Chew, E.Y.; Csaky, K.G.; Hall-Shimel, K.; Reed, G.F.; Caruso, R.C.; Ferris, F.L. Central visual function and the NEI-VFQ-25 near and distance activities subscale scores in people with type 1 and 2 diabetes. *Am. J. Ophthalmol.* **2005**, *139*, 1042–1050. [CrossRef] [PubMed]
23. Fenwick, E.K.; Xie, J.; Ratcliffe, J.; Konrad, P.; Finger, R.P.; Wong, T.Y.; Lamoureux, E.L. The impact of diabetic retinopathy and diabetic macular edema on health-related quality of life in type 1 and type 2 diabetes. *Investig. Ophthalmol. Vis. Sci.* **2012**, *53*, 677–684. [CrossRef] [PubMed]
24. Hart, H.E.; Bilo, H.J.G.; Redekop, W.K.; Stolk, R.P.; Assink, J.H.; Jong, B.M. Quality of life of patients with type I diabetes mellitus. *Qual. Life Res.* **2003**, *12*, 1089–1097. [CrossRef] [PubMed]
25. Hart, H.E.; Redekop, W.K.; Berg, M.; Bilo, H.J.G.; Meyboom-De Jong, B. Factors that predicted change in health-related quality of life were identified in a cohort of diabetes mellitus type 1 patients. *J. Clin. Epidemiol.* **2005**, *58*, 1158–1164. [CrossRef]

26. Mata, A.R.; Álvares, J.; Diniz, L.M.; Ruberson Ribeiro da Silva, M.; Alvernaz dos Santos, B.R.; Guerra Júnior, A.A.; Cherchiglia, M.L.; Andrade, E.I.; Godman, B.; Acurcio, F.D. Quality of patients with diabetes mellitus types 1 and 2 from a referal health care center in Minas Gerais, Brazil. *Expert Rev. Clin. Pharmacol.* **2016**, *9*, 739–746. [CrossRef]
27. Solli, O.; Stavem, K.; Kristiansen, I.S. Health-related quality of life in diabetes: The associations of complications with EQ-5D scores. *Health Qual. Life Outcomes* **2010**, *8*, 1–8. [CrossRef]
28. Peasgood, T.; Brennan, A.; Mansell, P.; Elliott, J.; Basarir, H.; Kruger, J. The impact of diabetes-related complications on preference-based measures of health-related quality of life in adults with type I diabetes. *Med. Decis. Mak.* **2016**, *36*, 1020–1033. [CrossRef]
29. Jansson, R.W.; Hufthammer, K.O.; Krohn, J. Diabetic retinopathy in type 1 diabetes patients in Western Norway. *Acta Ophthalmol.* **2018**, *96*, 465–474. [CrossRef]
30. Weisman, A.; Lovblom, L.E.; Keenan, H.A.; Tinsley, L.J.; D'Eon, S.; Boulet, G.; Farooqi, M.A.; Lovshin, J.A.; Orszag, A.; Lytvyn, Y.; et al. Diabetes care disparities in long-standing type 1 diabetes in Canada and the U.S.: A Cross-sectional comparison. *Diabetes Care* **2018**, *41*, 88–95. [CrossRef]
31. Mauricio, D. Quality of life and treatment satisfaction are highly relevant patient-reported outcomes in type 2 diabetes mellitus. *Ann. Transl. Med.* **2018**, *6*, 220. [CrossRef]
32. Granado-Casas, M.; Alcubierre, N.; Martín, M.; Real, J.; Ramírez-Morros, A.M.; Cuadrado, M.; Alonso, N.; Falguera, M.; Hernández, M.; Aguilera, E.; et al. Improved adherence to Mediterranean Diet in adults with type 1 diabetes mellitus. *Eur. J. Nutr.* **2018**, 1–9. [CrossRef] [PubMed]
33. Wilkinson, C.P.; Ferris, F.L.; Klein, R.E.; Lee, P.P.; Agardh, C.D.; Davis, M.; Dills, D.; Kampik, A.; Pararajasegaram, R.; Verdaguer, J.T.; et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology* **2003**, *110*, 1677–1682. [CrossRef]
34. Bernstein, M.S.; Morabia, A.; Sloutskis, D. Definition and prevalence of sedentarism in an urban population. *Am. J. Public Health* **1999**, *89*, 862–867. [CrossRef]
35. Cabrera de León, A.; Rodríguez-Pérez, M.D.C.; Rodríguez-Benjumeda, L.M.; Anía-Lafuente, B.; Brito-Díaz, B.; Muros de Fuentes, M.; Almeida-González, D.; Batista-Medina, M.; Aguirre-Jaime, A. Sedentary lifestyle: Physical activity duration versus percentage of energy expenditure. *Rev. Esp. Cardiol.* **2007**, *60*, 244–250.
36. Bradley, C.; De Pablos-Velasco, P.; Parhofer, K.G.; Eschwge, E.; Gönder-Frederick, L.; Simon, D. PANORAMA: A European study to evaluate quality of life and treatment satisfaction in patients with type-2 diabetes mellitus—Study design. *Prim. Care Diabetes* **2011**, *5*, 231–239. [CrossRef]
37. Bradley, C.; Todd, C.; Gorton, T.; Symonds, E.; Martin, A.; Plowright, R. The development of an individualised questionnaire measure of perceived impact of diabetes on quality of life: The ADDQoL. *Qual. Life Res.* **1999**, *8*, 79–81. [CrossRef]
38. Depablos-Velasco, P.; Salguero-Chaves, E.; Mata-Poyo, J.; Derivas-Otero, B.; Garcia-Sanchez, R.; Viguera-Ester, P. Quality of life and satisfaction with treatment in subjects with type 2 diabetes: Results in Spain of the PANORAMA study. *Endocrinol. Nutr.* **2014**, *61*, 18–26. [CrossRef] [PubMed]
39. Bradley, C. Diabetes Treatment Satisfaction Questionnaire (DTSQ). In *Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetes Research and Practice*; Harwood Academic Publishers: Amsterdam, The Netherlands, 1994; pp. 111–112.
40. Gomis, R.; Herrera-Pombo, J.; Calderón, A.; Rubio-Terrés, C.; Sarasa, P. Validación del cuestionario "Diabetes treatment satisfaction questionnaire" (DTSQ) en la población española. *Pharmacoeconomics* **2006**, *3*, 7–20. [CrossRef]
41. R Core Team. R: A language and environment for statistical computing. Available online: https://www.r-project.org (accessed on 20 June 2018).
42. Granado-Casas, M.; Martínez-Alonso, M.; Alcubierre, N.; Ramírez-Morros, A.; Hernández, M.; Castelblanco, E.; Torres-Puiggros, J.; Mauricio, D. Decreased quality of life and treatment satisfaction in patients with latent autoimmune diabetes of the adult. *PeerJ* **2017**, *5*, e3928. [CrossRef] [PubMed]
43. Collins, M.; O'Sullivan, T.; Harkins, V.; Perry, I. Quality of life and quality of care in patients with diabetes experiencing different models of care. *Diabetes Care* **2009**, *32*, 603–605. [CrossRef]

44. Gawlik, N.R.; Bond, M.J. The role of negative affect in the assessment of quality of life among women with type 1 diabetes mellitus. *Diabetes Metab. J.* **2018**, *42*, 130–136. [CrossRef]
45. Biderman, A.; Noff, E.; Harris, S.B.; Friedman, N.; Levy, A. Treatment satisfaction of diabetic patients: What are the contributing factors? *Fam. Pract.* **2009**, *26*, 102–108. [CrossRef]

5.5. Artículo 5

Minerva Granado-Casas, Mariona Martín, Montserrat Martínez-Alonso, Nuria Alcubierre, Marta Hernández, Núria Alonso, Esmeralda Castelblanco, Dídac Mauricio. The Mediterranean Diet is associated with an improved quality of life in adults with type 1 diabetes. Nutrients (aceptado).

Resumen

Objetivos

Existe muy poca evidencia científica publicada en relación con la adherencia a la Dieta Mediterránea y su asociación con los resultados percibidos por el paciente en población adulta con DM1. El objetivo del estudio fue determinar la potencial asociación entre los patrones dietéticos (Dieta Mediterránea y alimentación saludable) con los resultados percibidos por el paciente en un grupo de participantes adultos con DM1.

Materiales y métodos

El diseño del estudio fue transversal y multicéntrico. Se disponía de una muestra de 258 pacientes con DM1 del Hospital Universitari Arnau de Vilanova de Lleida y del Hospital Universitari Germans Trias i Pujol de Badalona. Se administró, mediante entrevista personal, el cuestionario de frecuencia de consumo alimentario validado en población española, el cuestionario específico de calidad de vida *Audit of Diabetes Dependent Quality of Life* (ADDQoL-19) y el *Diabetes Treatment Satisfaction Questionnaire* (DTSQ) validados en población diabética española. La adherencia a la Dieta Mediterránea se calculó mediante el *alternate Mediterranean Diet Score* (aMED) y el patrón de alimentación saludable con el *alternate Healthy Eating Index* (aHEI). Se realizaron análisis bivariables y multivariables.

Resultados

La adherencia a la Dieta Mediterránea moderada y alta se asoció positivamente con la calidad de vida relacionada con la diabetes ($p = 0.029$). No se observó asociación entre la satisfacción con el tratamiento global y los índices de calidad dietética. Los ítems específicos "conveniencia" y "flexibilidad" del cuestionario DTSQ se relacionaron positivamente con el aHEI ($p = 0.042$ y $p = 0.011$, respectivamente); sin embargo, el ítem "recomendar a otros" se asoció negativamente con el aHEI ($p = 0.042$).

Conclusiones

La adherencia a la Dieta Mediterránea moderada y alta se asoció con una mejor calidad de vida. Aunque la satisfacción con el tratamiento no se asoció con los índices de calidad alimentaria,

algunos ítems específicos se relacionaron con el aHEI. Se necesitan más estudios para evaluar el auto-manejo de la terapia médico-nutricional y su impacto en los resultados percibidos por el paciente en esta población.

nutrients

MDPI

Article

The Mediterranean Diet is Associated with an Improved Quality of Life in Adults with Type 1 Diabetes

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Abstract: This study aimed to assess the potential association between dietary patterns (i.e., the Mediterranean Diet (MedDiet) and healthy eating) and patient-reported quality of life (QoL) and treatment satisfaction (TS) in adults with type 1 diabetes (T1D). A food frequency questionnaire, the Audit of Diabetes-Dependent Quality of Life (ADDQoL-19), and the Diabetes Treatment Satisfaction Questionnaire-status version (DTSQ-s) were administered via personal interviews to 258 participants with T1D. Multivariable analysis showed that a moderate or high adherence to the MedDiet was associated with greater diabetes-specific QoL (β = 0.32, 95% CI = 0.03; 0.61; $p = 0.029$). None of the dietary quality indexes (i.e., the alternate Mediterranean Diet Score (aMED) and the alternate Healthy Eating Index (aHEI)) were associated with the overall TS. However, the aHEI was positively associated with the specific items of TS "convenience" and "flexibility" (β = 0.03, 95% CI = 0.00; 0.06; $p = 0.042$ and β = 0.04; 95% CI = 0.01; 0.06; $p = 0.011$, respectively). On the other hand, the aHEI was negatively associated with the dimension "recommend to others" (β = −0.5, 95% CI = −0.99; −0.02; $p = 0.042$). In conclusion, a moderate and high adherence to the MedDiet was associated with greater QoL. Although neither aMED nor aHEI were associated with the overall TS, some specific items were positively (i.e., "convenience", "flexibility") or negatively ("recommend to others") related to the aHEI. Further research is needed to assess how to improve medical nutrition therapy and its impact on patient-reported outcomes in people with T1D.

Keywords: Mediterranean Diet; quality of life; treatment satisfaction; type 1 diabetes; dietary pattern; patient-reported outcomes; nutrient intake

1. Introduction

People with type 1 diabetes (T1D) need specific treatment, including insulin therapy and advice on physical activity and medical nutrition therapy to ensure optimal self-management of the disease [1]. In Catalonia (Spain), carbohydrate counting and a healthy eating pattern such as the Mediterranean Diet (MedDiet) are included in medical nutrition therapy for people diagnosed with T1D [1–3]. This dietary pattern is important for preventing cardiovascular diseases in people with T1D who have a high cardiovascular risk; these people often show an unfavorable lipid profile associated with poorer glycemic control [4].

Fung et al. demonstrated that both the alternate Healthy Eating Index (aHEI) and the alternate Mediterranean Diet score (aMED) were strongly correlated with lower concentrations of biomarkers of inflammation and endothelial dysfunction, related with the development of cardiovascular diseases and diabetes mellitus [5]. Furthermore, both scores focus on dietary patterns rich in fruits and vegetables, whole grains, nuts, fish, and moderate alcohol consumption; therefore, these two indexes are useful measures of dietary patterns and the associated cardiovascular risk. Scientific evidence has shown that the presence of cardiovascular diseases and late diabetic complications have a negative impact on the quality of life (QoL) and treatment satisfaction (TS) of people with T1D [6]. Furthermore, a study performed in children and adolescents (between 13 and 19 years old) described that insulin treatment and dietary limitations in the management of T1D may have several effects on QoL [7].

A recent systematic review of dietary patterns and QoL in older adults with diabetes reported a lack of scientific evidence that relates dietary patterns to QoL in this population [8]. Specifically, the few studies that have looked at the adherence to the MedDiet in relation to QoL and TS found an improved QoL and TS in people with type 2 diabetes who had a higher adherence to the MedDiet [9–11]. On the other hand, another study performed in people with diabetes (without identifying the type of diabetes) found a higher health-related quality of life (HRQoL) associated with the combination of multiple healthy lifestyle habits (no smoking, regular physical activity, and a higher intake of fruits and vegetables) [12]. Other cross-sectional studies have only assessed the relationship between TS and adherence to medical nutrition therapy in people with type 2 diabetes [13,14]; they found a higher TS in those who showed a higher adherence to the nutritional recommendations. In adults with T1D, no studies have been designed to assess the potential impact of dietary pattern on QoL and TS. Moreover, no studies have assessed the relationship between the dietary pattern of adults with T1D using dietary quality indexes (i.e., aMED and aHEI) and diabetes-specific QoL instruments. Only one cross-sectional study was performed in adolescents and children (from 13 to 19 years) to assess the relationship between unhealthy lifestyle habits and QoL [7]. However, they found that a combination of unhealthy lifestyle habits (poor adherence to the MedDiet, low physical activity levels, and high sedentary behavior score) was related to a poorer QoL in these participants. Additionally, a case-control study designed to audit diabetes management and QoL in adults with T1D did not find a relationship between dietary pattern and QoL [15]. Other recent studies performed in adults with T1D with celiac disease found a better QoL in those with a higher adherence to a gluten-free diet [16,17]. Finally, a recent meta-analysis of the effectiveness and safety of the possible effect of carbohydrate counting on glycemic control and QoL in people with T1D reported a lack of scientific evidence in terms of QoL and TS [18].

A previously published study revealed that people with type 2 diabetes with a higher adherence to the MedDiet from Catalonia, a Mediterranean region of Spain, had improved QoL and TS [10]. Furthermore, we have previously investigated the dietary pattern and patient-reported outcomes in two studies in people with T1D in this region [19,20]. The first study assessed differences in terms of a MedDiet and healthy eating pattern between participants with and without T1D [19]. The second study assessed the relationship between the presence of diabetic retinopathy and patient-reported outcomes (i.e., QoL and TS) [20]. We found that participants with T1D had a higher adherence to the MedDiet in comparison with a group without diabetes. Additionally, diabetic retinopathy was negatively associated with QoL and TS. Further, we also found that factors related with the lifestyle of the participants (i.e., non-smokers and practice of regular physical activity) were associated with a

higher adherence to the MedDiet and a greater QoL. In this context, we hypothesized that as people with T1D receive regular and individual medical nutrition therapy to ensure an optimal management of the disease, improved adherence to the MedDiet and a healthy eating pattern could be associated with better QoL and TS. Thus, the aim of the study was to determine the association between the dietary patterns (i.e., MedDiet and healthy eating) with patient-reported outcomes (i.e., QoL and TS) in people with T1D from a Mediterranean country. To our knowledge, this is the first study specifically designed to assess the relationship between QoL and TS and dietary patterns in adults with T1D.

