Genetic variability and telomere length in bariatric surgery outcomes in obese patients

Elionora Peña Lozano

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Variabilitat genètica i longitud telomèrica en la resposta a la cirurgia bariàtrca en pacients amb obesitat

Memòria presentada per
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For the mad people, the only people for me are the mad ones, the ones who are mad to live, mad to talk, mad to be saved, desirous of everything at the same time, the ones who never yawn or say a commonplace thing, but burn, burn, burn like fabulous yellow roman candles exploding like spiders across the stars and in the middle you see the blue centerlight pop and everybody goes

J.K

"Corpulence [obesity] is not only a disease itself, but the harbinger of others"

-Hippocrates, 460-370 BC-

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1. Introduction

1.1. Obesity

Obesity is a worldwide public health problem that has been increasing in the last decades. According to the World Health Organization (WHO), obesity and overweight are defined as "abnormal or excessive fat accumulation that may impair health" [1]. However, no precise definition of 'excess' exists, and the degree of adiposity is a continuous trait without any clear division between normal and abnormal [2]. Increased consumption of highly caloric food, without an equal increase in energy expenditure, mainly by physical activity, leads to an unhealthy increase in weight; decreased levels of physical activity will result in an energy imbalance and will lead to weight gain.

The most used measurement to assess weight status is **body mass index** (BMI). It is defined as a person's weight in kilograms divided by the square of the person's height in meters (kg/m^2). The WHO recommends the following BMI cut points to classify weight status for adults over 20 years old (Table 1).

Table 1. Weight status classification for adults according to BMI.

Category	BMI, kg/m^2
Underweight	< 18.5
Normal weight	18.5 - 24.9
Pre-obesity	25.0 - 29.9
Obesity class I	30.0 - 34.9
Obesity class II	35.0 - 40
Obesity class III	> 40

BMI was developed as a risk indicator of disease; as BMI increases, so does the risk for some diseases. BMI is very easy to measure and to calculate and is therefore the most frequently used tool to correlate risk of health problems with the weight at population level. However, like any other measure it is not perfect because it is only dependent on height and weight and it does not take into consideration different levels of adiposity based on age, physical activity levels and sex. For this reason, it is expected that it overestimates adiposity in some cases and underestimates it in others.

Other measures, such as **waist circumference** (WC) and **waist-hip ratio** (WHR) are used in many cases to determine abdominal obesity status and can complement BMI estimates. The recommend WC cut points for determining abdominal obesity status as ≥ 102 cm in men and ≥ 88 cm in women of non-Asian origin and ≥ 90 cm in Asian men and ≥ 80 cm in Asian women [3]. According to guidelines from the WHO, abdominal obesity status can be identified as a WHR of >0.90 in men and >0.85 in women [4]. Furthermore, for an accurate assessment of body composition a number of established methods and techniques can be used such as anthropometry, densitometry, imageing and bioimpedance. Each method has its strengths and limitations, and scientific acceptability and appropriateness of each method depends upon the situation [5].

1.2. Epidemiology

Obesity has become a global epidemic problem and it represents one of the **primary causes of preventable deaths**. According to the WHO, in 2016 an estimated 1.9 billion adults were considered overweight and more than 650 million adults were obese, translating to 13% of the worldwide adult population (11% of men and 15% of women) [1].

It is estimated that by the year 2030, about 57.8% (3.3 billion) of adult population worldwide might be overweight or obese, with higher rates in developing countries than in developed countries [1,6].

Levels of **childhood obesity** have also increased at an alarming rate. Globally, in 2016 the number of overweight children under the age of five, was estimated to be over 41 million [7]. The development of obesity in childhood is associated with higher risk for obesity in adulthood and with an increased risk of non-communicable diseases in later life, such as type 2 diabetes (T2D), cardiovascular diseases (CVD) or different cancers [8]. The increasing prevalence of obesity is associated with **higher mortality, morbidity and disability** and consequently with years of life characterised by deteriorated health and low quality of life. In a meta-analysis study of 2.88 million individuals, obesity was associated with an increase in mortality rate, with a hazard ratio of 1.18 (95% CI, 1.12–1.25) [9]. In this regard, a person with a BMI of 30 kg/m^2 has about a 50% higher risk of dying than someone with a healthy BMI.

In Europe it has been estimated that approximately 25% of schoolchildren have excess weight with higher rates in Spain, Malta, Italy, the United Kingdom and Greece. Focusing on **Spanish population**, two studies of Aranceta-Bartrina and colleagues estimated the prevalence of overweight and obesity in childhood and adult population taking data from the Nutritional Study of the Spanish Population study (ENPE). Both cross-sectional observational studies were designed to collect recent data on consumer dietary habits, anthropometric data, and physical activity in the noninstitutionalized Spanish population aged above 3 years.

The study in Spanish population aged between 3 and 24 years estimated a prevalence of excess weight of 34% with higher prevalence in males than in female participants [10]. Regarding adult population, the prevalence of excess weight was 60.9%, with a 39.3% of the individuals suffering overweight and 21.6% obesity [11] (Table 2).

Table 2. Prevalence of overweight (OW) and obesity (OB) in childhood and adult Spanish population. Measure data collected between 2014-2015.

Study	Age range	Total sample	Female	Male
Aranceta et al 2020	3-8	39.8% of EW - 23.9% OW - 15.9% OB	EW: 37.7% OW: 24.4% OB: 13.3%	EW: 41.9% OW: 23.5% OB: 18.4%
	9-18	34.0% of EW - 22.4% OW - 11.6% OB	EW: 25.8% OW: 17.3% OB: 8.5%	EW: 41.6% OW: 27.0% OB: 14.6%
Aranceta et al 2016	25-64	60.9% of EW -39.3% OW - 21.6% OB 33.4% abdominal obesity	EW: 52.6% OW: 32.1% OB: 20.5% AB: 43.3%	EW: 69.3% OW: 46.5% OB: 22.8% AB: 23.3%

EW: Excess weight, AB: Abdominal obesity.

1.3. Mechanisms underlying obesity

As stated before, obesity is the condition under which adipose tissue is increased resulting in excessive fat accumulation. It is also characterised by an increased systemic inflammation and oxidative stress.

Adipose tissue (AT) represents around 20-30% of the body mass composition. However, in individuals with obesity, it may constitute more than 50%. AT is the main organ for energy storage, but it can also be seen as an endocrine organ that is involved in the coordination of a variety of biological processes including energy metabolism, neuroendocrine function, and immune function [12].

AT produces and releases a variety of **adipokines and cytokines**, including leptin, adiponectin, resistin, as well as tumor necrosis factor -α (TNF-α) and interleukin- 6 (IL-6), among others [13,14]. The physiological functions of these factors, secreted by the adipose tissue are the regulation of: insulin sensitivity, inflammation, cardiovascular function, behavior and cell growth, which results in the development of obesity-induced metabolic diseases [15] (Figure 1). The excess or deficiency of the AT can have adverse metabolic consequences given the important endocrine function of this organ [12].

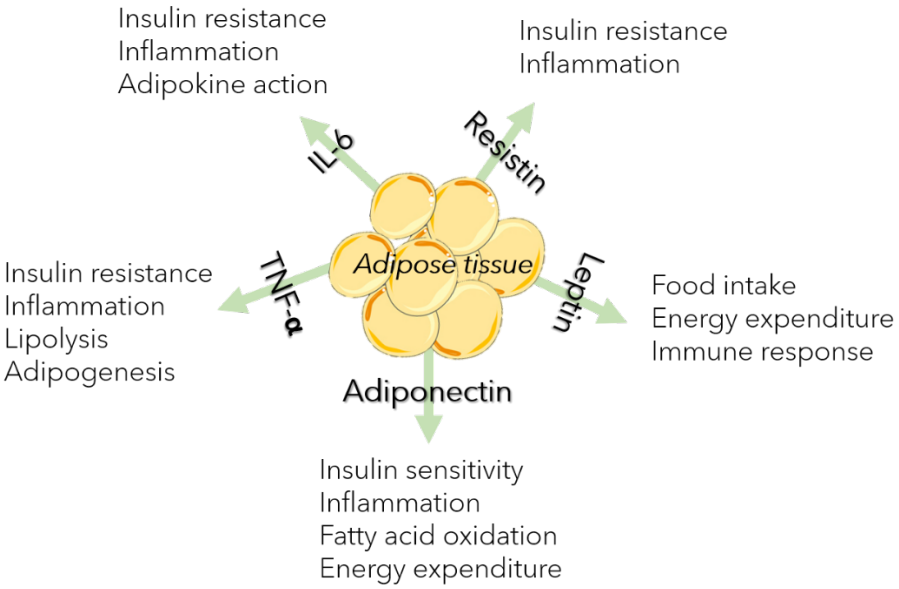

Figure 1. Some of the factors secreted by adipose tissue and its physiological functions.

1.3.1. Inflammation and obesity

The overexpression of pro-inflammatory cytokines including TNF-α and IL-6 by adipose tissue in individuals with obesity is considered the link between obesity and inflammation [16]. Furthermore, it results in a chronic activation of the innate immune system which can, subsequently, lead to insulin resistance, impaired glucose tolerance and even diabetes, co-morbidities found in obese patients [17]. Adipose tissue in patients with obesity is also characterised by macrophage infiltration which represents another source of inflammation in this tissue [18,19]. This state can finally derive in a chronic systemic inflammation, affecting the physiology and metabolism of different tissues such as skeletal muscle, liver, and brain, among others [17].

1.3.2. Oxidative stress and obesity

Oxidative stress (OS) is a state of imbalance between the oxidative and antioxidative systems of cells and tissues, resulting in the production of excessive oxidative free radicals and reactive oxygen species (ROS) [20]. The increase of oxidative stress associated with obesity is probably due to the presence of excessive adipose tissue. When obesity persists for a long time, antioxidant sources can be depleted, decreasing the activity of antioxidant enzymes that protect cells from radical attacks and lower levels of antioxidants (vitamin A, E, C) compared to normoweight individuals [21,22].

High levels of ROS can contribute to the development of metabolic diseases such as obesity, through different mechanisms including chronic adipocyte inflammation, fatty acid oxidation, overconsumption of oxygen and accumulation of cellular damage, and mitochondrial activity.

Furthermore, it has been observed that OS controls food intake and body weight by upholding some effects on hypothalamic neurons with impact on satiety and hunger [23].