2. Materials and Methods

This was a two-center cross-sectional study. The study participants were individuals diagnosed with T1D who were regularly cared for at the reference hospital and who were from a rural/semi-urban area or an urban area. This is a sub-study of a previously published study performed to assess adherence to the MedDiet between a T1D group and a group without diabetes [19]. From the total sample of 259 participants with T1D included in that study, one participant was excluded because he did not answer all of the questionnaires. Therefore, a final sample of 258 participants with T1D was included. More details of the study design are provided in the previous publication [19]. The inclusion criteria were a diagnosis of T1D with a disease duration of more than one year and a current age older than 18 years. The exclusion criteria were: The presence of psychological or cognitive deterioration; being a healthcare professional; the presence of previous clinical cardiovascular diseases or diabetic foot disease; pregnancy; having advanced complications or conditions that require a specific medical nutrition therapy, such as macroalbuminuria (urine albumin/creatinine ratio > 299 mg/g); and renal insufficiency (estimated glomerular filtration rate < 60 mL/min). The ethics committees of the participating centers (University Hospital Arnau de Vilanova, Lleida, Spain and University Hospital Germans Trias i Pujol, Badalona, Spain) approved the study (PI-13-095 and PI-15-147, respectively), and written informed consent was obtained from all of the study participants.

2.1. Clinical Variables

Trained researchers interviewed all of the participants individually, and clinical records were thoroughly reviewed to collect all the relevant study data. Blood and urine samples were collected in the fasting state. Low-density lipoprotein cholesterol was estimated by the Friedewald formula. Glycated hemoglobin (HbA1c) was determined by HPLC (VariantTM, Bio-Rad Laboratories S.A., Madrid, Spain) and its concentrations were expressed in National Glycohemoglobin Standardization Program/Diabetes Control and Complications trial units. Urine albumin was measured with an immunoturbidimetric method and a Roche/Hitachi Modular P analyzer (Roche Diagnostics, Barcelona, Spain). Waist circumference was measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest. Hypertension and dyslipidemia were defined by the use of drugs for treating these conditions. Microalbuminuria was defined as an albumin-to-creatinine ratio >30 mg/g. Physical activity was assessed using the method of Bernstein et al., which was designed with people aged 35 to 74 years from Switzerland [21], and validated by Cabrera de León et al. in Spanish people aged 18 to 75 years [22]; participants were classified as performing regular physical activity if they spent at least 4 metabolic equivalents (METs) participating in any activity, such as walking or cycling for more than 25 min/day, and were classified as sedentary if they spent up to 25 min/day. Educational level was classified as lower if the participant did not have a university degree and as a graduate or higher if he or she had a university education. Retinopathy was assessed and classified by an ophthalmologist. Tobacco exposure included current and former smokers.

2.2. Dietary Pattern Assessment

A food frequency questionnaire (FFQ) was individually administered by two trained researchers [23,24]. This is a semiquantitative questionnaire that has been validated and adapted for the Spanish population. This was based on the Nurses' Health Study and was used in our previously

published study [19]. The FFQ used was a modified version from a previous FFQ based on the Harvard questionnaire [23]. This version was developed and validated using four 1-week dietary records performed during one year in an adult population in Spain. Individual nutrient intake and food consumption were validated, adjusting for energy intake. Moreover, this FFQ was administered at six years after the baseline assessment and compared with these 1-week dietary records to assess the validity and reproducibility at six years of follow-up. Subsequently, the authors performed a specific validation analysis using nutrients related with pregnancy (i.e., carotenoids, folate, vitamin B12, vitamin C, and α-tocopherol); these were adjusted for energy intake and validated with their concentration in blood specimens [24]. The questionnaire contains 101 items, which are used to record the usual consumption over the previous year prior to the visit [25].

The adherence to the MedDiet was assessed using the aMED score based on the MedDiet scale [26]. The aMED score ranges from 0 (minimal adherence) to 9 (maximal adherence). This includes vegetables, legumes, fruits, nuts, whole grain, red and processed meat, fish, monounsaturated fatty acid-to-saturated fatty acid ratio, and alcohol consumption. Additionally, we determined the aHEI based on the Dietary Guidelines for Americans and the Food Guide Pyramid [5]. This includes vegetables, fruits, nuts, soy, white to red meat ratio, cereal fiber, trans fat, polyunsaturated fatty acid-to-saturated fatty acid ratio, alcohol consumption, and long-term multivitamin use. The score ranges from 0 (lower quality diet) to 80 (higher quality diet), excluding long-term multivitamin use in the Spanish population [19]. Daily nutrient intake was calculated by adjusting for energy intake and was estimated by multiplying the frequency of use for each food by the nutrient composition of the portion/size specified by each individual on the FFQ; these results were added across all foods [24].

2.3. Patient-Reported Outcomes

The Audit of Diabetes-Dependent Quality of Life (ADDQoL-19) was administered to assess QoL; this is a disease-specific measure designed and validated for Spanish people with diabetes [27–29]. This instrument contains 21 items, of which 19 are related to specific life domains. The impact of diabetes on each domain is weighted according to the importance grade that each participant reported on the QoL. The mean of the 19 specific domains is determined with the average weighted impact (AWI) score. The scores range from +3 (maximum positive impact) to −9 (maximum negative impact). Moreover, five of the 19 items that might not be relevant to some participants are included in a preliminary question that can be ignored if it is not applicable. In this questionnaire, two general items are scored separately; one of them measures the present QoL and ranges from +3 (excellent) to −3 (very bad). The other measures diabetes-specific QoL and ranges from −3 (maximum negative impact) to +1 (maximum positive impact).

TS was measured with the Diabetes Treatment Satisfaction Questionnaire-status version (DTSQ-s), a diabetes-specific questionnaire validated for Spanish people with diabetes, and this questionnaire was individually administered [30,31]. This instrument consists of 8 items scored on a 6-point scale, ranging from 0 (never) to 6 (always). The final score is calculated by adding the scores of the six items and ranges from 36 (very satisfied) to 0 (very unsatisfied). The other two items are calculated separately and measure the perceived frequency of hyperglycemia and hypoglycemia. They are scored from 0 (never) to 6 (always).

2.4. Data Analysis

Descriptive analysis included median and interquartile range for quantitative variables and frequency and percentages for qualitative variables. Multivariable linear regression models were fit to explain QoL, as well as TS total scores. Specifically, we modeled six response variables, including present quality of life (QoL), diabetes-specific QoL, and the AWI score (ADDQoL-19 summary score), as well as the perceived frequencies of hyperglycemia/hypoglycemia and TS (DTSQ-s summary score). Initially, simple regression models were fit to assess the statistical significance of the association between each explanatory variable and each outcome. Then, a first multivariable regression model for

each outcome was built by starting with all candidate variables with a univariate Wald test p-value below 0.20 (showed in the previous simple linear regression models) and testing the deletion of each variable whose exclusion gives the most insignificant impact on the model fit (Wald-test based), and repeating this procedure until all variables in the model showed a statistically significant contribution. Variables out of the multivariable model were assessed and added if they showed a statistically significant contribution (Wald test) on the confounding effect (change in the coefficients of the model higher than 10%). Finally, interactions with diabetes duration and sex were also examined. All statistical analyses were performed with R [32], and a significance level of 0.05 was applied.

3. Results

The clinical and sociodemographic characteristics according to aMED and aHEI are shown in Tables 1 and 2, respectively. The prevalence of retinopathy in the study participants was 42.1%. In addition, they showed a fair lipid profile. In terms of dietary quality index, aHEI was frequently low (75.6%), although a high proportion of participants with low aHEI exhibited a low and moderate adherence to the MedDiet (100.0% and 75.9% for the aMED, respectively; $p < 0.001$). Furthermore, in rural and semi-urban areas, there was a higher proportion of participants with moderate and high adherence to the MedDiet (51.2% and 56.3%, respectively; $p = 0.010$) and healthy eating (71.4% for the aHEI; $p < 0.001$). Participants with T1D and moderate or high aMED scores showed more favorable high-density lipoprotein cholesterol levels ($p = 0.025$) (Table 1). Finally, increasing age was associated with higher aHEI scores ($p = 0.010$) (Table 2). The daily nutrient and food intake of the study group is shown in Tables S1 and S2 of the Supplementary Materials.

Table 1. Descriptive analysis of the characteristics of the study participants according to the alternate Mediterranean Diet score.

	All (n = 258)	**Low (0–2) (n = 60)**	**Moderate (3–5) (n = 166)**	**High (6–9) (n = 32)**	**p**
Sex (men)	117 (45.3)	30 (50.0)	77 (46.4)	10 (31.3)	0.206
Age (years)	43.0 [36.0; 50.0]	41.5 [35.0; 49.0]	43.0 [37.0; 50.0]	46.0 [37.8; 51.8]	0.240
Ethnicity (Caucasian)	254 (98.4)	58 (96.7)	164 (98.8)	32 (100.0)	0.436
Site					0.010
Rural and semi-urban area	121 (46.9)	18 (30.0)	85 (51.2)	18 (56.2)	
Urban area	137 (53.1)	42 (70.0)	81 (48.8)	14 (43.8)	
Educational level [1]					0.462
Lower	185 (74.9)	47 (81.0)	115 (72.8)	23 (74.2)	
Graduate or higher	62 (25.1)	11 (19.0)	43 (27.2)	8 (25.8)	
Regular physical activity	186 (72.1)	38 (63.3)	121 (72.9)	27 (84.4)	0.093
Tobacco exposure	128 (49.6)	30 (50.0)	79 (47.6)	19 (59.4)	0.474
BMI (kg/m^2)	25.0 [22.6; 27.6]	25.0 [22.0; 28.3]	25.2 [22.8; 27.4]	24.7 [22.2; 26.9]	0.686
Waist (cm)	88.0 [79.0; 96.2]	89.0 [81.0; 99.0]	88.0 [79.0; 96.0]	87.0 [75.0; 95.5]	0.397
Retinopathy	102 (42.1)	23 (38.3)	66 (39.8)	13 (40.6)	0.949
Microalbuminuria	19 (7.4)	6 (10.0)	12 (7.2)	1 (3.1)	0.552
Hypertension	64 (24.8)	11 (18.3)	45 (27.1)	8 (25.0)	0.403
Dyslipidemia	102 (39.5)	24 (40.0)	67 (40.4)	11 (34.4)	0.815
Diabetes duration (years)	20.0 [14.0; 29.0]	20.5 [15.0; 27.8]	20.0 [14.0; 29.0]	20.5 [14.8; 30.0]	0.785
HbA1c (%)	7.4 [7.0; 8.0]	7.5 [7.1; 8.1]	7.4 [6.9; 8.0]	7.3 [7.0; 8.1]	0.857
HbA1c (mmol/mol)	57.4 [53.0; 63.9]	57.9 [53.8; 64.5]	57.4 [52.2; 63.9]	56.3 [53.0; 65.3]	0.857
Total cholesterol (mg/dL)	176.0 [162.0; 200.0]	174.0 [160.0; 193.0]	176.0 [162.0; 200.0]	186 [167.0; 202.0]	0.459
LDL-c (mg/dL)	100.0 [85.7; 115.0]	102.0 [85.2; 116.0]	98.1 [84.2; 115.0]	103.0 [90.3; 114.0]	0.711
HDL-c (mg/dL)	63.0 [53.0; 75.0]	57.5 [48.5; 72.2]	63.5 [54.0; 75.8]	69.0 [60.0; 73.8]	0.025
Triglycerides	65.0 [52.0; 83.8]	66.0 [52.8; 83.5]	67.5 [53.0; 85.0]	56.5 [47.8; 69.2]	0.197
aHEI					<0.001
Low (<45)	195 (75.6)	60 (100.0)	126 (75.9)	9 (28.1)	
High (≥45)	63 (24.4)	0 (0.0)	40 (24.1)	23 (71.9)	
aMED	4.0 [3.0; 5.0]	2.0 [1.0; 2.0]	4.0 [3.0; 5.0]	6.0 [6.0; 7.0]	<0.001

Data are shown as the median [interquartile range] or n (%). [1] There were 11 cases with missing information for educational level. Tobacco exposure, current or former smoker; BMI, body mass index; HbA1c, glycated hemoglobin; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; aHEI, alternate Healthy Eating Index; aMED, alternate Mediterranean Diet Score.

Table 2. Descriptive analysis of the characteristics of the study participants according to the alternate Healthy Eating Index.

	All (n = 258)	Low (<45) (n = 195)	High (≥45) (n = 63)	p
Sex (men)	117 (45.3)	96 (49.2)	21 (33.3)	0.040
Age (years)	43.0 [36.0; 50.0]	42.0 [36.0; 49.0]	48.0 [38.5; 54.0]	0.010
Ethnicity (Caucasian)	254 (98.4)	191 (97.9)	63 (100.0)	0.575
Site				<0.001
Rural and semi-urban area	121 (46.9)	76 (39.0)	45 (71.4)	
Urban area	137 (53.1)	119 (61.0)	18 (28.6)	
Educational level [1]				0.436
Lower	185 (74.9)	135 (73.4)	50 (79.4)	
Graduate or higher	62 (25.1)	49 (26.6)	13 (20.6)	
Regular physical activity	186 (72.1)	135 (69.2)	51 (81.0)	0.101
Tobacco exposure	128 (49.6)	95 (48.7)	33 (52.4)	0.718
BMI (kg/m^2)	25.0 [22.6; 27.6]	25.2 [22.9; 27.8]	24.6 [22.3; 27.1]	0.277
Waist (cm)	88.0 [79.0; 96.2]			
Retinopathy	102 (42.1)	78 (40.0)	24 (38.1)	1.000
Microalbuminuria	19 (7.4)	15 (7.7)	4 (6.3)	1.000
Hypertension	64 (24.8)	45 (23.1)	19 (30.2)	0.335
Dyslipidemia	102 (39.5)	79 (40.5)	23 (36.5)	0.677
Diabetes duration (years)	20.0 [14.0; 29.0]	20.0 [14.0; 27.5]	23.0 [15.0; 30.0]	0.090
HbA1c (%)	7.4 [7.0; 8.0]	7.4 [7.0; 8.0]	7.5 [7.0; 8.0]	0.911
HbA1c (mmol/mol)	57.4 [53.0; 63.9]	57.4 [53.0; 63.9]	58.5 [53.0; 63.9]	0.911
Total cholesterol (mg/dL)	176.0 [162.0; 200.0]	174.0 [160.0; 200.0]	187.0 [166.0; 202.0]	0.170
LDL-c (mg/dL)	100.0 [85.7; 115.0]	99.0 [84.0; 115.0]	103.0 [89.5; 120.0]	0.175
HDL-c (mg/dL)	63.0 [53.0; 75.0]	62.0 [52.0; 74.0]	64.0 [57.5; 77.5]	0.050
Triglycerides	65.0 [52.0; 83.8]	67.0 [52.5; 85.0]	59.0 [49.5; 80.5]	0.322
aMED				<0.001
Low (0–2)	60 (23.3)	60 (30.8)	0 (0.0)	
Moderate (3–5)	166 (64.3)	126 (64.6)	40 (63.5)	
High (6–9)	32 (12.4)	9 (4.6)	23 (36.5)	
aHEI	40.0 [37.0; 44.0]	38.0 [35.5; 41.0]	48.0 [46.0; 50.5]	<0.001

Data are shown as the median [interquartile range] or n (%). [1] There were 11 cases with missing information for educational level. Tobacco exposure, current or former smoker; BMI, body mass index; HbA1c, glycated hemoglobin; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; aHEI, alternate Healthy Eating Index; aMED, alternate Mediterranean Diet Score.

3.1. Quality of Life and Dietary Pattern

Regarding the dietary quality index, the multivariable analysis showed that moderate and high adherence to the MedDiet were associated with greater diabetes-related QoL (p = 0.029) after adjusting for age, tobacco exposure, and physical activity (Table 3). However, neither of the dietary quality indexes (i.e., aMED and aHEI) were related to the current QoL and AWI scores. No association was found between the dietary quality indexes and other items of the ADDQoL-19 questionnaire.

Table 3. Multivariable analysis of the Audit Diabetes-Dependent Quality of Life (ADDQoL-19) questionnaire with the alternate Mediterranean Diet Score and alternate Healthy Eating Index.

Items	aMED	β (95% CI)	p	aHEI	β (95% CI)	p
Present QoL [a]	>2	0.05 (−0.23; 0.33)	0.742	>44	−0.23 (−0.52; 0.05)	0.103
Diabetes-specific QoL [b]	>2	0.32 (0.03; 0.61)	0.029	-	0.02 (0.00; 0.04)	0.055
AWI [c]	>2	0.08 (−0.31; 0.48)	0.680	>44	0.00 (−0.39; 0.39)	0.992

[a] Adjusted by age and retinopathy. [b,c] Adjusted by age, tobacco exposure, and physical activity. aMED, alternate Mediterranean Diet score; AWI, average weighted impact score; aHEI, alternate Healthy Eating Index; CI, confidence interval; QoL, quality of life.

3.2. Treatment Satisfaction and the Mediterranean Diet

In the multivariable analysis, none of the dietary quality measures were related to global TS (Table 4). However, aHEI was positively associated with some items of DTSQ-s, i.e., "convenience" (p = 0.042) and "flexibility" (p = 0.011); the latter depended on the interaction between diabetes duration

and aHEI (β = −0.01, 95% CI = 0.00; 0.00, p = 0.048). On the other hand, a high adherence to a healthy eating pattern was negatively associated with the dimension "recommend to others" (this specific item assesses the recommendation of this treatment to someone with a diabetes condition similar to yours) (p = 0.042). No associations were observed with the other TS items.

Table 4. Multivariable analysis of the Diabetes Treatment Satisfaction Questionnaire-status (DTSQ-s) with the alternate Mediterranean Diet Score and alternate Healthy Eating Index.

Items	aMED	β (95% CI)	*p*	aHEI	β (95% CI)	*p*
Hyperglycemia frequency perception [a]	>2	−0.33 (−0.74; 0.08)	0.118	>44	−0.07 (−0.47; 0.34)	0.743
Hypoglycemia frequency perception [b]	>2	−0.41 (−0.83; 0.02)	0.060	>44	−0.26 (−0.69; 0.17)	0.231
Convenience [c]	-	0.08 (−0.04; 0.21)	0.194	-	0.03 (0.00; 0.06)	0.042
Flexibility [d]	-	0.06 (−0.06; 0.17)	0.328	-	0.04 (0.01; 0.06)	0.011
Recommend to others [e]	>2	−0.11 (−0.61; 0.39)	0.668	>44	−0.5 (−0.99;−0.02)	0.042
Final score [f]	>2	0.39 (−1.21; 2.00)	0.629	>44	0.31 (−1.29; 1.90)	0.706

[a] Adjusted by glycated hemoglobin. [b] Adjusted by sex and retinopathy. [c] Adjusted by sex and tobacco exposure. [d] Adjusted by diabetes duration and the interaction between diabetes duration and aHEI or aMED. [e] Adjusted by hypertension and diabetes duration. [f] Adjusted by diabetes duration. aHEI, alternate Healthy Eating Index; aMED, alternate Mediterranean Diet Score; CI, confidence interval.

4. Discussion

Our results indicate that moderate and high adherence to the MedDiet was associated with greater diabetes-related QoL in participants with T1D. However, none of the dietary quality indexes were associated with the overall TS. The aHEI was positively associated with "convenience" and "flexibility" items of the TS questionnaire; however, the aHEI was negatively associated with the dimension "recommend to others".

There is only one cross-sectional study that has been performed with young people with T1D (from 13 to 19 years old) that associated diabetes-specific QoL with the MedDiet pattern [7]. The researchers did not find any relationship between the MedDiet and QoL in this population, a finding that is in contrast with our results. However, this may be due to a smaller sample size of participants with T1D and a lower dietary quality index in that study (n = 31). However, a few studies have assessed the relationship between the MedDiet and QoL in people with type 2 diabetes [9–11]. Toobert et al. [9] and Galilea-Zabalza et al. [11] found an improved HRQoL with a higher adherence to the MedDiet in people with type 2 diabetes using generic instruments to measure QoL. Furthermore, similar results were observed in a previous study performed by our group in people with type 2 diabetes using a diabetes-specific questionnaire [10]. Finally, in line with the current results, a cross-sectional study showed an improved HRQoL in people with diabetes with a healthy lifestyle (type of diabetes was not specified) [12].

In terms of TS, we could not identify any study that assessed the relationship between dietary pattern and TS in people with T1D. Our group performed a previous study in people with type 2 diabetes and found an association of greater TS with higher adherence to the MedDiet [10]. Two cross-sectional studies performed in people with type 2 diabetes only found a positive relationship between TS and the adherence to medical nutrition therapy [13,14]; however, despite observing a relationship between aHEI and some items of TS in this study, we did not find any association between the dietary pattern and the overall TS. This could be due to the small number of participants included in our study with a poorer TS final score. Furthermore, these differences between the published studies and our results could be explained, in part, by the fact of people with T1D are treated with intensive insulin therapy from the onset of the disease. However, people with type 2 diabetes are treated with diet, hypoglycemic agents, or insulin depending on their glycemic control, other aspects of the management of the disease and the presence of complications. The relationship between healthy dietary patterns and TS could be due to the fact that diet and nutritional recommendations based on the MedDiet are included in the treatment of people with T1D.

This study has some limitations. This is a sub-study of a previously published study specifically designed to assess the degree of adherence to the MedDiet in people with T1D [19]. Due to the cross-sectional study design, causal relationships between the variables cannot be established. Moreover, changes in lifestyle over time cannot be assessed in this study design. However, this study has several strengths. This is the first study designed to assess the relationship between dietary patterns and patient-reported outcomes, such as QoL and TS, in adults with T1D. Furthermore, the large sample size and the multicenter design, with a well-defined sample, allow us to account for the variability in different geographical areas (a rural/semi-urban and an urban population) of the same region. Additionally, the FFQ used has been shown to be representative of the previous five-year period of food and nutrient intake [33]. The final conclusions are potentially interesting in this research field, as this is the first study to assess the relationship between dietary pattern (Mediterranean Diet and healthy eating) and patient-reported outcomes in adults with T1D.

5. Conclusions

A moderate and higher adherence to the Mediterranean Diet was associated with greater QoL in participants with T1D. On the other hand, none of the dietary quality measures (i.e., aMED and aHEI) were associated with global TS, although a healthier eating pattern was related with some specific items. Further research is needed in this area to establish new approaches focused on the medical nutrition therapy and their influence on the quality of life and treatment satisfaction of people with T1D. In addition, a causal relationship and definitive conclusions would be necessarily determined by future randomized clinical trials.

Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6643/12/1/131/s1: Table S1. Daily food intake of the study group; Table S2. Daily nutritional intake of the study group.

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References

1. Bantle, J.P.; Wylie-Rosett, J.; Albright, A.L.; Apovian, C.M.; Clark, N.G.; Franz, M.J. Nutrition recommendations and interventions for diabetes: A position statement of the American Diabetes Association. *Diabetes Care* **2008**, *31*, S61–S78. [PubMed]
2. Catalan Association of Diabetes. *Documento de Consenso Sobre Recomendaciones Nutricionales y de Educación Alimentaria en la Diabetes*; ACD: Barcelona, Spain, 2013.
3. Mann, J.; Lean, M.; Toeller, M. Recommendations for the nutritional management of patients with diabetes mellitus. *Eur. J. Clin. Nutr.* **2000**, *54*, 353–355.
4. American Diabetes Association. Lifestyle management. Sec. 4. In Standards of Medical Care in Diabetes-2017. *Diabetes Care* **2017**, *40*, S33–S43.
5. Fung, T.T.; McCullough, M.L.; Newby, P.K.; Manson, J.E.; Meigs, J.B.; Rifai, N. Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. *Am. J. Clin. Nutr.* **2005**, *82*, 163–173. [CrossRef] [PubMed]

6. Trikkalinou, A.; Papazafiropoulou, A.K. Melidonis A Type 2 diabetes and quality of life. *World J. Diabetes* **2017**, *8*, 120–129. [CrossRef]
7. Mozzillo, E.; Zito, E.; Maffeis, C.; De Nitto, E.; Maltoni, G.; Marigliano, M. Unhealthy lifestyle habits and diabetes-specific health-related quality of life in youths with type 1 diabetes. *Acta Diabetol.* **2017**, *54*, 1073–1080. [CrossRef]
8. Govindaraju, T.; Sahle, B.; McCaffrey, T.; McNeil, J.; Owen, A. Dietary Patterns and Quality of Life in Older Adults: A Systematic Review. *Nutrients* **2018**, *10*, 971. [CrossRef]
9. Toobert, D.J.; Glasgow, R.E.; Strycker, L.A.; Barrera, M.; Radcliffe, J.L.; Wander, R.C. Biologic and Quality-of-Life Outcomes From the Mediterranean Lifestyle Program. *Diabetes Care* **2003**, *26*, 2288–2293. [CrossRef]
10. Alcubierre, N.; Martinez-Alonso, M.; Valls, J.; Rubinat, E.; Traveset, A.; Hernández, M. Relationship of the adherence to the Mediterranean diet with health-related quality of life and treatment satisfaction in patients with type 2 diabetes mellitus: A post-hoc analysis of a cross-sectional study. *Health Qual. Life Outcomes* **2016**, *14*, 69. [CrossRef]
11. Galilea-Zabalza, I.; Buil-Cosiales, P.; Salas-Salvadó, J.; Toledo, E.; Ortega-Azorín, C.; Díez-Espino, J. Mediterranean diet and quality of life: Baseline cross-sectional analysis of the PREDIMED-PLUS trial. *PLoS ONE* **2018**, *13*, e0198974. [CrossRef]
12. Li, C.; Ford, E.S.; Mokdad, A.H.; Jiles, R.; Giles, W.H. Clustering of Multiple Healthy Lifestyle Habits and Health-Related Quality of Life Among, U.S. Adults With Diabetes. *Diabetes Care* **2007**, *30*, 1770–1776. [CrossRef] [PubMed]
13. Hayashi, I.; Watanabe, N.; Nakata, S.; Komatsu, R.; Motoda, S.; Fujita, Y. Factors associated with treatment satisfaction in patients with type 2 diabetes mellitus using oral glucose-lowering agents: A cross-sectional study in urban districts in Japan. *Endocr. J.* **2018**, *65*, 1001–1009. [CrossRef] [PubMed]
14. Abu Sheikh, B.; Arabiat, D.H.; Holmes, S.L.; Khader, Y.; Hiyasat, D.; Collyer, D. Correlates of treatment satisfaction and well-being among patients with type II diabetes. *Int. Nurs. Rev.* **2018**, *65*, 114–121. [CrossRef] [PubMed]
15. Tahbaz, F.; Kreis, I.; Calvert, D. An audit of diabetes control, dietary management and quality of life in adults with type 1 diabetes mellitus, and a comparison with nondiabetic subjects. *J. Hum. Nutr. Diet.* **2006**, *19*, 3–11. [CrossRef] [PubMed]
16. Pham-Short, A.; Donaghue, K.C.; Ambler, G.; Garnett, S.; Craig, M.E. Quality of Life in Type 1 Diabetes and Celiac Disease: Role of the Gluten-Free Diet. *J. Pediatr.* **2016**, *179*, 131–138.e1. [CrossRef] [PubMed]
17. Nunes-Silva, J.G.; Nunes, V.S.; Schwartz, R.P.; Mlss Trecco, S.; Evazian, D.; Correa-Giannella, M.L. Impact of type 1 diabetes mellitus and celiac disease on nutrition and quality of life. *Nutr. Diabetes* **2017**, *7*, 4–9. [CrossRef] [PubMed]
18. Vaz, E.C.; Porfírio, G.J.M.; Nunes HR de, C.; Nunes-Nogueira V dos, S. Effectiveness and safety of carbohydrate counting in the management of adult patients with type 1 diabetes mellitus: A systematic review and meta-analysis. *Arch. Endocrinol. Metab.* **2018**, *62*, 337–345. [CrossRef]
19. Granado-Casas, M.; Alcubierre, N.; Martín, M.; Real, J.; Ramírez-Morros, A.M.; Cuadrado, M. Improved adherence to Mediterranean Diet in adults with type 1 diabetes mellitus. *Eur. J. Nutr.* **2019**, *58*, 2271–2279. [CrossRef]
20. Granado-Casas, M.; Castelblanco, E.; Ramírez-Morros, A.; Martín, M.; Alcubierre, N.; Martínez-Alonso, M. Poorer Quality of Life and Treatment Satisfaction is Associated with Diabetic Retinopathy in Patients with Type 1 Diabetes without Other Advanced Late Complications. *J. Clin. Med.* **2019**, *8*, 377. [CrossRef]
21. Bernstein, M.S.; Morabia, A.; Sloutskis, D. Definition and prevalence of sedentarism in an urban population. *Am. J. Public Health* **1999**, *89*, 862–867. [CrossRef]
22. Cabrera de León, A.; Rodríguez-Pérez, M.D.C.; Rodríguez-Benjumeda, L.M.; Anía-Lafuente, B.; Brito-Díaz, B.; Muros de Fuentes, M. Sedentary lifestyle: Physical activity duration versus percentage of energy expenditure. *Rev. Esp. Cardiol.* **2007**, *60*, 244–250. [PubMed]
23. Willett, W.C.; Sampson, L.; Stampfer, M.J.; Rosner, B.; Bain, C.; Witschi, J. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am. J. Epidemiol.* **1985**, *122*, 51–65. [CrossRef] [PubMed]
24. Vioque, J.; Navarrete-Muñoz, E.-M.; Gimenez-Monzó, D.; García-de-la-Hera, M.; Granado, F.; Young, I.S. Reproducibility and validity of a food frequency questionnaire among pregnant women in a Mediterranean area. *Nutr. J.* **2013**, *12*, 26. [CrossRef] [PubMed]

25. Cuestionario de Frecuencia Alimentaria Nº 2. Available online: http://epinut.edu.umh.es/wp-content/uploads/sites/1365/2011/07/CFA101.pdf (accessed on 2 June 2019).
26. Trichopoulou, A.; Costacou, T.; Bamia, C.; Trichopoulos, D. Adherence to a Mediterranean diet and survival in a Greek population. *N. Engl. J. Med.* **2003**, *348*, 2599. [CrossRef] [PubMed]
27. Plowright, R.; Witthaus, E.; Bradley, C. Evaluating the 12-item well-being questionnaire for use in multinational trials. *Qual. Life Res.* **1999**, *8*, 650.
28. Bradley, C.; Todd, C.; Gorton, T.; Symonds, E.; Martin, A.; Plowright, R. The development of an individualised questionnaire measure of perceived impact of diabetes on quality of life: The ADDQoL. *Qual. Life Res.* **1999**, *8*, 79–81. [CrossRef] [PubMed]
29. Depablos-Velasco, P.; Salguero-Chaves, E.; Mata-Poyo, J.; Derivas-Otero, B.; Garcia-Sanchez, R.; Viguera-Ester, P. Quality of life and satisfaction with treatment in subjects with type 2 diabetes: Results in Spain of the PANORAMA study. *Endocrinol. Nutr.* **2014**, *61*, 18–26. [CrossRef]
30. Bradley, C. Diabetes Treatment Satisfaction Questionnaire (DTSQ). In *Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetes Research and Practice*; Harwood Academic Publishers: Amsterdam, The Netherlands, 1994; pp. 111–112.
31. Gomis, R.; Herrera-Pombo, J.; Calderón, A.; Rubio-Terrés, C.; Sarasa, P. Validación del cuestionario "Diabetes treatment satisfaction questionnaire" (DTSQ) en la población española. *Pharm. Span. Res. Artic.* **2006**, *3*, 7–20. [CrossRef]
32. R Core Team. R: A Language and Environment for Statistical Computing. Available online: https://www.r-project.org (accessed on 20 June 2018).
33. Vioque, J.; Gonzalez, L. Validity of the evaluation of dietary intake. In *Nutrition and Public Health. Methods, Scientific Bases and Applications*, 2nd ed.; Serra Majem, L., Aranceta Bartrina, J., Eds.; Masson-Elsevier: Barcelona, Spain, 2006; pp. 199–210.