Oxidative stress-derived tissue damage leads to an inflammatory response that produces increased inflammatory cytokine levels that in turns drives a further increase in OS. The complex and intimate association between increased OS and increased inflammation makes it difficult to establish the temporal sequence of both [24] (Figure 2).

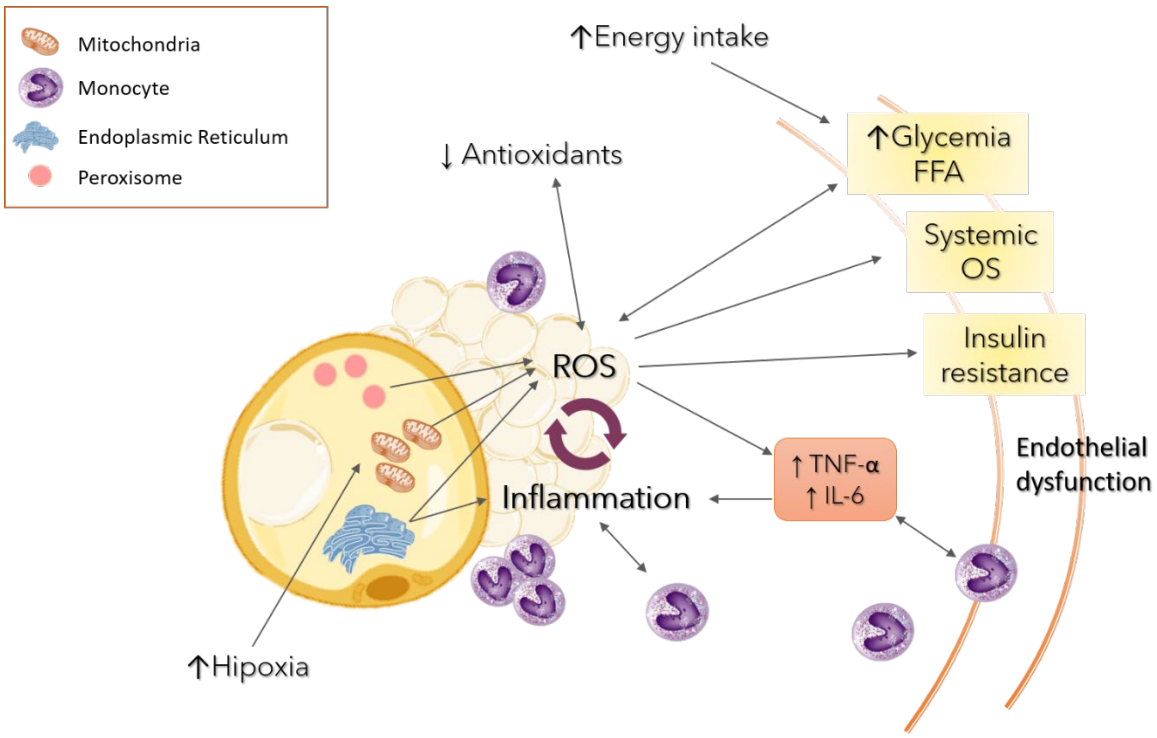

Figure 2. Obesity is associated with an increase in energy intake, which represents an increase in glycemia and in free fatty acids. This increased ROS is due to the overactivation of mitochondria and the endoplasmic reticulum in the cell. Obesity represents an increase of adipose tissue which leads to an inflammatory state and hypoxia. Furthermore, OS worsens the inflammation and alters adipokine secretion by adipose tissue. Many of these phenomena activates monocyte infiltration in adipose tissue which worsens again the inflammatory state. Hypoxia increases glucose uptake and thus mitochondrial function, further contributing to ROS production. Through those mechanisms, ROS contributes to the development of insulin resistance, systemic oxidative stress and endothelial damage. FFA: Free fatty acids; ROS: Reactive oxygen species; OS: Oxidative stress; TNF-α: Tumor necrosis factor; IL-6: Interleukin-6.

1.3.3 Hypothalamic-pituitary-adrenal (HPA) axis and obesity

The HPA axis is one of the main stress response pathways and it is also implicated in the modulation of several physiological processes such as immunity and fertility [25].

The HPA axis mediated the adaptative response to perceived stress. In the presence of a stressor, corticotropin-releasing hormone (CRH) is secreted from the hypothalamus, which acts on the pituitary gland and results in the release of adrenocorticoid hormone (ACTH). This stimulates the production and release of cortisol from the adrenal cortex, which binds to its receptor, the glucocorticoid receptor (GR), that once activated exerts a wide range of effects orchestrating the systemic stress response. Besides this, cortisol also inhibits the synthesis and release of CRH and ACTH in the hypothalamus and the pituitary, enabling a negative feedback regulation critical for the reduction of HPA axis activation and the restoration of homeostasis once the threat has subsided (Figure 3).

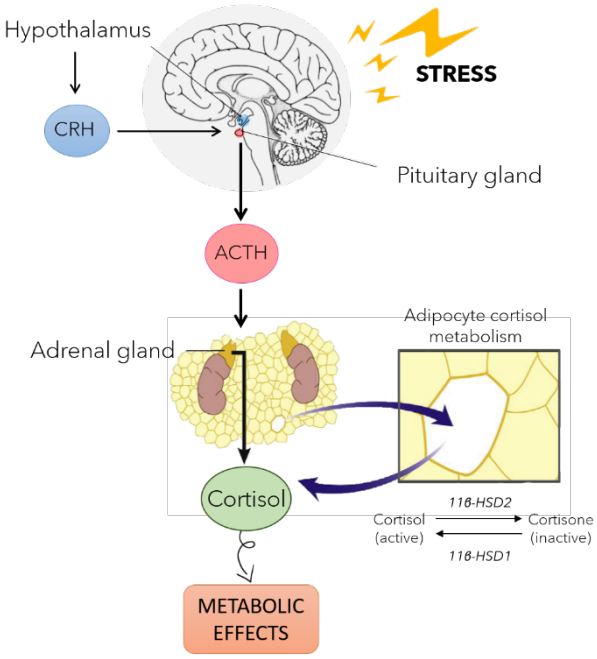

Figure 3. HPA axis functionality and adipocyte cortisol metabolism in the context of the axis.

Obesity would lead to prolonged stress-induced increase in cortisol concentrations and overall output, thus promoting further accumulation of adipose tissue via the upregulation of the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), also promotes increased visceral fat accumulation, thereby further suggesting that GCs may have a primary role in the development of central obesity and weight gain [26] [27] (Figure 3).

According to previous studies, the dysregulation of the HPA axis is not itself a marker of obesity, but rather, a key player in the development and course of obesity, especially abdominal obesity. The alterations in the HPA axis may link chronic stress with higher risks for obesity and the metabolic diseases suffered by these patients [28]. This dysregulation is also related to mental health conditions such as depression and cognitive impairment [29]. In this regard, different studies have pointed to a bidirectional relationship between physical and mental health, more specifically between obesity and depression [30]. Depressive symptomatology has been shown to predict higher body weight at follow-up in children and adolescents [31].

1.4. Etiology of obesity

Although obesity has been classically attributed to lifestyle factors (e.g.: diet, physical activity, socio-economic and cultural factors), it is well known that obesity runs in families. Furthermore, in populations sharing the same "obesogenic environment", there are both, individuals with obesity and normoweight individuals. This might suggest differential susceptibility to weigh gain between individuals. This difference could be explained by the individual genetic profile and other biological factors such as age, sex and ethnicity, among others [32]. In this regard, this seems to suggest that obesity is a **complex multifactorial disease**, which arises from the interaction between multiple genes of minor effect, environmental and behavioral risk factors. For this reason, the management and prevention of obesity constitute a challenging issue [33,34].

1.4.1. Lifestyle factors

It is well known that rapid globalization of westernized lifestyles has changed diet, activity patterns and social behaviors, contributing to the development and progression of obesity [35].

The nutritional transition has been characterised by the volume of food ingested, but also in the composition and quality of the diet. The dissemination of refined and processed foods, rich in fat and sugars, has decreased the consumption of fruits, green vegetables and milk [36,37]. This results in a continuous increase in adiposity with higher prevalence of overweight and obesity, not only in the adult population but also among children and adolescents [38].

At the same time, daily energy expenditure in **physical activity** has decreased, and the time spent in sedentary activities has increased [39,40]. Exercise has many benefits in weight stability, but also in psychological and physical traits [41].

In addition to the above mentioned factors, it is well established that psychological traits, cognition, and social factors, influence our short-term eating behavior [31]. Obesity is associated with mood, and psychiatric disorders including anxiety and depression, particularly among people with severe obesity [42,43].

1.4.2. Genetic factors

Family, twin and adoption studies provide strong evidence for large genetic influences on variations in body mass index (BMI), with heritability estimates ranging from 50% to over 90%, leaving the remaining variance attributed to environmental influences. However, these estimates have varied widely across studies due to differences in study types, populations, and ages targeted [44,45]. These heritabilities are similar to those found for other obesity-related traits, including WHR and different body fat indices [46,47].

First insights into the genetics of obesity come from studies looking for Mendelian transmission of obesity. **Monogenic forms** of obesity are rare in population (3-5%) and very severe, generally associated with an early-onset morbid obesity [48]. They are caused by a single gene mutation, primarily located in the leptin- melanocortin pathway, that consisted in mutations in human genes encoding for leptin (LEP), leptin receptor (LEPR), proopiomelanocortin (POMC), and

melanocortin-4 receptor (MC4R) [49]. However, the most common forms of obesity in modern societies have a polygenic component in which multiple common genetic variants with small effects contribute to individual susceptibility to gain weight [50].

There are different methodological approaches used for the search of genes involved in body weight regulation: linkage studies, case-control association studies and Genome-Wide Association studies (GWAS). The aim of all these approaches is to determine whether an association between a genetic variant and an obesity-related trait do exist, and to estimate the risk conferred.