Discusión

6. Discusión

La presente tesis doctoral ha permitido caracterizar los distintos aspectos del impacto de la educación nutricional que reciben los pacientes con DM1 en el campo de la adherencia a la Dieta Mediterránea, y su relación con la RD y los resultados percibidos por el paciente (calidad de vida y satisfacción con el tratamiento). Al no disponer de estudios previos realizados en este tipo de población, se diseñaron 5 estudios transversales llevados a cabo en dos centros hospitalarios de diferentes territorios de Catalunya: el Hospital Universitari Arnau de Vilanova de Lleida y el Hospital Universitari Germans Trias i Pujol de Badalona. Estos estudios se centraron en tres bloques principales que permitieron estudiar los hábitos dietéticos de los pacientes con diabetes autoinmune en distintas localidades y su relación con la presencia de RD y con los resultados percibidos por el paciente. Estos bloques son los siguientes:

- El patrón dietético en los pacientes con DM1 y su relación con los resultados percibidos por el paciente.
- Ingesta dietética y resultados percibidos por el paciente con DM1 y RD.
- Los resultados percibidos por el paciente con LADA.

El patrón dietético en los pacientes con DM1 y su relación con los resultados percibidos por el paciente.

Realizamos un estudio comparativo de los hábitos dietéticos entre los pacientes con DM1 y un grupo comparable de sujetos sin diabetes, para evaluar las posibles diferencias en el patrón dietético de ambos grupos. Además, determinamos la potencial asociación entre el patrón dietético (Dieta Mediterránea y alimentación saludable) con los resultados percibidos por el paciente. Los pacientes con DM1 tuvieron un índice aMED y aHEI más elevado como resultado de una mayor adherencia a la Dieta Mediterránea y una alimentación más saludable que el grupo control. Además, encontramos que la DM1, la realización de actividad física regular y una edad mayor se relacionaron con

puntuaciones más altas en ambos índices. El hecho de residir en una zona no urbana y tener un nivel educativo elevado se relacionó con una alimentación más saludable (mayores puntuaciones en el aHEI). En cambio, el sexo masculino se asoció con una alimentación menos saludable (menor puntuación en el aHEI). La adherencia a la Dieta Mediterránea moderada y alta se asoció con una mejor calidad de vida relacionada con la diabetes en los pacientes con DM1. La satisfacción con el tratamiento no se relacionó con el aMED ni el aHEI; sin embargo, los ítems "conveniencia" y "flexibilidad" del cuestionario DTSQ se relacionaron positivamente con el aHEI. Por otra parte, el ítem "recomendar a otros" (refiriéndose al hecho de recomendar el tratamiento a otros pacientes que presenten una diabetes similar a la suya) se asoció negativamente con el aHEI.

Cabe destacar, que este es el primer trabajo específicamente diseñado para evaluar la adherencia a la Dieta Mediterránea, el patrón dietético saludable y la ingesta de alimentos y nutrientes en pacientes adultos con DM1 en comparación con un grupo de población sin diabetes, y su relación con la calidad de vida y satisfacción con el tratamiento.

Los resultados de nuestro estudio fueron consistentes con otras evidencias científicas publicadas en relación a los hábitos dietéticos de los pacientes con DM1 (49,50,102–104); a pesar de que los pacientes con DM1 presentaron una moderada adherencia a la Dieta Mediterránea y a un patrón de alimentación saludable, la adherencia a las recomendaciones nutricionales establecidas por la ADA no fue óptima. Solamente existen tres estudios científicos que comparen los hábitos dietéticos entre los pacientes con DM1 y población no diabética (96,105,106). En dos de ellos se observó que los pacientes con DM1 tenían una menor ingesta energética y un consumo de proteínas y vegetales más elevado, hallazgos que son similares a los del presente estudio (105,106); por otra parte, los pacientes con DM1 mostraron una baja ingesta de carbohidratos y un consumo de ácidos grasos saturados (SFA) elevado, con un IG similar entre ambos grupos de estudio, contrariamente a lo que muestran nuestros resultados. Tahbaz et al. realizaron un estudio para auditar el manejo dietético de los adultos con DM1 (96). Los autores no encontraron diferencias en el consumo de

macronutrientes entre los pacientes con DM1 y los controles; reconocieron que el estudio presentaba un importante sesgo de selección, y, además, ambos grupos de estudio no fueron emparejados por edad y sexo. Este sesgo de selección se debió a que los pacientes incluidos en este estudio eran mayores en edad, y no en todos se disponía de valores de HbA1c de los seis meses previos al estudio; además, solamente algo más de la tercera parte estaban tratados con tratamiento intensivo con insulina, por lo que no es un grupo probablemente representativo de la población actual con DM1. Cabe destacar también que el grupo control se reclutó a partir de familiares y amigos de los pacientes, y el estudio presenta un importante porcentaje de datos dietéticos no respondidos.

Otros estudios con diseño de caso-control realizados en niños y adolescentes con DM1 han encontrado que los pacientes con DM1 presentaban unos hábitos dietéticos más saludables en comparación con los sujetos sin diabetes (107,108). Sin embargo, se ha descrito que los hábitos dietéticos de los niños y adolescentes con DM1 están principalmente determinados por los hábitos alimentarios de los progenitores (107,108).

En nuestro estudio, los pacientes con DM1 tuvieron un índice aMED y aHEI más favorable en comparación con el grupo control. Sin embargo, según la categorización del índice aHEI, la mediana fue baja en ambos grupos. Gingras et al. y Leroux et al. realizaron un estudio transversal en Canadá en el que se observó que el 49% de los pacientes con DM1 presentaba una adherencia a la Dieta Mediterránea moderada, dato similar a nuestros resultados (109,110); sin embargo, este estudio se realizó con una muestra de participantes pequeña y sin grupo control, por lo que no fue posible establecer conclusiones acerca del impacto que tiene la educación nutricional que reciben los pacientes con DM1.

El hecho de residir en una zona no urbana es un factor que está fuertemente relacionado con índices de calidad alimentaria más altos en los pacientes con DM1 en comparación con la población sin

diabetes. El contexto socio-geográfico tiene una importante influencia a la hora de determinar el patrón dietético de cualquier población. Por ello, se han encontrado resultados contradictorios en los diferentes estudios citados en este trabajo de investigación, ya que es un factor que no se ha tenido en cuenta previamente. Este punto es importante tenerlo en consideración en los futuros estudios de investigación, al igual que la selección de un grupo control comparable.

Respecto a la calidad de vida, solamente existe un estudio con diseño transversal realizado en jóvenes y adolescentes con DM1 que estudie la relación entre la adherencia a la Dieta Mediterránea y la calidad de vida (95), aunque no observaron asociación; quizás se debió a la muestra pequeña de participantes (n = 31) con una baja adherencia a la Dieta Mediterránea. Por otra parte, existen pocos estudios publicados sobre este tema en pacientes con DM2 (91–93). Un ensayo clínico aleatorizado diseñado para evaluar la efectividad de una intervención con Dieta Mediterránea en la reducción de los factores de riesgo cardiovascular en mujeres post-menopáusicas con DM2, encontró una mejor CVRS en aquellas mujeres que presentaban una mayor adherencia a la Dieta Mediterránea (91); adicionalmente, un sub-análisis transversal del estudio PREDIMED-PLUS observó la misma asociación (93). Sin embargo, ambos estudios utilizaron cuestionarios genéricos para medir la calidad de vida. Nuestro grupo realizó un estudio previo en pacientes con DM2 en el que encontramos una asociación positiva entre la Dieta Mediterránea y la calidad de vida (92); estos resultados son similares a los actuales. Finalmente, Li et al. realizaron un estudio transversal con una gran muestra de pacientes diabéticos (sin identificar el tipo) (n = 16.428) en el que observaron una asociación positiva entre la CVRS y un estilo de vida saludable (no fumar, consumir 5 raciones de frutas y verduras al día y realizar actividad física regular) (94); dichos hallazgos confirman nuestros resultados.

En relación con la satisfacción con el tratamiento, no hemos podido identificar ningún estudio que lo relacione con el patrón dietético en pacientes con DM1. En nuestro estudio previo realizado en

pacientes con DM2, encontramos una asociación entre una satisfacción con el tratamiento mayor y la adherencia a la Dieta Mediterránea alta (92). Otros estudios transversales realizados con este tipo de diabetes encontraron una asociación positiva con la adherencia a la terapia médico-nutricional (111,112). Sin embargo, aunque encontramos asociación con algunos ítems del cuestionario DTSQ, no observamos ninguna relación con la satisfacción con el tratamiento global; quizás se debió a una muestra de participantes con baja puntuación en la satisfacción con el tratamiento pequeña.

Ingesta dietética y resultados percibidos por el paciente con DM1 y RD.

Este estudio se diseñó para evaluar las diferencias en el consumo de alimentos y nutrientes entre los pacientes con DM1 que presentaban RD y aquellos sin dicha complicación, en ausencia de otras complicaciones avanzadas relacionadas con la enfermedad. Los resultados mostraron que la ingesta elevada de grasas totales, MUFA, ácido oleico y vitamina E se asoció con una menor prevalencia de RD en los pacientes con DM1. Sin embargo, el consumo elevado de carbohidratos complejos se relacionó con una presencia mayor de RD. Hasta donde llega nuestro conocimiento, este es el primer estudio que analiza la posible relación entre la ingesta de nutrientes y sus fuentes alimentarias con la presencia de RD en pacientes adultos con DM1. Por otra parte, evaluamos las diferencias en la calidad de vida y satisfacción con el tratamiento entre un grupo de pacientes con RD y sin RD. Los resultados indicaron que los pacientes con DM1 y RD presentaban una menor calidad de vida en comparación con aquellos sin RD. No se observaron diferencias entre ambos grupos en relación con la satisfacción con el tratamiento global, aunque los pacientes con RD mostraron una mayor frecuencia de hipoglucemias percibidas.

Un sub-análisis prospectivo del estudio DCCT encontró una asociación entre la ingesta elevada de grasas, SFA, MUFA y una mayor presencia de RD en pacientes con DM1, aunque los resultados no fueron ajustados por las variables de confusión potenciales, tales como edad, sexo, hábito tabáquico, duración de la enfermedad, HbA1c, IMC, hipertensión y dislipemia (53,59); estos

resultados se contraponen a los encontrados en nuestro estudio. Un estudio prospectivo de 6 años de seguimiento realizado con una gran muestra de pacientes con DM1 (n = 469) mostró que estos pacientes tenían un consumo de SFA, PUFA y colesterol elevado (54); no se observó relación entre la ingesta nutricional y la incidencia de RD. Otro estudio transversal realizado con una muestra de pacientes con DM1 y DM2 que presentaban un control glucémico óptimo obtuvo resultados similares (55). Por otra parte, nuestro grupo realizó un estudio en pacientes con DM2 en el que encontramos asociación entre la ingesta elevada de MUFA y una prevalencia y gravedad de la RD menor (113); estos resultados fueron similares a los que aquí se presentan. El estudio PREDIMED demostró que la Dieta Mediterránea suplementada con aceite de oliva virgen extra (rico en MUFA) estaba relacionada con una menor incidencia de RD en los pacientes con DM2 (114). Dos meta-análisis de ensayos clínicos demostraron que una dieta rica en MUFA mejora la HbA1c y la glucosa postprandial en pacientes con diabetes en comparación con una dieta baja en MUFA o rica en carbohidratos (115,116). Schwingshackl et al. describieron que los MUFA tienen potentes beneficios en el perfil lipídico (incrementando los niveles séricos de colesterol HDL) de los pacientes con diabetes (116). Es de gran relevancia tener en cuenta estos efectos debido al posible efecto protector de los MUFA en la prevención de complicaciones diabéticas a largo plazo. En relación al consumo de PUFA, el estudio PREDIMED demostró que una dieta rica en PUFA estaba relacionada con una menor incidencia de RD en pacientes con DM2 (117); estos resultados fueron confirmados por Sasaki et al. en un estudio transversal realizado con una muestra de pacientes diabéticos bien controlados (55). En cambio, el estudio DCCT encontró resultados contradictorios con estos últimos, al haberse observado un riesgo mayor de desarrollar RD asociado a una ingesta de PUFA alta (53). Sin embargo, nuestro estudio no observó asociación entre el consumo de PUFA y la RD. Finalmente, en un estudio prospectivo realizado por Roy et al. en 469 pacientes con DM1 se encontraron resultados similares (54).

Los resultados del presente estudio mostraron que la ingesta elevada de carbohidratos complejos se

asoció con mayor presencia de RD. El estudio EURODIAB halló que una dieta rica en carbohidratos complejos, sin tener en cuenta la fibra dietética, estaba asociada con mayores niveles de HbA1c, que a largo plazo determina un mayor riesgo de aparición de complicaciones crónicas de la diabetes (118); estos resultados apuntan en la misma dirección que los de nuestro estudio. En cambio, el estudio DCCT observó que una alta ingesta de carbohidratos y fibra dietética estaba relacionada con una menor presencia de RD en adolescentes y jóvenes con DM1 (53). Otros estudios realizados en pacientes con DM1 y DM2 no encontraron ninguna asociación entre la ingesta de carbohidratos y la RD (54,55,119,120). Por tanto, son necesarias nuevas investigaciones para aclarar este punto.

En relación con la ingesta de vitamina E, nuestros resultados asociaron la alta ingesta de dicha vitamina con una menor presencia de RD; esto podría deberse a un consumo de grasas vegetales elevado. Mayer-Davis et al. observaron que una ingesta alta de vitamina E estaba asociada con más riesgo de desarrollar RD en pacientes con DM2 (121); sin embargo, otros estudios prospectivos y transversales no encontraron dicha relación (55,122,123). Son necesarios más estudios para confirmar estos resultados debido a los pocos estudios y a la controversia que existe en la evidencia científica publicada.

En relación con los resultados percibidos por el paciente, un estudio que incluyó pacientes con DM1 y DM2 conjuntamente, no encontró asociación entre la calidad de vida y la RD (75); esta muestra presentaba, además, otras complicaciones que pudieron influir en los resultados finales, como por ejemplo, pie diabético. Este estudio mostró resultados contradictorios con los de nuestro estudio y, aunque los investigadores utilizaron un cuestionario específico de calidad de vida, su estudio no se diseñó específicamente para evaluar la relación entre la calidad de vida y la RD. Por otra parte, los estudios de carácter transversal realizados con cuestionarios genéricos en pacientes con DM1 no encontraron relación entre la RD y la calidad de vida (68,77,80). Fenwick et al. tampoco encontraron asociación entre la RD y la calidad de vida en una muestra de pacientes con DM1 y

DM2 utilizando un cuestionario genérico (78). Por otra parte, Hart et al. realizaron un estudio prospectivo en pacientes con DM1 utilizando instrumentos genéricos (79); observaron una asociación negativa entre la presencia de complicaciones diabéticas y la CVRS, a pesar de que los pacientes presentaban una elevada frecuencia de comorbilidades (58,1%) y otras complicaciones distintas de la RD. Además, un sub-estudio realizado a partir del estudio *Diabetes Adjustment For Normal Eating* (DAFNE) (83), un programa de educación con el objetivo de aprender a ajustar la dosis de insulina según las raciones de carbohidratos para mantener una alimentación normal en pacientes con DM1, encontró una menor CVRS en pacientes con DM1 que presentaban RD; estos resultados son consistentes con los del presente estudio. Aunque los investigadores de los estudios comentados previamente utilizaron instrumentos genéricos para medir una condición específica relacionada con la diabetes, la muestra de pacientes presentaba otras complicaciones y éstas, además, fueron auto-reportadas (79,83); todo ello pudo influir en los resultados finales de dichos estudios. Un estudio transversal realizado en pacientes con DM1 observó una menor CVRS en pacientes con RD grave (84); nuestros resultados están en línea con los de dicho estudio, aunque los autores no ajustaron los datos por otras complicaciones. Otros estudios transversales realizados en pacientes con DM1 y DM2 observaron que una menor CVRS estaba asociada con la presencia de RD (82,124); esto es similar a lo hallado en nuestro estudio, aunque los investigadores también utilizaron cuestionarios genéricos y los datos obtenidos con ambos tipos de diabetes estaban analizados conjuntamente. En el estudio previo realizado por nuestro grupo en pacientes con DM2, se observó el impacto negativo de la presencia y gravedad de la RD sobre la calidad de vida (86). Además, el estudio PANORAMA obtuvo resultados similares en una gran muestra de pacientes con DM2 (n = 5813) (88). Estos hallazgos son similares a los encontrados en el presente estudio en pacientes con DM1, aunque los dos tipos de diabetes presentan claramente distintas características clínicas.