Classical association studies analysed the variability of candidate genes mainly involved in body weight regulation, obesity-related traits or associated co-morbidities [51]. Consistent associations have been reported for only a handful of these candidate genes (e.g. *BDNF, MC4R, GIPR, PMS2L3*) [52]. However, this approach may not give full resolution in complex diseases such obesity, although they are useful helping to establish relationship between disease susceptibility and genetic variation. Hence, the emergence of GWAS have revolutionized the field of the genetics of complex diseases, identifying an unprecedented number of robustly associated loci over the past decade [53]. A recent meta-analysis of nearly 340,000 individuals identified 97 GWAS loci associated with BMI, 56 of which were novel. These loci accounted for 2.7% of the variation in BMI, and 21% of the BMI variation was accounted by common genetic variation. The authors provided robust evidence implicating genes and pathways affecting synaptic plasticity and glutamate receptor activity—pathways that respond to changes in feeding and fasting. Some of these genes are regulated by key obesity-related molecules such as *BDNF* and *MC4R*, and impact on key hypothalamic circuits [54]. BMI-associated loci also overlap with genes and pathways implicated in neurodevelopment and, particularly with genes expressed in the hypothalamus.

The complex interplay of genetic and environmental factors, the multiple genes involved and the modest individual effects of these genes in determining susceptibility for obesity make the genetic dissection of this disease a particularly daunting task. Although studies targeting gene-environment (GxE) and gene-gene interactions (GxG) have emerged rapidly in the last decade, the results are still rather inconclusive for BMI [55]. The main focus has been placed on the interactions between polymorphisms associated with obesity and environmental modulators of obesity risk such as age, sex, physical activity, diet, socioeconomic and educational status, and ethnicity. It is hypothesized that this interaction effects may account for some of the **'missing heritability'** in obesity, with multiple known obesity-predisposing gene variants interacting with lifestyle to modify the obesity risk [56].

1.5. Obesity and health (Comorbidities)

Obesity is a major risk factor for many metabolic disturbances and other comorbid conditions, including osteoarthritis, T2D, hypertension, dyslipidaemia, cardiovascular disease, and many cancers [57].

Insulin resistance (IR) is one of the principal causes of obesity, which progress to T2D and has been recognized as the integral feature of metabolic syndrome (MetS). In recent years, as

commented before, evidence has emerged pointing that inflammation has a crucial role in the development of IR, diabetes and cardiovascular diseases associated with obesity [58].

1.5.1. Type-2 Diabetes (T2D)

T2D is a heterogeneous group of conditions broadly characterised by IR, a state of reduced responsiveness of insulin-mediated glucose uptake to circulating insulin, and an inadequacy of the pancreatic β cells to provide enough insulin for current requirements [59]. IR is observed in 90% of patients with T2D and about 50% of patients with T2D are overweight or obese at the point of diagnosis. [60]. Epidemiological studies have highlighted many potential environmental factors as inducers of T2D such as physical inactivity, caloric excess, and endocrine disruptors, among others. The combination of these different environmental exposures may be shared between obesity and T2D. [61]. Furthermore, several common genetic variants have been robustly associated with T2D and obesity [62,63].
The long-term complications of T2D include cardiovascular diseases (CVD), stroke, peripheral vascular diseases, retinopathy, nephropathy, and neuropathy. Despite strong evidence linking T2D to higher mortality rates, 40% of patients with T2D do not meet their treatment goals. [64]. Weight control is perhaps the most important way to prevent and treat T2D, and ultimately to reduce morbidity and mortality [65]. However, patients with diabetes experience greater difficulty losing weight compared to nondiabetic obese patients [66]. Regarding this, bariatric surgery represents a suitable option for obese patients with T2D. Several studies have shown that surgical intervention in patients with recently diagnosed T2D have higher rates of remission of diabetes with better improvement in the glycemic state than patients with longer duration of the disease [67].

1.5.2. Metabolic syndrome (MetS)

MetS is defined as a combination of at least three of the following features: central obesity, high serum triglyceride (TG) levels, low serum high-density lipoprotein (HDL), cholesterol levels, hypertension, and elevated fasting blood glucose levels [68].

Abdominal adiposity and insulin resistance appear to be at the core of the pathophysiology of the MetS and its individual components. Most studies show that MetS double the risk for Cardiovascular disease (CVD), and increases five times the risk for T2D. Adipose tissue may be the origin of one or more interconnections between obesity and the MetS, as adipose tissue serves as storage and also as a place where lipids are mobilized [69].

In addition, the MetS is associated with a number of other comorbidities such as, sleep disorders, reproductive tract disorders, and microvascular disease [70] (Figure 4).

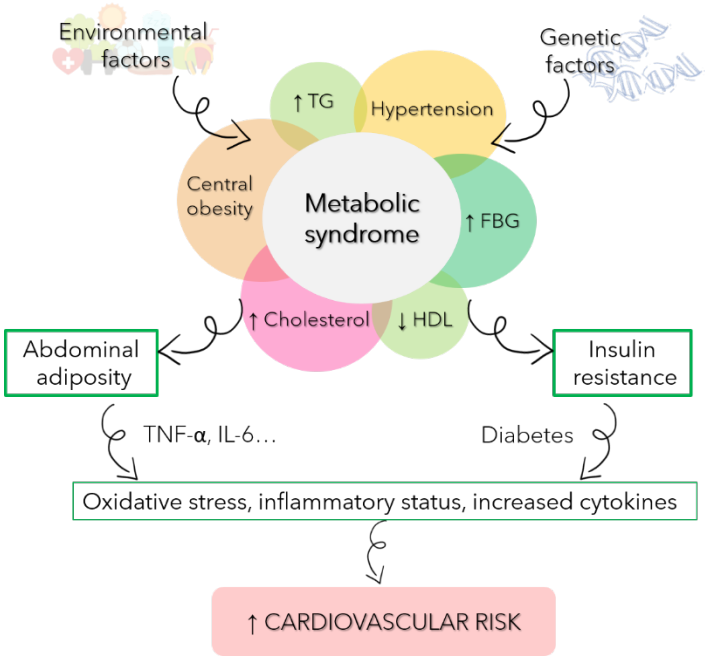

Figure 4. Schematic diagram of metabolic syndrome (MetS), its contributiory factors, causes and manifestations of the MetS.

1.5.3. Mental illness

The physical comorbidity burden in obesity has been well established but its relation to mental health has been relatively less explored [71]. Obesity is a stigmatized condition, and overweight individuals face social exclusion and discrimination in many areas of their lives [72]. It constitutes a stressful experience that is stable over time and across important areas of life, becoming a determinant of health.

Several studies suggest that weight stigma is associated with a range of adverse mental health outcomes, such as depression, anxiety, psychological distress, dysfunctional and disordered eating, and decreased quality of life, self-esteem, and body satisfaction [73]. Interestingly, studies provide evidences on double prevalence of depression in individuals with obesity compared to individuals with normal weight. There is potentially a bi-directional relationship between obesity and depression. Some research suggests that depression results in weight gain and obesity, and other studies have suggested that those with obesity are more likely to develop depression at a later stage [74].

1.6. Obesity and premature ageing. The role of telomere length

Ageing is a natural process which involves the gradual decline in physiological and cognitive functions. The effects of ageing are extremely "plastic" and variable from person to person. McEwen's concept of the "allostatic load" suggests that each person's signature of ageing is a result of interactions among genetic makeup, lifestyle, diet, and environmental challenges [75].

Telomere length (TL) has been proposed as a candidate biomarker of cell ageing and has been used to explore the effects of environment on premature cell ageing and age-related pathology. Telomeres are specialized structures that consist of repetitive nucleotide sequences (TTAGGG) that cap the ends of linear chromosomes [76]. Their main function is to maintain the integrity of chromosomes, preserving genomic information, and preventing inter-chromosomal fusion [76]. As cells divide, TL shortens as a result of the incomplete replication of chromosome ends during DNA replication (the 'end-replication problem'). When TL reaches a critical length, the cell stops dividing and becomes senescent [77]. Germ cells and stem cells, nonetheless, counteract progressive telomere erosion with the activity of the **telomerase**, an RNA-dependent reverse transcriptase, which can synthesize telomeric DNA *de novo*.

A reduction in the ability of cells to replace old and damaged cells contributes to tissue-level pathology (e.g. coronary plaque formation), risk for age-related disease, and an increased risk of mortality. Despite **TL shortening** is a natural process, it can be accelerated by factors that induce ageing, and attenuated by factors that improve health (Figure 5). Inflammation and oxidative stress have been described as the main cellular process that contribute to ageing and they are particularly associated with telomere attrition [78]. Regarding this, different health conditions modulated by these mechanisms have a negative influence on TL such as cardiovascular diseases, smoking and obesity among others [79].

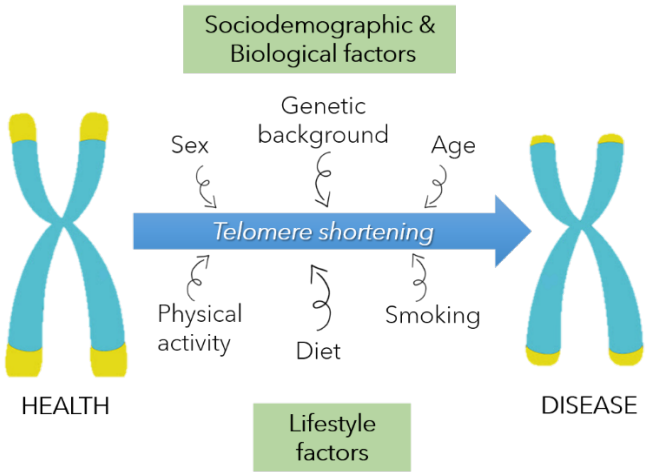

Figure 5. Some of the sociodemographic, biological and lifestyle factors implicated in the telomere shortening process.

1.6.1. Obesity and telomeres

As mentioned before, the excess of adiposity observed in patients with obesity, increases the production of an extensive range of adipokines including hormones, cytokines, and immunologic factors, that exhibit proinflammatory actions and oxidative stress[12]. The G triplets in telomeres are particularly vulnerable to these processes which promote an accelerated telomere erosion [80,81]. Short and dysfunctional telomeres are the starting point for cellular senescence, cell death, and DNA instability [82]. In the case of obesity, it has been suggested that telomere shortening not only increases the onset of metabolic imbalances, but also decreases life span and impacts cellular process in a manner similar to ageing [83]. Shorter telomeres have been associated with increased BMI and adiposity, and more recently, with increased WHR and visceral excess fat accumulation [84] (Figure 6).

Interestingly, TL shortening can be reversed, to an extent, by the initiation of specific environmental activities and lifestyle changes that activate endogenous telomere-lengthening mechanisms, such as the enzyme telomerase [85]. Therefore, it is suggested that telomere lengthening is correlated with weight loss, decrease of inflammation and oxidative stress. Diet is believed to be either a protective or a detrimental factor for telomere length, depending on its composition. Regarding this, studies in animal models have shown that caloric restriction extend lifespan and delay the onset of age associated phenotypes [86]. Weight loss intervention could play an important role not only in the prevention of telomere shortening, but also in telomere elongation.

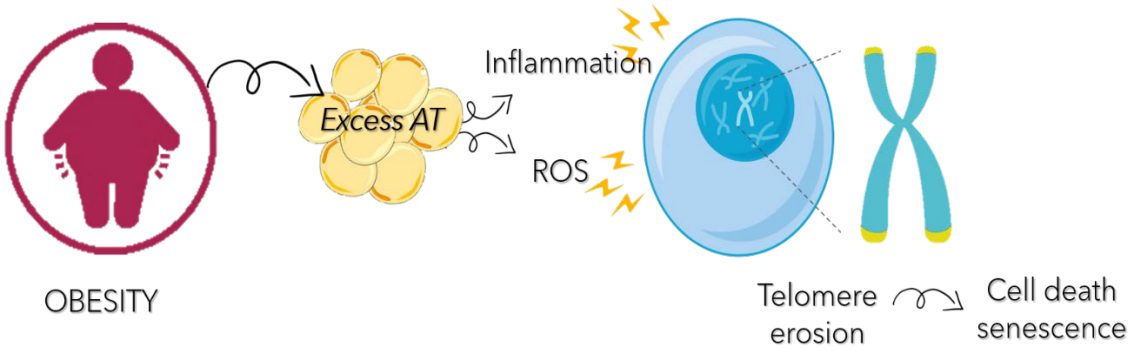

Figure 6. Schematic representation of plausible connexion between obesity and telomere length erosion

1.7. Treatment and weight loss strategies

There are many potential therapeutic interventions to treat obesity, aiming to induce weight loss and the improvement of comorbidities.

The primary option for weight management consists on a conservative therapy that do not require medications and includes **lifestyle interventions** (i.e. diet, physical activity, behaviour modification). These interventions have a low cost and minimal risk of complications [87].

Lifestyle intervention programs are a popular choice for weight loss for obese individuals. The core elements of such programs typically involve exercise training, dietary interventions, and behavioural patient education. In this intervention, the primary factor for successful response is patient's adherence. Although this type of interventions have been shown to result in clinically significant weight loss in patients with obesity, sustained weight loss for long periods have been demonstrated to be very difficult for many patients [88].

Pharmacological therapies are indicated for patients with obesity with a BMI of >30 kg/m2, or ≥27 kg/m2 with obesity-related comorbidities [89]. There are different available drugs for obesity based in five different mechanisms: i) lipase inhibitor, ii) 5-HT agonist, iii) Sympathomimetic and antiepileptic, iv) opioid antagonist and antidepressant and vi) GLP-1 agonist. These medications, when prescribed with lifestyle interventions have been shown to produce additional weight loss [90]. However, most of these therapies showed adverse effects related with gastrointestinal disturbances (i.e. nauseas and fatigue), headache, paresthesia, and dizziness that in most cases leads to different complications. Typically, pharmacotherapy is discontinued if the patient does not lose ≥5% of the starting body weight within 3 months (reviewed in Table 3).

Table 3. Summary of the pharmacs used for weight loss (WL). (*From McCafferty BJ et al 2020)*

Drug	Mechanism	WL (kg)	Patients with ≥5% WL	Complications
Orlistat	Lipase inhibitor	2.5-3.5	35%-73%	Liver failure, nephropathy
Lorcaserin	5-HT agonist	3.2	38%-48%	Serotonin syndrome, depressant effects
Phentermine-topiramate	Sympathomimetic and antiepileptic	6.7-8.9	45%-70%	Teratogenic, cardiovascular events
Naltrexone-bupropion	Opioid antagonist and antidepressant	2.0-4-1	36%-57%	Seizure risk, avoid in alcohol and drug abusers
Liraglutide	GLP-1 agonist	5.9	51%-73%	Pancreatitis, suicidality, thyroid cancer, renal failure

Bariatric surgery (BS) for morbid obesity is usually considered a last resort for people who have attempted first-line medical management (e.g., diet, behavior modification, increased physical activity, and drugs) but who have not lost weight permanently. BS involves surgical modifications of the normal gastrointestinal (GI) tract anatomy (Figure 7a) with the consequent alterations of nutrient flow affecting GI biology [91]. This surgery is restricted to people with morbid obesity (BMI > 40 kg/m2) or with a BMI of at least 35 kg/m2 and serious comorbid conditions [92]. It has emerged as the most effective weight loss strategy for people with obesity leading to reduced mortality and improvement in the associated comorbidities when compared with intensive medical and lifestyle interventions [93]. There are evidences that bariatric surgery is associated with a 50-85% of T2D remission in severely obese patients [94].

There are various bariatric surgical procedures and several different variations for each of these procedures. The surgical interventions can be divided into 2 general types: **malabsorptive** (bypassing parts of the gastrointestinal tract to limit the absorption of food), and **restrictive** (decreasing the size of the stomach so that the patient is satiated with less food). Globally, the most common procedures undertaken are Roux-en-Y gastric bypass (RYGB, 43%), and sleeve gastrectomy (SG, 49%).

Roux-en-Y gastric bypass (RYGB)

RYGB is assigned to patients with BMI between 40 and 55 kg/m^2. It consists in a division of the stomach generating a small gastric pouch (20–30 ml), which is then anastomosed with the mid-jejunum, creating the Roux or alimentary limb. Thus, ingested nutrients bypass most of the stomach, duodenum, and the proximal jejunum. Anastomosis of the biliopancreatic limb with the jejunum allows drainage of bile acids and pancreatic secretions, which mix with the nutrients in the jejunum (common limb) [95] (Fig. 7b).

Sleeve gastrectomy (SG)

This procedure is initially performed as a first stage to reduce weight in patients with a BMI between 35-40 or greater than 55 kg/m^2. SG involves transection along the greater curvature creating a tube-like new stomach removing the fundus and body [96] (Fig. 7c). Gastric contents pass rapidly into the duodenum. However, the significant sustained weight loss and metabolic benefits obtained by SG led to its adoption.

Nowadays, SG has become the most common bariatric procedure because it is an easier technique, it takes shorter operation time, and produce fewer surgical and nutritional complications, and similar short-term weight loss and clinical outcomes compared with RYGB [97].

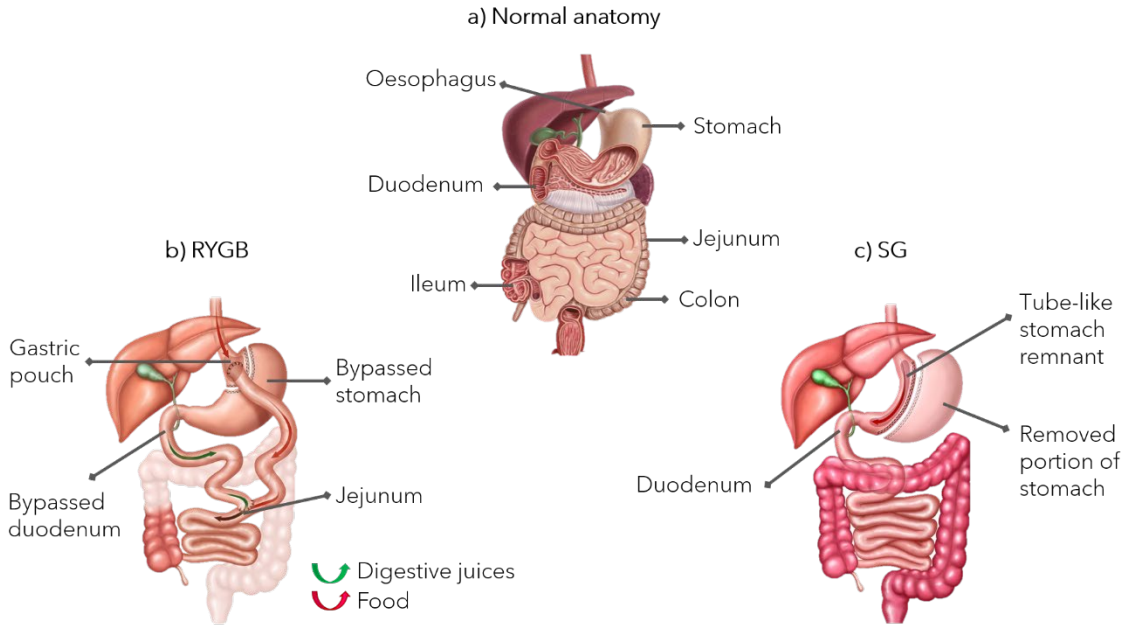

Figure 7. Schematic diagram of the normal upper gastrointestinal anatomy (a), and the two most common BS procedures; (b) Roux-en-Y gastric bypass and (c) Sleeve gastrectomy

Both procedures result in comparable reductions in excess body weight, typically >60% at 1 year. However, studies comparing the efficacy of RYGB against SG after 3-5 years results in favour of RYGB in terms of weight loss and resolution of obesity-related comorbidities, especially T2D [98]. Despite the positive effects of bariatric surgery, weight regain (recovery of 10 to 20% of the minimum weight achieved by the patient) occurs in between 30% and 50% of the patients at the post-operative period (between one and a half and 2 years after the procedure) [99].

Furthermore, there is considerable interindividual variation in surgery outcome. Studies to date have suggested a variety of complex factors potentially moderating weight loss outcomes (such as age, sex, baseline co-morbidities and BMI among others) and the identification of robust predictors as one of the top priorities in this field [100,101]. In the last decades, many efforts have been made to understand the variations in inter-individual responses to the same obesity treatment strategy. Genetic variation among individuals seems to play a role in the variety of physiological responses to the same environment and explains why some individuals are more likely to gain/lose weight than others in the same environmental conditions [102], including weight gain/loss after bariatric surgery. Larger studies with longer follow-ups are needed to clarify this differential impact of bariatric procedure in patients [103]

Mortality after bariatric surgery is a rare event. It is influenced by different risk factors including type of surgery, open surgery, prolonged operative time, comorbidities, and volume of activity. In defining the best bariatric procedure for each patient, the different mortality risks should be considered. Choice of the procedure, prevention, early diagnosis, and therapy for cardiovascular complications may reduce postoperative mortality [104].