En relación a la satisfacción con el tratamiento, nuestro estudio no obtuvo diferencias en la

puntuación global del DTSQ entre ambos grupos; esto fue similar a los resultados encontrados en el estudio PANORAMA y otras evidencias publicadas en pacientes con DM2 (86,88,125). En pacientes con DM1, no existen estudios publicados que relacionen la satisfacción con el tratamiento y la presencia de RD en este grupo de población. Observamos que la frecuencia de hipoglucemias percibidas por el paciente estuvo asociada con la RD en el presente estudio; este hecho probablemente estuvo relacionado con un control glucémico pobre.

Resultados percibidos por el paciente con LADA

Llevamos a cabo un estudio observacional, transversal, para evaluar las diferencias en la calidad de vida y satisfacción con el tratamiento entre los pacientes con LADA comparándolo con aquellos con DM1 y DM2. Los sujetos con LADA presentan un curso de la diabetes autoinmune que se expresa clínicamente de manera diferencial y diferente del de la DM1, incluyendo un manejo distinto de la propia diabetes. En este estudio, observamos que los pacientes con LADA presentaban una calidad de vida relacionada con la diabetes menor en comparación con los pacientes con DM2. El tratamiento con insulina tuvo un impacto negativo en la calidad de vida. El grupo de pacientes con LADA tratados con insulina mostró una calidad de vida más baja en comparación con los pacientes DM2 tratados con insulina. Además, los pacientes con LADA tratados con insulina y con presencia de RD fueron los que mostraron una calidad de vida global más baja. En relación con la satisfacción con el tratamiento, no hubo diferencias en la puntuación final entre grupos. Por otra parte, los pacientes con LADA tuvieron una mayor frecuencia en la percepción de hiperglucemias respecto los pacientes con DM1 y DM2, principalmente en el grupo de pacientes tratados con insulina. En cambio, los pacientes con DM1 tuvieron una frecuencia de hipoglucemias percibidas mayor en comparación con los pacientes con LADA.

El impacto negativo del tratamiento con insulina en los pacientes LADA está asociado a una menor autopercepción en su calidad de vida, que puede estar relacionado con el pobre control glucémico

que presentan estos pacientes al iniciar el tratamiento con insulina de forma tardía. El estudio PANORAMA realizado con una muestra de pacientes con DM2 en España, determinó que los pacientes diabéticos con un control metabólico deficiente presentaban una calidad de vida más pobre (126); en cambio, en el presente estudio no se encontraron diferencias relacionadas con el control glucémico.

Se ha descrito que los pacientes con DM1 y DM2 tratados con insulina y con presencia de complicaciones tardías de la diabetes presentan una menor calidad de vida (127). En un estudio previo realizado por nuestro grupo, observamos que los pacientes con DM2 y RD tenían una calidad de vida menor que aquellos que no presentaban esta complicación (86). Además, otros estudios han descrito que la terapia con insulina y las complicaciones tardías estaban asociadas a peor una calidad de vida en pacientes con DM2 (126–131); el presente estudio, por tanto, confirma los hallazgos previos publicados en sujetos con DM2.

En relación a la satisfacción con el tratamiento, los resultados mostraron una satisfacción elevada a pesar del impacto negativo de la diabetes en la calidad de vida de los pacientes; estos hallazgos ya habían sido descritos en varios estudios previos (66,128,130). No se observaron diferencias en la satisfacción con el tratamiento global entre ambos grupos; sin embargo, los pacientes LADA tratados con insulina tenían una autopercepción en la frecuencia de hiperglucemias mayor, aunque el control glucémico no fue distinto entre los grupos de estudio. Pensamos que este hecho se puede atribuir al pobre control glucémico que presentaban previamente los pacientes con LADA en comparación con los pacientes con DM1 bien controlados. Debemos destacar que los pacientes con LADA fueron reclutados de las consultas hospitalarias donde estos pacientes son derivados desde atención primaria por su dificultad para mantener un control glucémico óptimo. Por el contrario, los pacientes con DM1 tenían una mayor percepción en la frecuencia de hipoglucemias debido, probablemente, al tratamiento intensivo que reciben estos pacientes.

Entre las limitaciones de este trabajo de investigación se encuentra su diseño transversal, ya que no permite establecer relaciones de causalidad entre las variables de estudio; además, no pudimos evaluar los cambios producidos en los hábitos dietéticos de la población a lo largo del tiempo, de forma prospectiva. Probablemente, los hábitos dietéticos saludables de los pacientes con DM1 sean debidos, al menos en buena parte, a la educación nutricional recibida por parte de los profesionales de la salud, aunque no podamos concluir este hecho en nuestro estudio, ya que no se evaluó el grado de conocimiento sobre el manejo dietético de la diabetes. Tampoco podemos realizar recomendaciones nutricionales específicas a la población derivadas de este estudio. Además, los cambios experimentados en la calidad de vida y satisfacción con el tratamiento producidos a lo largo del tiempo no pueden ser evaluados. La neuropatía diabética no se evaluó en esta muestra de pacientes, y es una complicación que podría afectar en los resultados percibidos por el paciente, aunque el pie diabético fue un criterio de exclusión. Sin embargo, las variaciones producidas en la calidad de vida de los pacientes están fuertemente influenciadas por las características que no sufren cambios a lo largo del tiempo (77). Otra limitación es el tamaño muestral de los pacientes con LADA, el cual se debe tener especialmente en cuenta a la hora de extrapolar los resultados a la población. Además, un porcentaje elevado de pacientes con LADA rechazó la participación al estudio; no obstante, no se observaron diferencias estadísticamente significativas con los participantes del estudio en edad, sexo, tabaquismo, duración de la diabetes, presencia de hipertensión, dislipemia, RD, microalbuminuria y en el control glucémico. Como limitación cabe destacar el sesgo de selección de los pacientes LADA al ser reclutados en el ámbito hospitalario por presentar un control glucémico y de la enfermedad deficiente. Los pacientes con LADA que presentan un buen control glucémico siguen sin ser identificados en atención primaria, ya que principalmente, se diagnostican y tratan como pacientes con DM2. La calidad de vida es un aspecto primordial en estos pacientes que son derivados a atención hospitalaria por su pobre control glucémico y la necesidad de recibir tratamiento con insulina. Por último, el bienestar emocional es un aspecto que puede tener cierto impacto en los resultados de este estudio, aunque actualmente, no

existe un cuestionario específico validado en España para evaluar el bienestar emocional en pacientes diabéticos (72). Aun así, el cuestionario ADDQoL-19 utilizado en este trabajo está constituido por algunos ítems que son específicos para evaluar el aspecto emocional de los pacientes diabéticos.

Las fortalezas del estudio fueron el tamaño muestral, el diseño multicéntrico y la muestra cuidadosamente caracterizada y definida, que permitió establecer la variabilidad de las diferentes poblaciones (zona rural y semiurbana, y una zona totalmente urbana) y estilos de vida, a diferencia de los estudios publicados sobre el tema. El uso de un cuestionario de frecuencia de consumo de alimentos permitió estimar la ingesta de alimentos y de nutrientes; además, este cuestionario es representativo de la ingesta estimada durante los 5 años anteriores a la realización de la encuesta (132). También cabe destacar que es el primer estudio que evalúa el patrón dietético e ingesta nutricional en pacientes adultos con DM1 y su potencial relación con la calidad de vida y satisfacción con el tratamiento, utilizando cuestionarios específicos para ello. Adicionalmente, este es el primer estudio a nivel internacional que evalúa las diferencias en la calidad de vida y satisfacción con el tratamiento en pacientes con LADA, DM1 y DM2. Se han publicado muchos estudios en este campo que han utilizado instrumentos genéricos para medir dominios específicos de la calidad de vida relacionados con la diabetes. Sin embargo, se ha demostrado que existe una falta de sensibilidad de estos instrumentos en este tipo de estudios (72,89,133). Los resultados de nuestro trabajo se deben considerar como base para generar nuevas hipótesis que permitan abrir futuras líneas de investigación.

Conclusiones

7. Conclusiones

- Los pacientes con diabetes tipo 1 mostraron un patrón de alimentación más saludable y una adherencia a la Dieta Mediterránea mayor que los sujetos sin diabetes de la misma población. El hecho de residir en un área geográfica mediterránea no urbana se asoció con un patrón dietético más saludable.
- Los pacientes con diabetes tipo 1 sin retinopatía diabética tuvieron un consumo de grasas más saludable que los pacientes con retinopatía.
- La elevada ingesta de ácidos grasos monoinsaturados, ácido oleico y vitamina E se asoció con una menor presencia de retinopatía diabética en pacientes con diabetes tipo 1. En cambio, una ingesta elevada de carbohidratos se relacionó con la presencia de retinopatía diabética.
- Entre los pacientes con LADA procedentes de consultas especializadas, aquellos con retinopatía diabética tratados con insulina mostraron una menor calidad de vida en comparación con los pacientes con diabetes tipo 1 y tipo 2.
- En este mismo grupo de estudio, los pacientes con LADA presentaron una frecuencia de hiperglucemias percibidas mayor que los pacientes con diabetes tipo 1 y tipo 2.
- En los pacientes con diabetes tipo 1, la presencia de retinopatía diabética se asoció con una peor percepción de la calidad de vida.
- Además, estos pacientes con diabetes tipo 1 y retinopatía diabética mostraron una mayor frecuencia de hipoglucemias percibidas en comparación con los pacientes sin retinopatía diabética.
- La adherencia a la Dieta Mediterránea moderada y alta se asoció con una mejor calidad de vida en los pacientes con diabetes tipo 1.
- La satisfacción con el tratamiento no se relacionó con la Dieta Mediterránea ni el patrón de alimentación saludable en los pacientes con diabetes tipo 1.

Relevancia en la clínica y la investigación

8. Relevancia en la clínica y la investigación

Es necesario realizar más estudios de carácter prospectivo y de intervención que generen nuevo conocimiento y ayuden a diseñar nuevas estrategias nutricionales para aumentar la adherencia a la Dieta Mediterránea y obtener un patrón de alimentación más saludable en los pacientes con diabetes tipo 1. Además, los nuevos programas de educación nutricional podrían contribuir a mejorar el control glucémico y prevenir la aparición de complicaciones relacionadas con la diabetes, como la retinopatía diabética.

La terapia médico-nutricional dirigida a aumentar la adherencia a la Dieta Mediterránea y a un patrón dietético más saludable no solamente debe ir enfocada a mejorar los resultados clínicos de la enfermedad (control glucémico, perfil lipídico, factores de riesgo cardiovascular y aparición de complicaciones), sino también a los resultados percibidos por el paciente como la calidad de vida y satisfacción con el tratamiento. Esto es muy importante de cara a futuras líneas de investigación basadas en estos resultados, que permitan el diseño de programas y campañas de educación sanitaria y nutricional que mejoren la calidad de vida y satisfacción con el tratamiento de los pacientes con diabetes autoinmune.

En relación con los pacientes con diabetes LADA se pueden abrir nuevas líneas de investigación destinadas al diseño e implementación de programas que mejoren el diagnóstico temprano y su tratamiento para mejorar la calidad de vida de estos pacientes, reduciendo la aparición de complicaciones como la retinopatía diabética y estableciendo nuevos tratamientos focalizados en este tipo de pacientes. Además, los resultados presentados en este trabajo dan a conocer a los profesionales sanitarios la diabetes LADA y el impacto que ejerce en la calidad de vida de estos pacientes.

En definitiva, esta tesis doctoral permite dar conocimiento sobre el impacto que tienen los

programas de educación nutricional individual que se realizan actualmente en los pacientes con diabetes tipo 1. Además, con los resultados presentados se pueden diseñar nuevas líneas de investigación con estudios prospectivos y de intervención dirigidos a aumentar la adherencia a la Dieta Mediterránea y mejorar la calidad de vida y satisfacción con el tratamiento de los pacientes adultos con diabetes autoinmune. La presente tesis doctoral aporta conocimiento sobre un campo en el que existe una falta de estudios científicos que estén diseñados específicamente para evaluar los hábitos dietéticos y los resultados percibidos por el paciente en adultos con diabetes autoinmune.

Bibliografía

9. Bibliografía

1. Aguilar M. Prevención secundaria de la diabetes mellitus. In: Abordaje Integral de la Diabetes. 2006. p. 101–8.

2. Ruiz-Ramos M, Escolar-Pujolar A, Mayoral-Sánchez E, Corral-San Laureano F, Fernández-Fernándezc I. La diabetes mellitus en España: mortalidad, prevalencia, incidencia, costes económicos y desigualdades. Gac Sanit. 2006;20(Supl.1):15–24.

3. Goday A. Epidemiología de la diabetes y sus complicaciones no coronarias. Rev Española Cardiol. 2002;55(6):657–70.

4. Abellana R, Ascaso C, Carrasco JL, Castell C, Tresserras R. Geographical variability of the incidence of Type 1 diabetes in subjects younger than 30 years in Catalonia, Spain. Med Clin (Barc). 2009;132(12):454–8.

5. Mayoral González B, Riaño Galán I, Rodriguez Dehli C, Labra Alvarez R, Díaz Naya L, Menéndez Torre E. Epidemiología de la diabetes tipo 1 en Asturias: 2002-2011. Endocrinol Diabetes y Nutr. 2018;65(2):68–73.

6. Imkampe AK, Gulliford MC. Trends in Type1 diabetes incidence in the UK in 0- to 14-year-olds and in 15- to 34-year-olds, 1991-2008. Diabet Med. 2011;28(7):811–4.

7. Kyvik KO, Nystrom L, Gorus F, Songini M, Oestman J, Castell C, et al. The epidemiology of Type 1 diabetes mellitus is not the same in young adults as in children. Diabetologia. 2004;47(3):377–84.

8. International Diabetes Federation. IDF Diabetes Atlas Eighth Edition 2017. International Diabetes Federation. 2017. 150 p.

9. American Diabetes Association. Classification and diagnosis of diabetes: Standards of medical care in Diabetesd2018. Diabetes Care. 2018;41(Suppl 1):S13–27.

10. Skyler JS, Bakris GL, Bonifacio E, Darsow T, Eckel RH, Groop L, et al. Differentiation of diabetes by pathophysiology, natural history, and prognosis. Diabetes. 2017;66(2):241–55.

11. Insel RA, Dunne JL, Atkinson MA, Chiang JL, Dabelea D, Gottlieb PA, et al. Staging presymptomatic type 1 diabetes: A scientific statement of jdrf, the endocrine society, and the American diabetes association. Diabetes Care. 2015;38(10):1964–74.

12. Stenstrom G, Gottsater A, Bakhtadze E, Berger B, Sundkvist G. Latent Autoimmune Diabetes in Adults: Definition, Prevalence, -Cell Function, and Treatment. Diabetes. 2005;54(Supplement 2):S68–72.

13. Leslie RD, Palmer J, Schloot NC, Lernmark A. Diabetes at the crossroads: relevance of disease classification to pathophysiology and treatment. Diabetologia. 2016;59(1):13–20.

14. Hawa MI, Kolb H, Schloot N, Beyan H, Paschou SA, Buzzetti R, et al. Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: Action LADA 7. Diabetes Care. 2013;36(4):908–13.

15. Fourlanos S, Dotta F, Greenbaum CJ, Palmer JP, Rolandsson O, Colman PG, et al. Latent autoimmune diabetes in adults (LADA) should be less latent. Diabetologia. 2005;48(11):2206–12.

16. Hawa MI, Thivolet C, Mauricio D, Alemanno I, Cipponeri E, Collier D, et al. Metabolic syndrome and autoimmune diabetes: Action LADA 3. Diabetes Care. 2009;32(1):160–4.

17. Isomaa B, Almgren P, Henricsson M, Taskinen MR, Tuomi T, Groop L, et al. Chronic complications in patients with slowly progressing autoimmune type 1 diabetes (LADA). Diabetes Care. 1999;22(8):1347–53.

18. Mollo A, Hernandez M, Marsal JR, Esquerda A, Rius F, Blanco-Vaca F, et al. Latent autoimmune diabetes in adults is perched between type 1 and type 2: Evidence from adults in one region of spain. Diabetes Metab Res Rev. 2013;29(6):446–51.