2. Hypothesis and Objectives

Based on the background mentioned in the introduction showing i) that obesity have a polygenic nature with the implication of different genes of minor effect and lifestyle factors; ii) the high variability between individuals in weight loss outcome after bariatric surgery (BS) and iii) that obesity is associated with a chronic state of inflammation and oxidative stress that has been linked with accelerated ageing; the hypothesis and objectives of the present thesis are:

Hypothesis: At least a set of candidate genes related with obesity will be underlying the variability in weight loss outcome after bariatric surgery in obese patients. Moreover, the weight loss, the decrease of inflammatory state and oxidative stress, experienced by obese patients after bariatric surgery will be associated with a restore of telomere length (TL) in post-operative period in those patients.

To explore this hypothesis, the following objectives were established:

Main objectives: To identify specific genetic polymorphisms in candidate genes involved in the pathophysiology of obesity, clinical and sociodemographic factors that can predict long-term outcomes in patients submitted to bariatric surgery (section I). We also aim to investigate telomere length in different subtypes of obese patients, patients with depression and to examine changes in TL in relation to weight loss after bariatric surgery (section II). These objectives will be conducted in a cohort of patients with obesity submitted to bariatric surgery and followed-up for 24 months.

Specific objectives of section I:

1. To examine the role of the *FKBP5* gene, involved in the hypothalamic-pituitary-adrenal (HPA) axis, in relation to age, sex and type of surgery in weight loss after bariatric surgery in a sample of 151 severe obese patients with a 2-year follow-up after bariatric surgery.

2. To study the implication of a *BDNF* polymorphism (rs6265) on weight loss, and the effect of type-2 diabetes on weight changes experienced by a sample of 158 obese patients submitted to bariatric surgery with 2-year follow-up.

Specific objectives of section II:

3. To evaluate baseline differences in telomere length in different subtypes of obese patients, and to examine longitudinal changes in telomere length after bariatric surgery over a 2-year period in a cohort of 94 obese patients.

4. To review and discuss the published evidences about telomere length in obese patients submitted to bariatric surgery to better understand how efficacious bariatric surgery as an intervention is to promote telomere length restoration.

5. To review the literature regarding telomere length and depression, a disorder highly prevalent in obese patients.

3. Publications

Supervisor's report on impact factor

The doctoral thesis *"Genetic variability and telomere length on bariatric surgery outcomes in obesity patients"* is based on the original results obtained by Elionora Peña Lozano. These results have been published or have been submitted to international peer reviewed journals. The impact factors of these journals demonstrate the quality of the research conducted, and are as follows:

1. **Role of *FKBP5* polymorphism rs1360780, age, sex and type of surgery in weight loss after bariatric surgery: a follow-up study**, published in *Surgery for Obesity And Related Diseases (SOARD)**.

2. **Response to the letter to the editor to: FKBP5 polymorphism rs1360780 and weight loss after bariatric surgery,** published in *Surgery for Obesity And Related Diseases (SOARD)**.

3. **Influence of the BDNF Val66Met polymorphism on weight loss after bariatric surgery: a 24th months follow-up**, published *Surgery for Obesity And Related Diseases (SOARD)**.

4. **Longitudinal changes to telomere length in a cohort of obese patients submitted to bariatric surgery: A two-year follow-up**, published in *Surgery for Obesity And Related Diseases (SOARD)**.

* *Surgery for Obesity and Related Diseases (SOARD)* is the Official Journal of the American Society for Metabolic and Bariatric Surgery (ASMBS) and the Brazilian Society for Bariatric Surgery. It is an international journal devoted to the publication of peer-reviewed manuscripts of the highest quality with objective data regarding techniques for the treatment of severe obesity. Articles document the effects of surgically induced weight loss on obesity physiological, psychiatric and social co-morbidities. The Editorial Board includes internationally prominent individuals who are devoted to the optimal treatment of the severely obese and include internists, psychiatrists, surgeons, and nutritional experts. Manuscripts are blindly reviewed.
It is indexed in Journal Citation Reports (Science Edition) with a current impact factor of 3.812 and classified in the first quartile of the area of Surgery (ranking: 30/200).

5. **Leukocyte telomere length in obese patients submitted to bariatric surgery: a systematic review** (submitted to European Eating Disorders Review).
European Eating Disorders Review publishes authoritative and accessible articles, from all over the world, which review or report original research that has implications for the treatment and care of people with eating disorders, and articles which report innovations and experience in the clinical management of eating disorders. The journal focuses on implications for best practice in diagnosis and treatment, (rather than on research

methodology). The journal also provides a forum for discussion of the causes and prevention of eating disorders, and related health policy.
It is indexed in Journal Citation Reports (Science Edition) with a current impact factor of 3.560 and classified in the first quartile of the area of Clinical Psychology (ranking: 21/131).

I hereby confirm the quality of the published and submitted articles.

Signed by Dr. Araceli Rosa

Barcelona, September 2020

Section I: Genetic variability in bariatric surgery outcomes

3.1. Role of FKBP5 polymorphism rs1360780, age, sex and type of surgery in weight loss after bariatric surgery: a follow-up study

Elionora Peña, Assumpta Caixàs, Concepción Arenas, Mercedes Rigla, Sara Crivillés, Narcís Cardoner, Araceli Rosa.

Surgery of Obesity And Related Disease, 2020 Apr;16(4):581-589.

DOI: 10.1016/j.soard.2019.12.002.

Resum

Estudis recents posen de manifest com la proteïna *FKBP5 binding protein 51* (FKBP5/FKBP51) codificada pel gen *FKBP5* jugaria un paper en el pes i en la regulació metabòlica. L'al·lel T d'un polimorfisme funcional del gen *FKBP5* (rs1360780) ha estat associat amb la expressió de la proteïna FKBP51 i la pèrdua de pes després de dur-se a terme una cirurgia bariàtrica. L'objectiu del nostre estudi va ser examinar el paper que juga el polimorfisme rs1360780 del gen en relació a la pèrdua de pes en pacients amb obesitat severa després de sotmetre's a aquest tipus de cirurgia.

El nostre estudi es va du a terme en una cohort de 151 pacients amb obesitat severa que es van sotmetre a un '*Roux-en-Y Gastric Bypa*ss' (RYGB) o bé a un '*Sleeve Gastrectomy*' (SG) i que tenien un seguiment durant 24 mesos. Durant el període post-operatori (t_{1m}, t_{3m}, t_{6m}, t_{12m}, t_{24m}) es van avaluar l'índex de massa corporal (B*ody Mass Index*-BMI), el percentatge de l'excés de pes perdut (% *Excess Weight Loss*-%EWL) i el percentatge total de pes perdut (% *Total Weight Loss* -%TWL).

El nostre estudi va posar de manifest com el canvi en el BMI després de la intervenció es trobava influenciat per la interacció entre el genotip del *FKBP5* i el sexe del pacient (P = .0004). Addicionalment, vam trobar una interacció entre el genotip i el tipus de cirurgia (P = .048). Aquests resultats semblaven posar de manifest que els homes portadors de l'al·lel T presentaven un BMI més elevat 24 mesos després de la cirurgia (t_{24m}) comparat amb els homes no portadors. De la mateixa manera, els pacients portadors de l'al·lel T que se sotmetien a SG presentaven també un BMI més elevat a t_{24m}.

Quan vam estudiar l'efecte de l'edat vam veure que existia una interacció entre el genotip del *FKBP5* i l'edat del pacient pel %EWL i el BMI (P = 0.0005 i P = 1.5e-7, respectivament), de manera que els individus majors de 48 anys i portadors de l'al·lel T presentaven diferències estadísticament significatives per les variables analitzades a t_{24m} en comparació amb els homozigots per l'al·lel C que presentaven una pèrdua de pes major.

ELSEVIER

Surgery for Obesity and Related Diseases 16 (2020) 581–589

SURGERY FOR OBESITY AND RELATED DISEASES

Original article: Integrated health

Role of the *FKBP5* polymorphism rs1360780, age, sex, and type of surgery in weight loss after bariatric surgery: a follow-up study

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Received 3 October 2019; accepted 9 December 2019

Abstract

Background: Emerging evidence suggests that the FK506 binding protein 51 (FKBP5/FKBP51), encoded by the *FKBP5* gene, influences weight and metabolic regulation. The T allele of a functional polymorphism in *FKBP5* (rs1360780), has been associated with the expression of FKBP51 and weight loss after bariatric surgery.

Objective: To examine the role of the *FKBP5* rs1360780 polymorphism in relation to age, sex, and type of surgery in weight loss after bariatric surgery in patients with severe obesity.

Setting: University Hospital in Spain

Methods: A cohort of 151 obese patients submitted to Roux-en-Y gastric bypass (62.3%) and sleeve gastrectomy (37.7%) were followed-up during 24-months (t_{24m}; loss to follow-up: 0%). During the postoperative period body mass index (BMI) and percentage of excess and total weight loss were evaluated.

Results: The BMI analysis showed an effect of the interaction *FKBP5* genotype by sex ($P = .0004$) and a tendency to the interaction genotype by surgery ($P = .048$), so that men carrying the T allele had higher BMI at t_{24m} than those without the T allele, and T-allele carriers that underwent sleeve gastrectomy had higher BMI at t_{24m} than the noncarriers. Additionally, we found an interaction between *FKBP5* and age for the percentage of excess weight loss and BMI ($P = .0005$ and $P = 1.5e{-}7$, respectively), whereby individuals >48 years with the T allele displayed significant differences for the analyzed variables at t_{24m} compared with the homozygotes for the alternate C allele showing lower weight loss.

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E. Peña and A. Caixàs contributed equally to this study.

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Conclusion: *FKBP5* rs1360780 genotype has specific effects on weight loss outcomes after bariatric surgery depending on sex, age, and type of surgery, suggesting worse results in older males carrying the T allele who have undergone sleeve gastrectomy. (Surg Obes Relat Dis 2020;16:581–589.)

Key words: Obesity; Bariatric surgery; Weight loss outcomes; BMI; Follow-up; Sex; Age; *FKBP5* gene; rs1360780

Bariatric surgery is currently the most effective long-term treatment for severely obese patients. Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most common bariatric procedures. However, there is considerable interindividual variation in surgery outcome and particularly in relation to weight loss, clinical benefits, and in reductions in morbidity and mortality [1]. Given the costs and dangers surrounding bariatric surgery, there is an urgent need to identify predictors of response, that is, which individuals are most likely to respond well to the intervention, and those who may respond better to alternative treatments.

Studies to date have suggested a variety of complex factors as moderating weight loss outcomes, including clinical, psychologic, demographic, and biological factors. Specifically, previous studies have revealed age, sex, preoperative weight, and body mass index (BMI), physical activity, type 2 diabetes (T2D), or other obesity-associated disorders (e.g., anxiety or depression) as moderators of bariatric surgery outcomes [1,2].

Regarding age, some studies have revealed that RYGB is less effective at inducing weight loss in those over the age of 45 [3,4], while others have revealed no differences [5]. In relation to sex, it is well known that men and women differ in terms of fat storage and metabolism [6] and studies indicate that bariatric surgery may be more effective in men than women [7,8].

Approximately 3% to 4% of the cases of obesity are monogenic with early onset, abnormal feeding behavior, and neuroendocrine disorders, mainly caused by mutations in genes implicated in the leptin/melanocortin pathway [9]. However, most of the cases arise from the interplay of many genes of minor effect and environmental factors.

Biological factors should be also taken into account when studying weight loss outcomes after surgery [10]. Hatoum et al. [11] described a high concordance after RYGB within pairs of first-degree relatives, compared with cohabitating or unrelated individuals, suggesting weight loss response to surgery is also heritable. In this regard, the study of candidate genes on the outcomes of bariatric surgery suggests that specific variants in genes, such as the fat mass and obesity-associated gene (*FTO*), insulin-induced gene 2 (*INSIG2*), melanocortin 4 receptor gene (*MC4R*), and proprotein convertase subtilisin/kexin type 1 gene (*PCSK1*), play a role in the poorer weight loss outcomes after surgery [12].

A recent study investigated the association of the FK506 binding protein-5 gene (*FKBP5*), which encodes for the protein FKBP51 in the hypothalamic-pituitary-adrenal axis, and the outcome after bariatric surgery in obese patients [13]. FKBP5 is well recognized for its ability to be induced by exposure to psychologic stress, inhibiting the glucocorticoid receptor activity, and ultimately leading to the reduction of the hypothalamic-pituitary-adrenal axis activation [14,15]. Animal models demonstrated that *FKBP51* knockout mouse embryonic fibroblasts showed reduced lipid accumulation and expression of adipogenic genes compared with wild-type animals [16]. Additionally, higher levels of hypothalamic FKBP5 expression were related to increased weight gain [17].

Interestingly, the T allele of a functional polymorphism (rs1360780) in the *FKBP5* gene is associated with a greater induction of the *FKBP5* gene [18]. Hartmann et al. [13] found in a sample of 42 obese patients that carriers of the T allele (i.e., individuals with TT and CT genotype) had nearly 20% less excess weight loss (EWL) and 10% less total weight loss (TWL) compared with homozygotes of the alternate C allele over the 26-week follow-up period after surgery. Consequently, these findings provide evidence that a functional variant of the *FKBP5* gene moderates the clinical response of severe obesity to bariatric surgery. The aim of our study was to examine the role of *FKBP5* polymorphism (rs1360780) in a cohort of 151 obese patients submitted to bariatric surgery (RYGB or SG) and followed-up during 24 months. In addition to the genetic effect, we also aimed to explore the effect of other variables such as type of surgery, sex, and age that could have an impact on the outcome of surgery on weight loss.

Methods

Participants

The study recruited 151 morbidly obese patients awaiting bariatric surgery in the Hospital Universitari Parc Taulí, Sabadell, Spain. All the patients were $\geq$18 years, with BMI $\geq$35 kg/m^2, and underwent either RYGB or SG bariatric surgery between 2008 and 2015. All patients fulfilled the eligibility criteria for bariatric surgery and the type of technique was chosen according to European guidelines [19].

This cohort was evaluated pre-, peri-, and postoperatively by a multidisciplinary team (endocrinologists, clinical

nurses, surgeons, dieticians, and psychiatrists) in consecutive visits over a 2-year timespan according to the local protocol. This period was divided as follows: t_0: before surgery; t_{1m}: 1 month after surgery; t_{3m}: 3 months after surgery; t_{6m}: 6 months after surgery; t_{12m}: 12 months after surgery; and t_{24m}: 24 months after surgery.

Anthropometric assessment

Measurements of weight, height, and waist circumference were obtained from physical examination along the evaluated period.

To report weight loss, we calculated for all the assessments (from t_0 to t_{24m}) as follows: (1) BMI, (2) %EWL, and (3) %TWL. The 151 patients completed all the assessments.

BMI was calculated in kilograms per meter squared according to the following formula: weight (kg) / height (m^2). The %EWL was calculated as ([weight loss / excess weight] $\times$ 100), where excess weight was taken as the weight in kilograms above the weight corresponding to the BMI for 24.9 kg/m^2. The %TWL was calculated as ([weight loss / weight at t_0] $\times$ 100).

Ethics

All patients were informed about our study and invited to participate in this prospective cohort. Informed consent was obtained from all participants included in the study. The Institutional Ethics Committee of Hospital Universitari Parc Taulí approved the protocol, and all investigations complied with the Helsinki Declaration.

Laboratory analysis

Blood samples were collected from all patients and genomic DNA from blood was extracted using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Genotyping of the *FKBP5* polymorphism (rs1360780) was performed using TaqMan allelic discrimination assay from Life Technologies (Thermo Fisher Scientific, CA, USA). The assay was run in a 384-well plate on the ABI PRISM 7900 HT Fast Real-Time PCR System (Applied Biosystems, CA, USA) using standard conditions. The final volume of each well was 5 μL, which contained 5 ng of genomic DNA, 2.5 μL of TaqMan Master Mix, and .125 of 40$\times$ genotyping assay. SDS v.2.4 (Applied Biosystems) software was used for the data analysis of the genotypes. Testing for validity and accuracy of genotyping, we retested a 20% random sample. In all cases, genotypes were reproducible.

Statistical analysis

Variables are reported as mean $\pm$ standard deviations (SD) or percentages. The baseline characteristics of the sample were analyzed using the Pearson χ^2 test for contingency tables or the nonparametric Mann-Whitney *U* test for continuous variables. The Hardy-Weinberg equilibrium for genotype frequencies in patients was calculated using χ^2 tests [20]. As the present study consisted in a prospective analysis of the variation of %EWL, %TWL, and BMI changes in a follow-up of 24 months after bariatric surgery, generalized estimating equation models (GEE) were considered. The factors used in the models were time, *FKBP5* genotype, surgical technique, age, sex, T2D, and the interactions time $\times$ surgery, *FKBP5* genotype $\times$ sex, *FKBP5* genotype $\times$ surgery, *FKBP5* genotype $\times$ age, and sex $\times$ surgery $\times$ *FKBP5* genotype. Furthermore, the effect of the age was also studied considering GEE models with age as dichotomous variable using the value of the median to determine the 2 groups of age. The comparison between the 4 groups of patients determined by their genotype and the age groups, was performed using the Kruskal-Wallis test followed by Benjamini and Hochberg post hoc test. All analyses were performed using RStudio 1.1.463 (RStudio, Inc. Boston, MA) and P values $< .05$ were considered to be statistically significant.

Results

Characteristics of the sample

The sample consisted of 151 Caucasian individuals, mainly women (78.1%). The participants were aged between 21 and 61 years (mean age = 46.33, SD = 10.01). Males and females differed slightly in terms of age (mean = 43.1, SD = 11.2 and, mean = 47.2, SD = 9.5, respectively, $P = .04$). All of them underwent either RYGB (n = 94, 62.3%) or SG (n = 57, 37.7%), no differences on BMI were found between surgeries at baseline (mean = 44.19, SD = 6.01 and mean = 46.02, SD = 9.05, respectively, $P = .607$).

The *FKBP5* genotype frequencies were 67 CC (44.4 %), 69 CT (45.7%), and 15 TT (9.9%). No deviations from Hardy-Weinberg equilibrium in the examined single nucleotide polymorphism was detected ($\chi^2 = .21$, $P = .65$).These frequencies were similar to those found in European populations in 1000 genomes (CC = 45%, CT = 44%, TT = 10%). Based on previous reports, we assumed a dominant model and due to the low frequency of T allele, *FKBP5* genotype was converted into a binary variable for the analyses, CC genotype and T carriers (i.e., genotypes CT and TT). No differences were observed between genotypic frequencies (CC or T carriers), sex, surgery, age, weight, BMI, excess weight, and excess of BMI at baseline (Table 1).

In Table 2 we report information about waist circumference, metabolic variables, and co-morbidities in patients in pre- (t_0) and postoperative (t_{24}) period according to the genotype.

Longitudinal assessment

Main effects

The study included the 3 variables of interest, %EWL, %TWL, and BMI, assessed longitudinally. The effect of time,

Table 1
Baseline characteristics of the sample (t_0) according to *FKBP5* genotype

Variables	Total sample	CC (n = 67)	CT or TT (n = 84)	*P* value*
Sex, n (%)				
Male	33 (21.9)	12 (36.4)	21 (63.6)	.395
Female	118 (78.1)	55 (46.6)	63 (53.4)	
Surgery, n (%)				
RYGB	94 (62.3)	44 (46.8)	50 (53.2)	.545
SG	57 (37.7)	23 (40.4)	34 (59.6)	
Age, yr	46.33 ± 10.01	47.16 ± 10.06	45.67 ± 9.98	.316
Weight, kg	113.80 ± 19.16	113.05 ± 16.00	114.40 ± 21.43	.967
BMI	43.19 ± 6.34	43.27 ± 6.73	43.13 ± 6.04	.814
EW	48.03 ± 16.73	47.68 ± 13.71	48.31 ± 18.87	.615
EBMI	18.29 ± 6.34	18.37 ± 6.73	18.23 ± 6.04	.814

RYGB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy; BMI = body mass index; EW = excess weight; EBMI = excess BMI.