19. Rosário PWS, Reis JS, Amim R, Fagundes TA, Calsolari MR, Silva SC, et al. Comparison of clinical and laboratory characteristics between adult-onset type 1 diabetes and latent autoimmune diabetes in adults. Diabetes Care. 2005;28(7):1803–4.

20. Hernandez M, Mollo a, Marsal JR, Esquerda a, Capel I, Puig-Domingo M, et al. Insulin secretion in patients with latent autoimmune diabetes (LADA): half way between type 1 and type 2 diabetes: action LADA 9. BMC Endocr Disord. 2015;15(1):1.

21. World Health Organization. Classification of diabetes mellitus 2019. Clinics in Laboratory Medicine. Geneva; 2019.

22. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet. 2010;376:124–36.

23. Corcóstegui B, Durán S, González-Albarrán MO, Hernández C, Ruiz-Moreno JM, Salvador J, et al. Update on Diagnosis and Treatment of Diabetic Retinopathy: A Consensus Guideline of the Working Group of Ocular Health (Spanish Society of Diabetes and Spanish Vitreous and Retina Society). J Ophthalmol. 2017;2017.

24. Ting DSW, Cheung GCM, Wong TY. Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review. Clin Exp Ophthalmol. 2016;44(4):260–77.

25. Romero-Aroca P, Baget-Bernaldiz M, Fernandez-Ballart J, Plana-Gil N, Soler-Lluis N, Mendez-

Marin I, et al. Ten-year incidence of diabetic retinopathy and macular edema. Risk factors in a sample of people with type 1 diabetes. Diabetes Res Clin Pract. 2011;94(1):126–32.

26. American Diabetes Association. Microvascular complications and foot care: Standards of medical care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S105–18.

27. Mann JI. The role of nutritional modifications in the prevention of macrovascular complications of diabetes. Diabetes. 1997;46 Suppl 2:S125–30.

28. Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, Franz MJ, et al. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. Diabetes Care. 2008;31(Suppl 1):S61–78.

29. Mann J, Lean M, Toeller M. Recommendations for the nutritional management of patients with diabetes mellitus. Eur J Clin Nutr. 2000;54:353–5.

30. American Diabetes Association. Lifestyle management: Standards of medical care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S38–50.

31. Catalan Association of Diabetes. Documento de consenso sobre "Recomendaciones nutricionales y de educación alimentaria en la diabetes." ACD. Barcelona; 2013.

32. American Diabetes Association. Lifestyle management. Sec. 4. In Standards of Medical Care in Diabetes-2017. Diabetes Care. 2017;40(Suppl. 1):S33–43.

33. Rosolova H, Pelikanova T, Motovska Z. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with EASD. Summary of the document prepared by the Czech Society of Cardiology. Eur Heart J. 2013;34(39):3035–87.

34. Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013;368(14):1279–90.

35. Schoenaker DAJM, Toeller M, Chaturvedi N, Fuller JH, Soedamah-Muthu SS. Dietary saturated fat and fibre and risk of cardiovascular disease and all-cause mortality among type 1 diabetic patients: The EURODIAB Prospective Complications Study. Diabetologia. 2012;55:2132–41.

36. Buyken AE, Toeller M, Heitkamp G, Karamanos B, Rottiers R, Muggeo M, et al. Glycemic index in the diet of European outpatients with type 1 diabetes: Relations to glycated hemoglobin and serum lipids. Am J Clin Nutr. 2001;73:574–81.

37. Overby NC, Flaaten V, Veierød MB, Bergstad I, Margeirsdottir HD, Dahl-Jørgensen K, et al. Children and adolescents with type 1 diabetes eat a more atherosclerosis-prone diet than healthy control subjects. Diabetologia. 2007;50(2):307–16.

38. Beulens J, Kruidhof J, Grobbee D. Alcohol consumption and risk of microvascular complications in type 1 diabetes patients: the EURODIAB Prospective Complications Study. Diabetologia. 2008;51:1631–8.

39. Chimen M, Kennedy A, Nirantharakumar K, Pang TT, Andrews R, Narendran P. What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. Diabetologia. 2011;55:542–51.

40. Tielemans SMAJ, Soedamah-Muthu SS, De Neve M, Toeller M, Chaturvedi N, Fuller JH, et al. Association of physical activity with all-cause mortality and incident and prevalent cardiovascular disease among patients with type 1 diabetes: The EURODIAB Prospective Complications Study. Diabetologia. 2013;56:82–91.

41. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. BMJ. 2008;337:a1344.

42. Lairon D. Intervention studies on Mediterranean diet and cardiovascular risk. Mol Nutr Food Res. 2007;51(10):1209–14.

43. Vincent-Baudry S, Defoort C, Gerber M, Bernard M-CC, Verger P, Helal O, et al. The Medi-RIVAGE study: Reduction of cardiovascular disease risk factors after a 3-mo intervention with a Mediterranean-type diet or a low-fat diet. Am J Clin Nutr. 2005;82(5):964–71.

44. Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Ruiz-Gutiérrez V, Covas MI, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Ann Intern Med. 2006;145(1):1–11.

45. Pérez-Jiménez F, López-Miranda J, Pinillos MD, Gómez P, Paz-Rojas E, Montilla P, et al. A mediterranean and a high-carbohydrate diet improve glucose metabolism in healthy young persons. Diabetologia. 2001;44:2038–43.

46. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, et al. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA. 2004;292(12):1440–6.

47. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. PLoS Med. 2010;7(3):e1000252.

48. Guasch-Ferré M, Salas-Salvadó J, Ros E, Estruch R, Corella D, Fitó M, et al. The PREDIMED trial, Mediterranean diet and health outcomes: How strong is the evidence? Nutr Metab Cardiovasc Dis. 2017;27(7):624–32.

49. The Diabetes and Nutrition Study Group of the Spanish Diabetes Association. Diabetes Nutrition and Complications Trial: adherence to the ADA nutritional recommendations, targets of metabolic control, and onset of diabetes complications. A 7-year, prospective, population-based, observational multicenter study. J Diabetes Complications. 2006;20(6):361–6.

50. The Diabetes and Nutrition Study Group of the Spanish Association. Diabetes Nutrition and Complications Trial. Trends in nutritional pattern between 1993 and 2000 and targets of diabetes treatment in a sample of Spanish people with diabetes. Diabetes Care. 2004;27(4):2000–3.

51. Serra-Majem L, Ribas-Barba L, Salvador G, Jover L, Raidó B, Ngo J, et al. Trends in energy and nutrient intake and risk of inadequate intakes in Catalonia, Spain (1992-2003). Public Health Nutr. 2007;10(11 A):1354–67.

52. Klein R, Lee KE, Gangnon RE, Klein BEK. The 25-Year Incidence of Visual Impairment in Type 1 Diabetes Mellitus. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. Ophthalmology. 2010;117(1):63–70.

53. Cundiff DK, Nigg CR. Diet and diabetic retinopathy: insights from the Diabetes Control and Complications Trial (DCCT). MedGenMed. 2005;7(1):3.

54. Roy MS, Janal MN. High caloric and sodium intakes as risk factors for progression of retinopathy in type 1 diabetes mellitus. Arch Ophthalmol. 2010;128(1):33–9.

55. Sasaki M, Kawasaki R, Rogers S, Man REK, Itakura K, Xie J, et al. The associations of dietary intake of polyunsaturated fatty acids with diabetic retinopathy in well-controlled diabetes. Investig Ophthalmol Vis Sci. 2015;56(12):7473–9.

56. Engelen L, Soedamah-Muthu SS, Geleijnse JM, Toeller M, Chaturvedi N, Fuller JH, et al. Higher dietary salt intake is associated with microalbuminuria, but not with retinopathy in individuals with type 1 diabetes: the EURODIAB Prospective Complications Study. Diabetologia. 2014;57(11):2315–23.

57. Harjutsalo V, Feodoroff M, Forsblom C, Groop PH. Patients with Type 1 diabetes consuming alcoholic spirits have an increased risk of microvascular complications. Diabet Med. 2014;31(2):156–64.

58. Moss SE, Klein R, Klein BE. Alcohol consumption and the prevalence of diabetic retinopathy. Ophthalmology. 1992;99(6):926–32.

59. Wong MYZ, Man REK, Fenwick EK, Gupta P, Li L-J, van Dam RM, et al. Dietary intake and diabetic retinopathy: A systematic review. PLoS One. 2018;13(1):e0186582.

60. Dow C, Mancini F, Rajaobelina K, Boutron-Ruault M-C, Balkau B, Bonnet F, et al. Diet and risk of diabetic retinopathy: a systematic review. Eur J Epidemiol. 2018;33(2):141–56.

61. Howard-Williams J, Patel P, Jelfs R, Carter RD, Awdry P, Bron A, et al. Polyunsaturated fatty acids and diabetic retinopathy. Br J Ophthalmol. 1985 Jan 1;69(1):15–8.

62. Roig-Revert MJ, Lleó-Pérez A, Zanón-Moreno V, Vivar-Llopis B, Marín-Montiel J, Dolz-Marco R, et al. Enhanced Oxidative Stress and Other Potential Biomarkers for Retinopathy in Type 2 Diabetics: Beneficial Effects of the Nutraceutic Supplements. Biomed Res Int. 2015;2015:1–12.

63. Villar-López J, Lizán-Tudela L, Soto-Alvarez J P-MS. Treatment satisfaction. Atención Primaria. 2009;41(11):637–45.

64. Mauricio D. Quality of life and treatment satisfaction are highly relevant patient-reported outcomes in type 2 diabetes mellitus. Ann Transl Med. 2018;6(11):220.

65. Doward LC, Mckenna SP. Defining Patient-Reported Outcomes. Value Heal. 2004;7(Suppl 1):S4-8.

66. Speight J, Reaney MD, Barnard KD. Not all roads lead to Rome-a review of quality of life measurement in adults with diabetes. Diabet Med. 2009;26(4):315–27.

67. Miranda Velasco MJ, Domínguez Martín E, Arroyo Díez FJ, Méndez Pérez P, González de Buitrago Amigo J. Calidad de vida relacionada con la salud en la diabetes mellitus tipo 1. An Pediatría. 2012;77(5):329–33.

68. Ahola AJ, Saraheimo M, Forsblom C, Hietala K, Sintonen H, Groop P-H, et al. Health-related quality of life in patients with type 1 diabetes-association with diabetic complications (the FinDiane Study). Nephrol Dial Transplant. 2010;25(6):1903–8.

69. Imayama I, Plotnikoff RC, Courneya KS, Johnson JA. Determinants of quality of life in adults with type 1 and type 2 diabetes. Heal Qual Life Outcomes. 2011;9(1):115.

70. Logtenberg SJ, Kleefstra N, Houweling ST, Groenier KH, Gans RO, Bilo HJ. Health-Related Quality of Life, Treatment Satisfaction, and Costs Associated With Intraperitoneal Versus Subcutaneous Insulin Administration in Type 1 Diabetes. Diabetes Care. 2010;33(6):1169.

71. Bradley C, Todd C, Gorton T, Symonds E, Martin A, Plowright R. The development of an individualised questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL. Qual Life Res. 1999;8:79–81.

72. Sánchez-Lora FJ, Santana TT, Trigueros AG. Instrumentos específicos de medida de la calidad de vida relacionada con la salud en la diabetes mellitus tipo 2 disponibles en España. Med Clin (Barc). 2010;135(14):658–64.

73. Hendrick AM, Gibson M V., Kulshreshtha A. Diabetic Retinopathy. Prim Care Clin Off Pr. 2015;42(3):451–64.

74. van Hecke M V, Dekker JM, Stehouwer CDA, Polak BCP, Fuller JH, Sjolie AK, et al. Diabetic retinopathy is associated with mortality and cardiovascular disease incidence: the EURODIAB prospective complications study. Diabetes Care. 2005 Jun;28(6):1383–9.

75. Nyanzi R, Wamala R, Atuhaire LK. Diabetes and quality of life: A Ugandan perspective. J Diabetes Res. 2014;2014.

76. Ahola AJ, Saraheimo M, Forsblom C, Hietala K, Sintonen H, Groop PH. Health-related quality of life in patients with type 1diabetes--association with diabetic complications (the FinnDiane Study). Nephrol Dial Transplant. 2010;25(6):1903–8.

77. Alva M, Gray A, Mihaylova B, Clarke P. The effect of diabetes complications of health-related quality of life: the importance of longitudinal data to address patient heterogeneity. Health Econ. 2014;23:487–500.

78. Fenwick EK, Xie J, Ratcliffe J, Konrad P, Finger RP, Wong TY, et al. The impact of diabetic retinopathy and diabetic macular edema on health-related quality of life in type 1 and type 2 diabetes. Investig Ophthalmol Vis Sci. 2012;53:677–84.

79. Hart HE, Redekop WK, Berg M, Bilo HJG, Meyboom-De Jong B. Factors that predicted change in health-related quality of life were identified in a cohort of diabetes mellitus type 1 patients. J Clin Epidemiol. 2005;58(11):1158–64.

80. Hart HE, Bilo HJG, Redekop WK, Stolk RP, Assink JH, Jong BM. Quality of life of patients with type I diabetes mellitus. Qual Life Res. 2003;12:1089–97.

81. Rodrigues da Mata A, Álvares J, Diniz LM, Ribeiro da Silva MR, Rodrigues Alvernaz dos Santos B, Guerra Júnior AA, et al. Quality of life of patients with diabetes mellitus types 1 and 2 from a referal health centre in Minas Gerais, Brazil. Expert Rev Clin Pharmacol. 2016;9(5):739–46.

82. Solli O, Stavem K, Kristiansen IS. Health-related quality of life in diabetes: The associations of complications with EQ-5D scores. Health Qual Life Outcomes. 2010;8:1–8.

83. Peasgood T, Brennan A, Mansell P, Elliott J, Basarir H, Kruger J. The Impact of Diabetes-Related Complications on Preference-Based Measures of Health-Related Quality of Life in Adults with Type I Diabetes. Med Decis Mak. 2016;36(8):1020–33.

84. Jansson RW, Hufthammer KO, Krohn J. Diabetic retinopathy in type 1 diabetes patients in Western Norway. Acta Ophthalmol. 2018;1–10.

85. Weisman A, Lovblom LE, Keenan HA, Tinsley LJ, D'Eon S, Boulet G, et al. Diabetes care disparities in longstanding type 1diabetes in Canada and the U.S.: A cross-sectional comparison. Diabetes Care. 2018;41(1):88–95.

86. Alcubierre N, Rubinat E, Traveset A, Martinez-Alonso M, Hernandez M, Jurjo C, et al. A prospective cross-sectional study on quality of life and treatment satisfaction in type 2 diabetic patients with retinopathy without other major late diabetic complications. Health Qual Life Outcomes. 2014;12:131.

87. Bradley C. Importance of differentiating health status from quality of life. Lancet. 2001;357:7–8.

88. Bradley C, Eschwège E, de Pablos-Velasco P, Parhofer KG, Simon D, Vandenberghe H, et al. Predictors of Quality of Life and Other Patient-Reported Outcomes in the PANORAMA Multinational Study of People With Type 2 Diabetes. Diabetes Care. 2018 Feb;41(2):267–76.

89. Fenwick EK, Pesudovs K, Rees G, Dirani M, Kawasaki R, Wong TY, et al. The impact of diabetic retinopathy: Understanding the patient's perspective. Br J Ophthalmol. 2010;95(6):774–82.

90. Govindaraju T, Sahle B, McCaffrey T, McNeil J, Owen A. Dietary Patterns and Quality of Life in Older Adults: A Systematic Review. Nutrients. 2018;10(8):971.

91. Toobert DJ, Glasgow RE, Strycker LA, Barrera M, Radcliffe JL, Wander RC, et al. Biologic and Quality-of-Life Outcomes From the Mediterranean Lifestyle Program. Diabetes Care. 2003;26:2288–93.

92. Alcubierre N, Martinez-Alonso M, Valls J, Rubinat E, Traveset A, Hernández M, et al. Relationship of the adherence to the Mediterranean diet with health-related quality of life and treatment satisfaction in patients with type 2 diabetes mellitus: A post-hoc analysis of a cross-sectional study. Health Qual Life Outcomes. 2016;14(1):4–9.

93. Galilea-Zabalza I, Buil-Cosiales P, Salas-Salvadó J, Toledo E, Ortega-Azorín C, Díez-Espino J, et al. Mediterranean diet and quality of life: Baseline cross-sectional analysis of the PREDIMED-PLUS trial. PLoS One. 2018;13(6):2017–9.

94. Li C, Ford ES, Mokdad AH, Jiles R, Giles WH. Clustering of Multiple Healthy Lifestyle Habits and Health-Related Quality of Life Among U.S. Adults With Diabetes. Diabetes Care. 2007;30:1770–6.

95. Mozzillo E, Zito E, Maffeis C, De Nitto E, Maltoni G, Marigliano M, et al. Unhealthy lifestyle habits and diabetes-specific health-related quality of life in youths with type 1 diabetes. Acta Diabetol. 2017;54(12):1073–80.

96. Tahbaz F, Kreis I, Calvert D. An audit of diabetes control, dietary management and quality of life in

adults with type 1 diabetes mellitus, and a comparison with nondiabetic subjects. J Hum Nutr Diet. 2006;19(1):3–11.

97. Pham-Short A, Donaghue KC, Ambler G, Garnett S, Craig ME. Quality of Life in Type 1 Diabetes and Celiac Disease: Role of the Gluten-Free Diet. J Pediatr. 2016;179:131-138.e1.

98. Nunes-Silva JG, Nunes VS, Schwartz RP, Mlss Trecco S, Evazian D, Correa-Giannella ML, et al. Impact of type 1 diabetes mellitus and celiac disease on nutrition and quality of life. Nutr Diabetes. 2017;7(1):4–9.

99. Vaz EC, Porfírio GJM, Nunes HR de C, Nunes-Nogueira V dos S. Effectiveness and safety of carbohydrate counting in the management of adult patients with type 1 diabetes mellitus: a systematic review and meta-analysis. Arch Endocrinol Metab. 2018;(4):337–45.

100. Alcubierre N, Martinez-Alonso M, Valls J, Rubinat E, Traveset A, Hernández M, et al. Relationship of the adherence to the Mediterranean diet with health-related quality of life and treatment satisfaction in patients with type 2 diabetes mellitus: A post-hoc analysis of a cross-sectional study. Health Qual Life Outcomes. 2016;14:69.

101. Granado-Casas M, Alcubierre N, Martín M, Real J, Ramírez-Morros AM, Cuadrado M, et al. Improved adherence to Mediterranean Diet in adults with type 1 diabetes mellitus. Eur J Nutr. 2019;58(6):2271–9.

102. Ahola AJ, Mikkilä V, Mäkimattila S, Forsblom C, Freese R, Groop P-H, et al. Energy and nutrient intakes and adherence to dietary guidelines among Finnish adults with type 1 diabetes. Ann Med. 2012;44(1):73–81.

103. Soedamah-Muthu SS, Chaturvedi N, Fuller JH, Toeller M. Do European people with type 1 diabetes consume a high atherogenic diet? 7-year follow-up of the EURODIAB Prospective Complications Study. Eur J Nutr. 2013;52(7):1701–10.

104. Mayer-Davis EJ, Nichols M, Liese AD, Bell RA, Dabelea DM, Johansen JM, et al. Dietary Intake among Youth with Diabetes: The SEARCH for Diabetes in Youth Study. J Am Diet Assoc. 2006;106(5):689–97.

105. Snell-Bergeon JK, Chartier-Logan C, Maahs DM, Ogden LG, Hokanson JE, Kinney GL, et al. Adults with type 1 diabetes eat a high-fat atherogenic diet that is associated with coronary artery calcium. Diabetologia. 2009;52(5):801–9.

106. Jaacks LM, Du S, Mendez MA, Crandell J, Liu W, Ji L, et al. Comparison of the dietary intakes of individuals with and without type 1 diabetes in China. Asia Pac J Clin Nutr. 2015;24(4):639–49.

107. Maffeis C, Morandi A, Ventura E, Sabbion A, Contreas G, Tomasselli F, et al. Diet, physical, and biochemical characteristics of children and adolescents with type 1 diabetes: Relationship between dietary fat and glucose control. Pediatr Diabetes. 2012;13(2):137–46.

108. Lodefalk M, Aman J. Food habits, energy and nutrient intake in adolescents with Type 1 diabetes mellitus. Diabet Med. 2006;23(11):1225–32.

109. Gingras V, Leroux C, Desjardins K, Savard V, Lemieux S, Rabasa-Lhoret R, et al. Association between Cardiometabolic Profile and Dietary Characteristics among Adults with Type 1 Diabetes Mellitus. J Acad Nutr Diet. 2015;115(12):1965–74.

110. Leroux C, Gingras V, Desjardins K, Brazeau AS, Ott-Braschi S, Strychar I, et al. In adult patients with type 1 diabetes healthy lifestyle associates with a better cardiometabolic profile. Nutr Metab Cardiovasc Dis. 2015;25(5):444–51.

111. Hayashi I, Watanabe N, Nakata S, Komatsu R, Motoda S, Fujita Y, et al. Factors associated with treatment satisfaction in patients with type 2 diabetes mellitus using oral glucose-lowering agents: a cross-sectional study in urban districts in Japan. Endocr J. 2018;65(10):1001–9.

112. Abu Sheikh B, Arabiat DH, Holmes SL, Khader Y, Hiyasat D, Collyer D, et al. Correlates of treatment satisfaction and well-being among patients with type II diabetes. Int Nurs Rev. 2018;65(1):114–21.

113. Alcubierre N, Navarrete-Muñoz EM, Rubinat E, Falguera M, Valls J, Traveset A, et al. Association of low oleic acid intake with diabetic retinopathy in type 2 diabetic patients: a case–control study. Nutr Metab (Lond). 2016;13:40.

114. Díaz-López A, Babio N, Martínez-González MA, Corella D, Amor AJ, Fitó M, et al. Mediterranean Diet, Retinopathy, Nephropathy, and Microvascular Diabetes Complications: A Post Hoc Analysis of a Randomized Trial. Diabetes Care. 2015;38(11):2134–41.

115. Schwingshackl L, Strasser B, Hoffmann G. Effects of monounsaturated fatty acids on glycaemic control in patients with abnormal glucose metabolism: A systematic review and meta-analysis. Ann Nutr Metab. 2011;58(4):290–6.

116. Schwingshackl L, Hoffmann G. Monounsaturated fatty acids and risk of cardiovascular disease: Synopsis of the evidence available from systematic reviews and meta-analyses. Nutrients. 2012;4(12):1989–2007.

117. Sala-Vila A, Díaz-López A, Valls-Pedret C, Cofán M, García-Layana A, Lamuela-Raventós R-M, et al. Dietary Marine ω-3 Fatty Acids and Incident Sight-Threatening Retinopathy in Middle-Aged and Older Individuals With Type 2 Diabetes: Prospective Investigation from the PREDIMED Trial.

JAMA Ophthalmol. 2016;134(10):1142.

118. Buyken AE, Toeller M, Heitkamp G, Irsigler K, Holler C, Santeusanio F, et al. Carbohydrate sources and glycaemic control in type 1 diabetes mellitus. Diabet Med. 2000;17:351–9.

119. Alcubierre N, Navarrete-Muñoz EM, Rubinat E, Falguera M, Valls J, Traveset A, et al. Association of low oleic acid intake with diabetic retinopathy in type 2 diabetic patients: A case-control study. Nutr Metab. 2016;13:40.

120. Horikawa C, Yoshimura Y, Kamada C, Tanaka S, Tanaka S, Matsunaga S, et al. Is the proportion of carbohydrate intake associated with the incidence of diabetes complications?—an analysis of the Japan diabetes complications study. Nutrients. 2017;9(2):1–10.

121. Mayer-Davis EJ, Bell R a, Reboussin B a, Rushing J, Marshall J a, Hamman RF. Antioxidant nutrient intake and diabetic retinopathy. Ophthalmology. 1998;105(12):2264–70.

122. Millen AE, Klein R, Folsom AR, Stevens J, Palta M, Mares JA. Relation between intake of vitamins C and E and risk of diabetic retinopathy in the Atherosclerosis Risk in Communities Study. Am J Clin Nutr. 2004;79(5):865–73.

123. Tanaka S, Yoshimura Y, Kawasaki R, Kamada C, Tanaka S, Horikawa C, et al. Fruit Intake and Incident Diabetic Retinopathy with Type 2 Diabetes. Epidemiology. 2013 Mar;24(2):204–11.

124. Rodrigues da Mata A, Álvares J, Diniz LM, da Silva , Michael Ruberson Ribeiro Alvernaz dos Santos BR, Afonso, Guerra Júnior Augusto Cherchiglia ML, Gurgel Andrade EI, et al. Quality of patients with diabetes mellitus types 1 and 2 from a regerral health care center in Minas Gerais, Brazil. Expert Rev Clin Pharmacol. 2016;9(5):739–46.

125. Biderman A, Noff E, Harris SB, Friedman N, Levy A. Treatment satisfaction of diabetic patients: What are the contributing factors? Fam Pract. 2009;26(2):102–8.

126. Depablos-Velasco P, Salguero-Chaves E, Mata-Poyo J, Derivas-Otero B, Garcia-Sanchez R, Viguera-Ester P. Quality of life and satisfaction with treatment in subjects with type 2 diabetes: results in Spain of the PANORAMA study. Endocrinol Nutr. 2014;61(1):18–26.

127. Collins M, O'Sullivan T, Harkins V, Perry I. Quality of Life and Quality of Care in Patients With Diabetes Experiencing Different Models of Care. Diabetes Care. 2009;32:603–5.

128. Bradley C, Speight J. Patient perceptions of diabetes and diabetes therapy: assessing quality of life. Diabetes Metab Res Rev. 2002;18:S64-9.

129. Shim YT, Lee J, Toh MPHS, Tang WE, Ko Y. Health-related quality of life and glycaemic control in patients with Type 2 diabetes mellitus in Singapore. Diabet Med. 2012;29(8):e241-8.

130. Speight J, Bradley C. ADDQoL indicates negative impact of diabetes on quality of life despite high levels of satisfaction with treatment. Diabetologia. 2000;43(Suppl 1):A225.

131. Sundaram M, Kavookjian J, Patrick JH, Miller L-A, Madhavan SS, Scott VG. Quality of life, health status and clinical outcomes in Type 2 diabetes patients. Qual Life Res. 2007;16(2):165–77.

132. Vioque J, Gonzalez L. Validez de la evaluación de la ingesta dietética. In: Serra Majem L, Aranceta Bartrina J, editors. Nutrición y salud pública Métodos, bases científicas y aplicaciones. 2ª edición. Barcelona: Masson-Elsevier; 2006. p. 199–210.

133. Rubin RR, Peyrot M. Quality of Life and Diabetes. Diabetes Metab Res Rev. 1999;15:205–18.

Anexo 1

Audit of Diabetes-Dependent Quality of Life Questionnaire (ADDQoL-19)

ADDQoL

Este cuestionario trata sobre su calidad de vida, en otras palabras, en qué medida le parece que su vida es buena o mala.

Por favor, marque con una "X" la casilla que mejor indique su respuesta a cada pregunta.

Lo que queremos saber es cómo se siente con su vida actualmente.

I) En general, mi calidad de vida actualmente es:

☐ excelente	☐ muy buena	☐ buena	☐ ni buena ni mala	☐ mala	☐ muy mala	☐ malísima

Ahora, nos gustaría saber cómo afecta a su calidad de vida la diabetes, su control (incluyendo medicación, visitas al médico, alimentación…) y las complicaciones que usted pudiera tener.

II) Si *no* tuviera diabetes, mi calidad de vida sería:

☐ muchísimo mejor	☐ mucho mejor	☐ un poco mejor	☐ igual	☐ peor

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En las páginas siguientes encontrará una serie de preguntas más concretas. Por favor, responda a todas ellas. Para cada aspecto de la vida que se describa, encontrará dos apartados:

En el apartado a)	marque con una "X" la casilla que indique cómo afecta la diabetes a ese aspecto de su vida;
En el apartado b)	marque con una "X" la casilla que indique hasta qué punto ese aspecto de su vida es importante para su calidad de vida.

1	(a)	**Si *no* tuviera diabetes, podría disfrutar de mis actividades de ocio:**				
		☐ muchísimo más	☐ mucho más	☐ un poco más	☐ igual	☐ menos
	(b)	**Mis actividades de ocio son:**				
		☐ muy importantes	☐ importantes	☐ un poco importantes	☐ nada importantes	

Anexo 2

Diabetes Treatment Satisfaction Questionnaire (DTSQ)

Cuestionario de Satisfacción con el Tratamiento para la Diabetes: DTSQs

Las siguientes preguntas están relacionadas con el tratamiento de su diabetes (incluyendo insulina, comprimidos y/o dieta) y su experiencia en estas últimas semanas. Por favor conteste a cada pregunta haciendo un círculo en un número de cada una de las escalas.

1. ¿En qué medida está Vd. satisfecho/a con su tratamiento actual?

   muy satisfecho/a 6 5 4 3 2 1 0 muy insatisfecho/a

2. Últimamente, ¿con qué frecuencia ha considerado que su nivel de azúcar en la sangre era inaceptablemente alto?

   la mayoría del tiempo 6 5 4 3 2 1 0 nunca

Anexo 3

Cuestionario de Frecuencia de Consumo Alimentario

CUESTIONARIO DE FRECUENCIA ALIMENTARIA (UMH)

IDNUM | | | | |

Esta parte de la encuesta es para conocer su dieta habitual. Sus respuestas serán muy útiles, y por ello, le agradecemos sinceramente que preste la máxima atención y colaboración. Cuando un alimento no se adapte plenamente a su consumo habitual, trate de aproximar su respuesta a las cantidades indicadas, con ayuda de ejemplos e indicaciones que se le den.

Para cada alimento, señalar cuantas veces como media ha tomado la cantidad que se indica durante el último año. Debe tener en cuenta las veces que toma el alimento solo y cuando lo añade a otro alimento o plato. Por ejemplo, en el caso del huevo, considere cuando lo toma solo (Ej. frito o cocido) y cuando lo toma añadido o mezclado con otros platos (ej. tortilla, revueltos). Si en este tiempo meses ha comido habitualmente una tortilla de 2 huevos cada 2 días, deberá marcar para el huevo "1 por día". No debe considerar el huevo que va con los productos de bollería o dulces.