Values are expressed as mean ± standard deviation unless marked otherwise.

* Pearson X^2 test for sex and surgery; Mann-Whitney *U* test for the other variables.

age, sex, surgery, T2D, and *FKBP5* genotype on the variables (%EWL, %TWL, and BMI) was explored using a generalized estimating equation model, including the previously mentioned variables and the interactions time × surgery, *FKBP5* genotype × sex, *FKBP5* genotype × surgery, *FKBP5* genotype × age, and sex × surgery × *FKBP5* genotype.

The test of model effects reported an effect of time on the variation of all the variables with $P < 2e{-}16$ for %EWL, % TWL, and BMI. The effect of surgery and T2D was only significant on BMI ($P = .01$ and .003, respectively). Additionally, a strong effect of age was found for the % EWL ($P = 6.2e{-}09$) and %TWL ($P = 4.5e{-}14$) but not for BMI.

Interaction effects

For %EWL and %TWL we found a statistically significant interaction between time and surgery ($P = .00089$ and .00083, respectively). Thus, patients submitted to SG lost 8.58% and 4.01% less %EWL and %TWL, respectively, at t_{24m} than patients who underwent RYGB ($P = .020$ and .006, respectively; Fig. 1A, B). Furthermore, men with SG lost 4.52% less TWL than those with RYGB at t_{12m} but not at t_{24m} ($P = .034$; Fig. 1 E).

Regarding the interaction between *FKBP5* and sex, it was only significant for BMI ($P = .0004$). These results pointed out that men carrying the T allele had higher BMI at t_{24m} than noncarriers (Fig. 2F). Additionally, a marginally significant effect of the interaction *FKBP5* and surgery was found on BMI ($P = .048$)

Table 2
Anthropometric and metabolic variables and co-morbidities of the sample according to *FKBP5* genotype in the pre- (t0) and postoperative (t24) period

Variables	Preoperative (t_0)		Postoperative (t_{24})	
	CC (n = 67)	CT/TT (n = 84)	CC (n = 67)	CT/TT (n = 84)
WC, cm	132.5 (14.53)	132.71 (13.48)	102.59 (13.14)	102.31 (10.98)
FPG, mg/dL	104.66 (31.82)	113.30 (39.15)	88.44 (27.19)	88.76 (25.23)
Insulin, µUI/mL	21.41 (18.46)	22.87 (16.03)	6.63 (3.46)	7.45 (3.13)
HbA1C, %	6.16 (1.05)	6.29 (1.27)	5.56 (.98)	5.53 (.76)
Co-morbidities, n (%)				
HTA				
No	26 (39.4)	28 (33.7)	45 (71.4)	58 (71.6)
Yes	40 (60.4)	55 (66.3)	18 (28.6)	23 (28.4)
DLP				
No	39 (59.1)	41 (49.4)	53 (84.1)	68 (84)
Yes	27 (40.9)	42 (50.6)	10 (15.9)	13 (16)
T2D				
No	49 (73.1)	52 (61.9)	63 (94)	77 (91.7)
Yes	18 (26.9)	32 (38.1)	4 (6)	7 (8.3)

WC = waist circumference; FPG = fasting plasma glucose; HbA1C = glycosylated hemoglobin; HTA= hypertension; DLP = dyslipoproteinemia; T2D = type 2 diabetes.

Values are expressed as mean ± standard deviation.

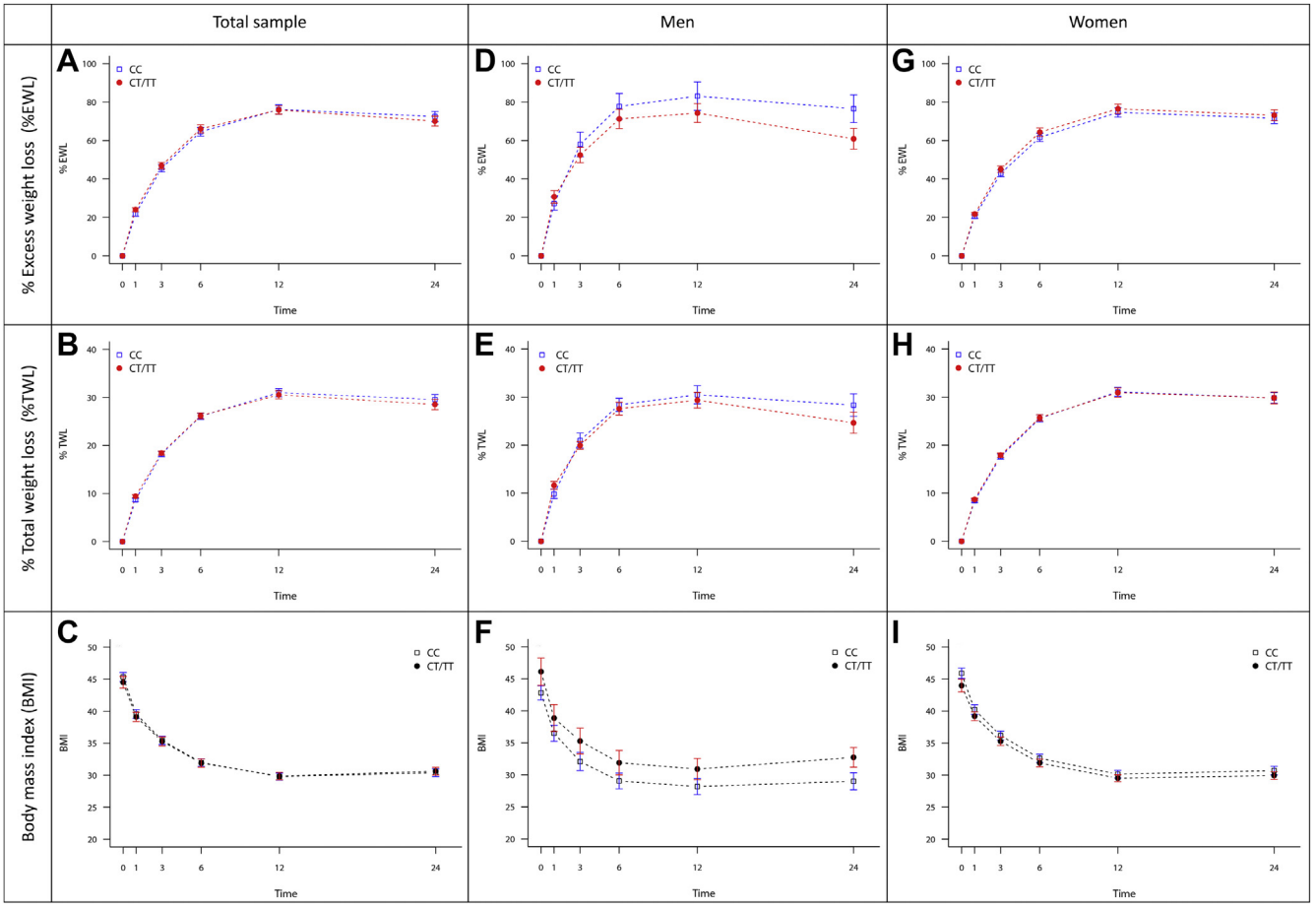

Fig. 1. Evolution of the 3 analyzed variables (percent excess weight loss, percent total weight loss, and body mass index) over time and according to surgery (Roux-en-Y gastric bypass versus sleeve gastrectomy) in the total sample and by sex.

The interaction between age and *FKBP5* genotype was significant for BMI and %EWL (P = 6.8e−07 and P = .0007, respectively), and the interaction between sex, *FKBP5*, and surgery for the 3 variables, %EWL, %TWL, and BMI, was significant (P = 9.2e−05, 8.4e−05, and .0001, respectively). These results show significant differences in the outcome after surgery depending on *FKBP5* genotype, sex of the individuals, and surgery, pointing out worst results in males carrying the T allele submitted to SG.

Given the strong effect of age reported before, we tried to study the influence of this factor in more depth. To this aim as the median of age was 48 years, we generated 2 groups, (1) individuals <48 years (n = 74) and (2) individuals aged ≥48 years (n = 77). Using the generalized estimating equation model, we explored the effect of age using this new binary variable (i.e., AgeD) on the %EWL, %TWL, and BMI. The model included time, surgery, *FKBP5* genotype, sex, AgeD, and the interaction *FKBP5* × AgeD. According with the results previously reported, the analysis showed a strong effect of AgeD on the variables %EWL and %TWL for the total sample (P = 3.54e−08 and 3.61e−11, respectively). Similar results were found in men (P = 7.97e−05 for %EWL and P = 4.24e−05 for %TWL) and women (P = .0002 for %EWL and P = 4.03e−08 for %TWL).

Furthermore, we found a significant interaction *FKBP5* × AgeD on the %EWL and BMI for the total sample (P = .0005 and P = 1.48e−07, respectively) and by sex, in men (P = .0002 and P = 8.39e−07, respectively) and women (P = .018 and P = .0004, respectively).