I. LACTEOS	Nunca ó <1 mes	1-3 por mes	1 por sem	2-4 por sem	5-6 por sem	1 por día	2-3 por día	4-5 por día	6+ por día
1. Leche entera (1 vaso o taza, 200 cc)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
2. Leche semi-desnatada (1 vaso, 200cc)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
3. Leche desnatada (1 vaso, 200cc)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
4. Leche condensada (1 cucharada)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
5. Nata o crema de leche (1 cucharada)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
6. Yogur entero (uno, 125 gramos)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
7. Yogur desnatado (uno, 125 gramos)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
8. Requesón, queso blanco o fresco (una porción o ración, 100 g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
9. Queso curado, semicurado, o cremoso (un trozo, 50 gramos)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
10. Natillas, flan, puding (uno)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
11. Helados (1 cucurucho, vasito o bola)	①	②	③	④	⑤	⑥	⑦	⑧	⑨

II. HUEVOS, CARNES, PESCADOS	Nunca ó <1 mes	1-3 por mes	1 por sem	2-4 por sem	5-6 por sem	1 por día	2-3 por día	4-5 por día	6+ por día
12. Huevos de gallina (uno)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
13. Pollo CON piel (1 plato mediano o pieza)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
14. Pollo SIN piel (1 plato mediano o pieza)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
15. Carne de ternera, cerdo, cordero como plato principal (1 plato mediano o pieza)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
16. Carne de caza: conejo, codorniz, pato (1 plato)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
17. Hígado de ternera, cerdo, pollo (1 plato, ración o pieza mediana)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
18. Vísceras: callos, sesos, mollejas (1 ración, 100 g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
19. Embutidos: jamón, salchichón, salami, mortadela, (1 ración de unos 50 g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
20. Salchichas y similares (una mediana)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
21. Patés, foie-gras (media ración, 50 g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
22. Hamburguesa (una mediana, 100 g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
23. Tocino, beicon, panceta (2 tiras o lonchas, 50 g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
24. Pescado frito variado (1 plato mediano o ración)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
25. Pescado hervido o plancha BLANCO: merluza, lenguado, dorada (1 plato o ración)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
26. Pescado hervido o plancha AZUL: atún, emperador, bonito, (plato o ración)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
27. Otros pescados azules: caballa, sardinas, boquerón/anchoas, salmón	①	②	③	④	⑤	⑥	⑦	⑧	⑨
28. Una lata pequeña de conserva de atún o bonito en aceite	①	②	③	④	⑤	⑥	⑦	⑧	⑨
29. Una lata pequeña de conserva de sardinas o caballa en aceite	①	②	③	④	⑤	⑥	⑦	⑧	⑨
30. Pescados en salazón y/o ahumados: anchoas, bacalao, salmón (media ración, 50g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
31. Almejas, mejillones, ostras (1 ración, 100 g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
32. Calamares, chipirones, sepia, choco, pulpo (1 ración o plato, 100 g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
33. Marisco: gambas, cangrejo, langostino, langosta (1 ración 100 g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨

III. VERDURAS, LEGUMBRES.	Nunca ó <1 mes	1-3 por mes	1 por sem	2-4 por sem	5-6 por sem	1 por día	2-3 por día	4-5 por día	6+ por día
34. Espinacas o acelgas cocinadas (1 plato mediano)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
35. Col, coliflor, brócolis cocinadas (1 plato mediano)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
36. Lechuga, endibias, escarola (1 plato mediano)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
37. Tomate (uno mediano)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
38. Cebolla (una mediana)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
39. Zanahoria, calabaza (una o plato pequeño)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
40. Judías verdes cocinadas (1 plato)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
41. Berenjenas, calabacines, pepinos (uno)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
42. Pimientos (uno)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
43. Alcachofas (una ración o plato mediano, 100 g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
44. Espárragos (una ración o plato)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
45. Maíz hervido (plato o lata pequeña, 82 g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
46. Legumbres: lentejas, garbanzos, judías pintas o blancas (1 plato mediano)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
IV. FRUTAS	Nunca ó <1 mes	1-3 por mes	1 por sem	2-4 por sem	5-6 por sem	1 por día	2-3 por día	4-5 por día	6+ por día
47. Naranjas, mandarinas (Una)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
48. Zumo de naranja natural (un vaso pequeño, 125 cc)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
49. Plátano (uno)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
50. Manzana, pera (una mediana)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
51. Melocotón, nectarina, albaricoque (uno mediano)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
52. Sandía, melón (1 tajada o cala, mediana)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
53. Uvas (un racimo mediano o plato de postre)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
54. Prunas, ciruelas frescas/secas (una, 37 g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
55. Kiwi (una unidad)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
56. Aceitunas (un platito o tapa de unas 15 unidades pequeñas)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
57. Frutos secos: almendras, cacahuetes, piñones, avellanas (1 platito o bolsita, 30g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
V. PAN, CEREALES Y SIMILARES	Nunca ó <1 mes	1-3 por mes	1 por sem	2-4 por sem	5-6 por sem	1 por día	2-3 por día	4-5 por día	6+ por día
58. Pan blanco (Una pieza pequeña o 3 rodajas de pan de molde, 60 g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
59. Pan integral (Pieza pequeña o 3 rodajas de pan de molde)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
60. Cereales desayuno (30 g en seco)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
61. Patatas fritas (1 ración o plato, 100 g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
62. Patatas cocidas, asadas (1 patata mediana)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
63. Bolsa de patatas fritas (1 bolsa pequeña, 25-30 g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
64. Arroz cocinado (1 plato mediano)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
65. Pastas: espaguetis, fideos, macarrones y similares (1 plato)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
66. Pizza (1 porción o ración, 200 g)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
VI. ACEITES, GRASAS Y DULCES	Nunca ó <1 mes	1-3 por mes	1 por sem	2-4 por sem	5-6 por sem	1 por día	2-3 por día	4-5 por día	6+ por día
67. Aceite de oliva añadido en la mesa a ensalada, pan y a platos (1 cucharada sopera)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
68. Otros aceites vegetales (ídem): girasol, maíz, soja (1 cucharada sopera)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
69. Margarina añadida al pan o la comida (1 cucharada o untada)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
70. Mantequilla añadida al pan o la comida (1 cucharada o untada)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
71. Galletas tipo María (1 galleta)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
72. Galletas con chocolate (1 galleta doble)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
73. Bollería: croissant, donut, magdalena, bizcocho, tarta o similar (uno o porción)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
74. Chocolate, bombones y similares (1 barrita o 2 bombones)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
75. Chocolate en polvo, cola-cao y similares (1 cucharada sopera)	①	②	③	④	⑤	⑥	⑦	⑧	⑨

VII. BEBIDAS Y MISCELANEAS	Nunca ó <1 mes	1-3 por mes	1 por sem	2-4 por sem	5-6 por sem	1 por día	2-3 por día	4-5 por día	6+ por día
76. Vino tinto (1 vaso, 125 cc)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
77. Vino blanco o rosado (1 vaso, 125 cc)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
78. Jerez, vinos secos, vermú (copa, 50 cc)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
79. Cerveza (una caña o botellín 1/5, 200 cc)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
80. Cerveza sin alcohol (una caña o botellín 1/5, 200 cc)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
81. Licores (20-25º): de frutas (manzana), de crema (Catalana, Bayleys) (1 copa, 50 cc)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
82. Brandy, ginebra, ron, whisky, vodka, aguardientes 40º (1 copa, 50 cc)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
83. Refrescos normales de cola, naranja, limón (ej. coca-cola, fanta) (Uno, 250 cc)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
84. Refrescos sin azúcar cola, naranja, limón (ej. coca-cola o pepsi *light*) (Uno, 250 cc)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
85. Agua del grifo (1 vaso, 250 cc)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
86. Agua embotellada sin gas (1 vaso, 250 cc)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
87. Agua embotellada con gas (1 vaso, 250 cc)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
88. Zumo de frutas envasado (1 vaso o envase de 200cc)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
89. Café (1 taza)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
90. Café descafeinado (1 taza)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
91. Té o infusiones (1 taza)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
92. Sopa o puré de verduras (un plato)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
93. Croquetas de pollo, jamón (una)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
94. Croquetas, palitos o delicias de pescado fritos (una)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
95. Mayonesa (1 cucharada)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
96. Salsa de tomate (media taza)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
97. Ketchup ó catchup (1 cucharada sopera)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
98. Sal añadida a los platos en la mesa (1 pizca del salero o pellizco con dos dedos)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
99. Ajo (1 diente)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
100. Mermeladas, miel (1 cucharada)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
101. Azúcar (ej. en el café, postres, etc.) (1 cucharadita)	①	②	③	④	⑤	⑥	⑦	⑧	⑨
¿Consume algún otro alimento regularmente al menos una vez a la semana?									
_ _	①	②	③	④	⑤	⑥	⑦	⑧	⑨
_ _	①	②	③	④	⑤	⑥	⑦	⑧	⑨

Consumo de suplementos vitamínicos o minerales

1. Durante el último año, ¿ha tomado suplementos de vitaminas o minerales?

	Nombre comercial y presentación	**Dosis semanal dosis,/sem.**	**Pauta habitual de uso** 1 1-3 meses; 2 4-6 meses 3 7-9 meses ; 4 10-12 meses	**¿Sigue tomándolo?**	**Si no, fecha de finalización**
a. Sal yodada	_ _ _ _ _ _ _ _ _ _ _ _ _	_ _ _ _ _ _ _ _	1 2 3 4	1 Si 2 No	_ _ _ / _ _ _ _ _
e. Fibra/supl ricos en fibra	_ _ _ _ _ _ _ _ _ _ _ _ _	_ _ _ _ _ _ _ _	1 2 3 4	1 Si 2 No	_ _ _ / _ _ _ _ _
f. Multivitaminas	_ _ _ _ _ _ _ _ _ _ _ _ _	_ _ _ _ _ _ _ _	1 2 3 4	1 Si 2 No	_ _ _ / _ _ _ _ _
g. Acido fólico	_ _ _ _ _ _ _ _ _ _ _ _ _	_ _ _ _ _ _ _ _	1 2 3 4	1 Si 2 No	_ _ _ / _ _ _ _ _
h. Complejo A + E	_ _ _ _ _ _ _ _ _ _ _ _ _	_ _ _ _ _ _ _ _	1 2 3 4	1 Si 2 No	_ _ _ / _ _ _ _ _
i. Vitamina A	_ _ _ _ _ _ _ _ _ _ _ _ _	_ _ _ _ _ _ _ _	1 2 3 4	1 Si 2 No	_ _ _ / _ _ _ _ _
j. Vitamina E	_ _ _ _ _ _ _ _ _ _ _ _ _	_ _ _ _ _ _ _ _	1 2 3 4	1 Si 2 No	_ _ _ / _ _ _ _ _
k. Vitamina C	_ _ _ _ _ _ _ _ _ _ _ _ _	_ _ _ _ _ _ _ _	1 2 3 4	1 Si 2 No	_ _ _ / _ _ _ _ _
l. Hierro	_ _ _ _ _ _ _ _ _ _ _ _ _	_ _ _ _ _ _ _ _	1 2 3 4	1 Si 2 No	_ _ _ / _ _ _ _ _
m. Calcio	_ _ _ _ _ _ _ _ _ _ _ _ _	_ _ _ _ _ _ _ _	1 2 3 4	1 Si 2 No	_ _ _ / _ _ _ _ _
n. Complejo B	_ _ _ _ _ _ _ _ _ _ _ _ _	_ _ _ _ _ _ _ _	1 2 3 4	1 Si 2 No	_ _ _ / _ _ _ _ _
o. Zinc	_ _ _ _ _ _ _ _ _ _ _ _ _	_ _ _ _ _ _ _ _	1 2 3 4	1 Si 2 No	_ _ _ / _ _ _ _ _
p. Otros Suplementos (Anotar) _ _ _ _ _ _ _ _ _ _ _ _ _		_ _ _ _ _ _ _ _	1 2 3 4	1 Si 2 No	_ _ _ / _ _ _ _ _

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1. ¿Ha seguido usted algún tipo de dieta desde la última entrevista?

*(Si responde **NO** pasar a pregunta 3)*

① No ② Sí ⑨ No sabe/No contesta

2. ¿Podría indicar el motivo de seguir esta dieta? *Puede marcar más de una respuesta*

① para controlar su peso
② porque tiene colesterol
③ porque tiene azúcar o diabetes
④ porque tiene problemas de estómago
⑤ porque tiene problemas de vesícula o hígado
⑥ porque tiene problemas de tensión alta o de corazón
⑦ porque tiene problemas de riñón
⑧ porque tiene alergia a algunos alimentos
⑨ porque tiene ácido úrico o gota
⑩ porque es vegetariana
①① por otro motivo, ¿cual? _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

3. Desde la última entrevista ¿cómo ha cambiado su ingesta para los siguientes grupos de alimentos, con respecto a la del año antes del embarazo?

	Eliminado	↓	Igual	↑	Ns/Nc
a. Lácteos y derivados	①	②	③	④	⑨
b. Huevos	①	②	③	④	⑨
c. Carne	①	②	③	④	⑨
d. Pescado	①	②	③	④	⑨
e. Verduras	①	②	③	④	⑨
f. Legumbres	①	②	③	④	⑨
g. Frutas	①	②	③	④	⑨
h. Pan	①	②	③	④	⑨
i. Aceite de oliva	①	②	③	④	⑨
j. Mantequilla/margarina	①	②	③	④	⑨
k. Azúcar/dulces	①	②	③	④	⑨
l. Bebidas alcohólicas	①	②	③	④	⑨

4. ¿Con qué frecuencia come comidas fritas?

① A diario.
② 5-6 veces por semana.
③ 2-4 veces por semana.
④ 1 vez por semana.
⑤ Menos de 1 vez por semana. ⑨ Ns/Nc

5. ¿Cuándo come carne, cómo de hecha le gusta comerla?

① No como carne (*pasar a pregunta 9*)
② Cruda
③ Poco hecha
④ Hecha
⑤ Muy hecha. ⑨ Ns/Nc

6. ¿Qué hace Vd. con la grasa visible, cuando come carne?

① La quita toda.
② Quita la mayoría.
③ Quita un poco.
④ No quita nada. ⑨ Ns/Nc

7. ¿Cómo suele comer la carne

	Nunca	Veces al Mes	Semana	Día	Ns/Nc
a. A la plancha	___	___	___	___	___
b. A la parrilla (grill)	___	___	___	___	___
c. Asada (horno)	___	___	___	___	___
d. Frita en aceite	___	___	___	___	___
e. Guisada	___	___	___	___	___

8. ¿Cómo de frecuente come lo tostado o quemado de la carne?

① Nunca o menos de una vez al mes
② Una vez al mes
③ 2-3 veces al mes
④ 1 vez a la semana
⑤ 2 o más veces a la semana ⑨ Ns/Nc

9. ¿Cómo de frecuente come la parte tostada del pescado?

① Nunca o menos de una vez al mes
② Una vez al mes
③ 2-3 veces al mes
④ 1 vez a la semana
⑤ 2 o más veces a la semana ⑨ Ns/Nc

10. ¿Cómo de frecuente come el tostado (*socarrat*) de la paella?,

① Nunca o menos de una vez al mes
② Una vez al mes
③ 2-3 veces al mes
④ 1 vez a la semana
⑤ 2 o más veces a la semana ⑨ Ns/Nc

11. ¿Qué clase de grasa o aceite usa para:

	Mantequilla	Margarina	Ac.Oliva	Ac.Ol virgen	Ac. Veg	Mezcla Ac.
ALIÑAR	___	___	___	___	___	___
COCINAR	___	___	___	___	___	___
FREIR	___	___	___	___	___	___

ACTIVIDAD FISICA Y EJERCICIO durante el embarazo *(desde la última entrevista)*

1. Desde la última entrevista, ¿podría indicarme Vd. cuántas horas al día suele dormir, incluida la siesta?

_ _ _ _ _ _ horas

2. ¿Cuántos minutos de <u>siesta</u> suele dormir al día?

_ _ _ _ _ _ _ min.

3. ¿Cuántas horas ve usted la televisión, a la semana? *(ajustar al número entero más cercano)*

_ _ _ _ _ _ horas

4. En su actividad en el trabajo u ocupación principal está...

① Casi siempre sentado
② Sentado la mitad del tiempo
③ Casi siempre de pie, quieto
④ Casi siempre caminando, levantando y llevando pocas cosas
⑤ Casi siempre caminando, levantando y llevando muchas cosas
⑥ Trabajo manual pesado

5. ¿Cuánto tiempo camina o hace bicicleta al día?

① Casi nunca
② Menos de 20 minutos al día
③ 20-40 minutos al día
④ 40-60 minutos al día
⑤ Entre 1 y 1 hora y media al día
⑥ Más de 1 hora y media al día

6. ¿Cuánto tiempo dedica a actividades o tareas en casa?

① Menos de 1 hora al día
② 1-2 horas / día
③ 3-4 horas / día
④ 5-6 horas / día
⑤ 7-8 horas / día
⑥ Más de 8 horas / día

7. En su actividad en tiempo libre, ¿cuánto tiempo dedica a ver televisión, ordenador o leer?

① Menos de 1 hora al día
② 1 hora / día
③ 2 horas / día
④ 3 horas / día
⑤ 4 horas / día
⑥ 5-6 horas / día
⑦ Más de 6 horas / día

8. En su actividad en tiempo libre, ¿cuánto tiempo dedica a hacer ejercicio o deporte

① Menos de 1 hora a la semana
② 1 hora / semana
③ 2 horas / semana
④ 3 horas / semana
⑤ 4-5 horas / semana
⑥ Más de 5 horas / semana

9. Considerando <u>toda</u> su actividad física (trabajo u ocupación principal, hogar y tiempo libre), ¿cómo se considera Vd.?

① **Sedentaria** (sentado casi siempre, sin actividad física, sin deporte, bajo cuidados).
② **Poco activa** (profesiones o actividades sentadas, amas de casa con electrodomésticos, escaso deporte).
③ **Moderadamente activa** (trabajos manuales, amas de casa sin electrodomésticos, deporte ligero, etc)
④ **Bastante activa** (trabajos o actividades de pie-andando, deporte intenso, etc.).
⑤ **Muy activa** (Trabajo muy vigoroso, deporte fuerte diario)
⑨ No sabe / no contesta