To better understand the interaction between *FKBP5* genotype and AgeD after 2 years of the surgery (t_{24m}), we divided patients into the following 4 groups according to their genotype and age group: group 1 with individuals with age <48 and CC genotype (n = 30), group 2 with individuals with age <48 and CT or TT genotype (i.e., T carriers, n = 44), group 3 with individuals >48 years and CC genotype (n = 37), and group 4 with individuals >48 years and T carriers (n = 40). In Table 3 we report mean and SD

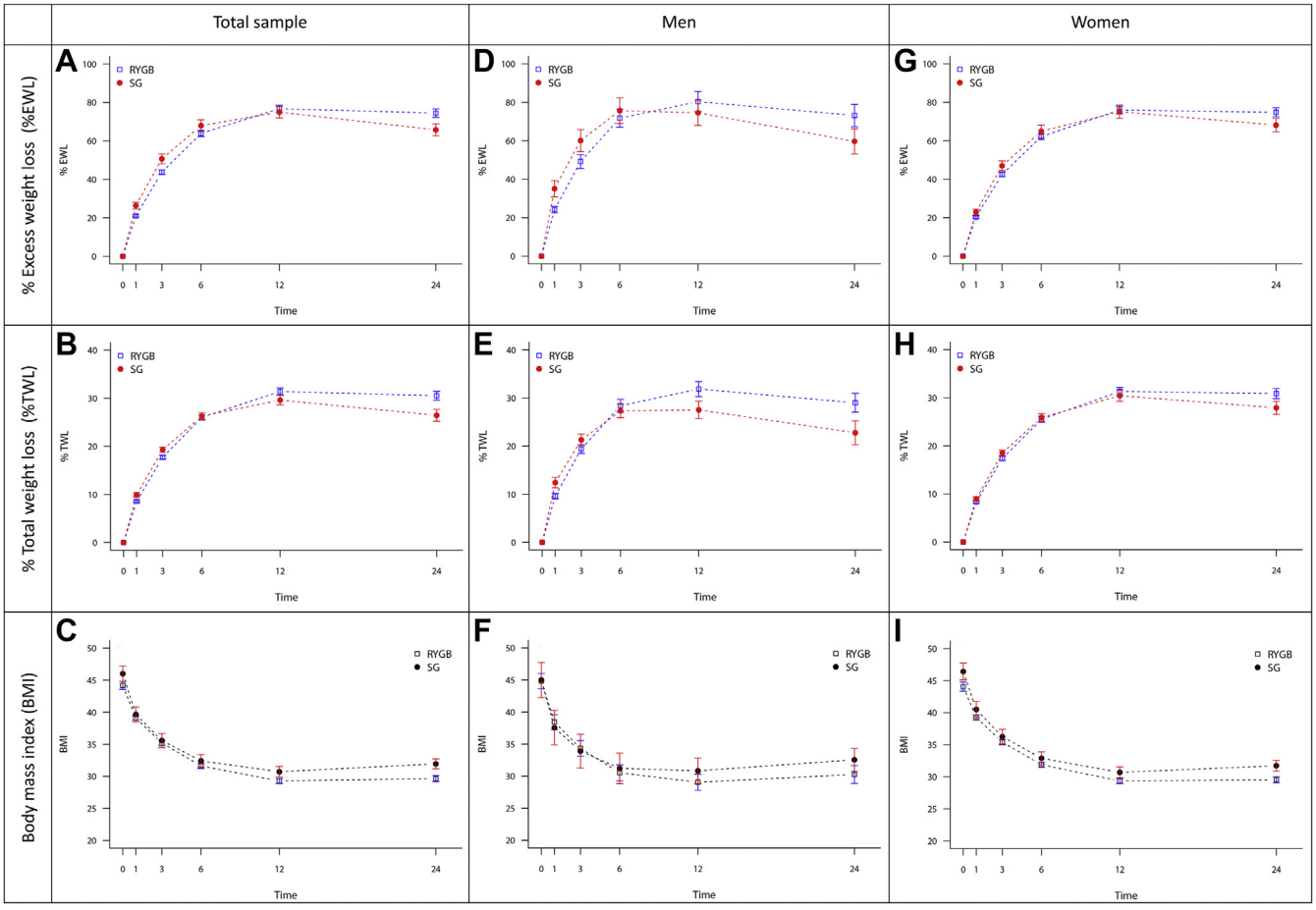

Fig. 2. Evolution of the 3 analyzed variables (percent excess weight loss, percent total weight loss, and body mass index) over time and according to genotype (CC or T carriers) in the total sample and by sex.

for the analyzed variables (%EWL, %TWL, and BMI) for each group at 24 months (t_{24m}). For the 3 outcomes patients of group 4 (≥48 and T carriers) displayed the worse scores. These differences were statistically significant for the 3 variables analyzed (Table 3).

Post hoc analysis showed for %EWL significant differences between groups 1 and 3 ($P = .010$) and groups 1 and 4 ($P = .021$). For the %TWL the differences were found between groups 1 and 3, groups 1 and 4, and groups 2 and 4 ($P = .039$, .016, and .016, respectively). Finally, for BMI differences were found between groups 1 and 3 ($P = .027$) (Fig. 3).

Discussion

Our study aimed to explore the role of different factors, including type of surgery, age, sex, and *FKBP5* genotype, on weight loss outcomes after bariatric surgery

Table 3
Mean (standard deviations) for %EWL, %TWL, and BMI at t_{24m} for the 4 groups based on age (AgeD) and *FKBP5* genotype

	Group 1	Group 2	Group 3	Group 4	*P* value*
%EWL	81.31 (21.02)	75.03 (21.15)	65.35 (19.11)	64.64 (24.99)	.004
%TWL	32.07 (7.61)	31.35 (8.38)	27.51 (8.31)	25.42 (10.82)	.004
BMI	28.69 (4.57)	30.43 (5.93)	31.78 (4.77)	30.84 (5.02)	.032

%EWL = percentage of excess weight loss; %TWL = percentage of total weight loss; BMI = body mass index.

Group 1: age <48 and CC; Group 2: age <48 and T carriers; Group 3: age ≥48 and CC; Group 4: age ≥48 and T carriers.

* Kruskal-Wallis test.

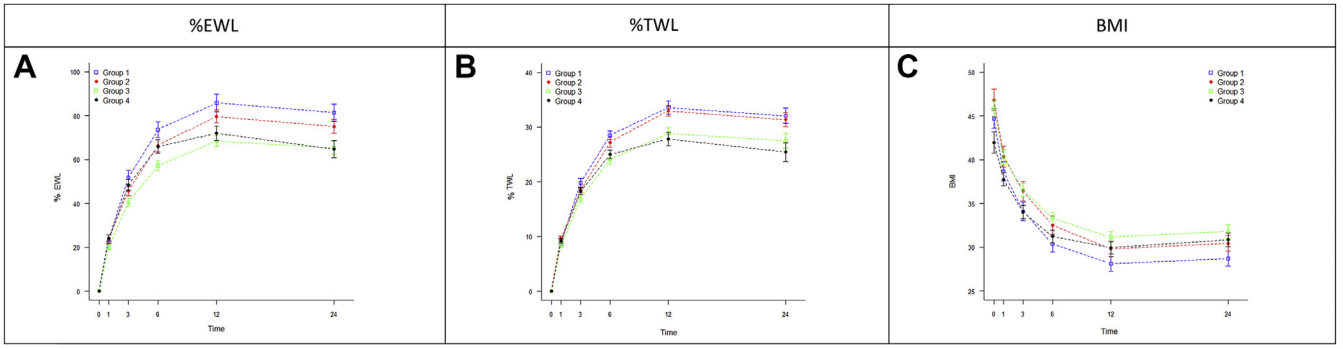

Fig. 3. Evolution of the 3 analyzed variables (percent excess weight loss, percent total weight loss, and body mass index) over time and according to age group (<48 and ≥48 years) and genotype (CC and T carriers). The groups correspond to groups 1 (<48 + CC), 2 (<48 + T carriers), 3 (≥48 + CC), and 4 (≥48 + T carriers).

over 24 months in a sample of 151 patients with severe obesity.

The main finding was that males >48 years old, who were T-allele carriers of *FKBP5* polymorphism (rs1360780) and had undergone SG, displayed the worst weight loss outcome at 24 months after surgery.

As expected, our results seem to indicate an effect of the type of surgery on weight loss during the postoperative period. In this regard, individuals submitted to RYGB seem to have better outcomes at t_{24} compared with those individuals submitted to SG. These two bariatric procedures are the most commonly used in severe obese patients and are effective at promoting weight loss. Several studies have compared whether the results of these two techniques are equivalent. A recent meta-analysis pointed out that both procedures result in similar %EWL and BMI reduction levels at 6 and 12 months. However, %EWL and BMI reduction were significantly greater in the RYGB group 24 months after surgery [21]. These findings seem to support the trend observed in our cohort.

We studied the effect of age both as a continuous and dichotomous variable. In both cases we found a strong effect of age on the analyzed variables, whereby individuals >48 years showed less weight loss after surgery. The implications of age on weight loss after surgery are still controversial, with some studies showing no significant difference [22,23] and others demonstrating less EWL among patients >60 years in comparison with younger patients [24,25]. A later publication where the authors applied a lower age limit, as we did in our study, reported differences in the percentage of excess BMI loss 12 months after surgery, whereby younger patients responded better [4]. One plausible explanation for this effect could be the impaired metabolic capacity and decrease in energy requirements in the elderly compared with young individuals as well as hormonal factors, especially in women. Only one previous study has reported a sex-specific effect of age on weight loss after bariatric surgery. In this study, Ochner et al. [26] found that weight loss in the postoperative period was significantly reduced in women aged 55 to 65 years compared with women aged 20 to 45, but not in men. In addition to metabolic rate and physical activity, the authors suggested that the menopausal status of these women could explain these findings. However, surprisingly, the effect of menopausal age on weight loss appeared to depend on surgery type because significant effects were detected in women undergoing gastric banding, but not RYGB. Unfortunately, we did not report menopausal status in our cohort.

Thus, pooling all these studies together, available data so far suggest that different types of bariatric surgery may have different effects on weight loss depending on sex and age, shedding some light on the etiologic complexity of obesity.

Our data on the variability of the *FKBP5* gene and its association with weight loss after bariatric surgery did not show a direct association between genotype and the analyzed outcomes. Only one previous study by Hartmann et al. [13] explored this hypothesis. They reported that T-allele carriers at rs1360780 had nearly 20% less EWL and 10% less TWL compared with the CC individuals after a 26-week follow-up in a cohort of 42 obese patients. The study by Hartmann is similar to ours regarding the analyzed polymorphism, age range and mean, design, follow-up of weight loss and analyzed variables (i.e., BMI, %EWL, and %TWL). However, our study has several strengths. It includes a considerably bigger sample (n = 151 patients, loss of follow-up was 0%), with a higher proportion of males. On the other hand, in the Hartmann et al. [13] study all patients were submitted to RYGB, whereas in our study 37.7% underwent SG, allowing us to compare the effectiveness of both surgical methods. With an expanded sample size and considering age and type of surgery followed by the patients, we pointed out how these variables were not independent to explain the complexity of weight loss after bariatric surgery. In this regard, males carrying the T allele of *FKBP5* rs1360780 and submitted to SG, displayed worse scores for %EWL, % TWL, and BMI. Also, bariatric surgery was less

effective on older individuals (≥48 yr). To the best of our knowledge, this is the first study exploring this polymorphism and its interaction with determinant factors associated with weight loss.

FKBP5 is well known for its important role as a molecular co-chaperone that inhibits glucocorticoid receptors activity, and consequently suppresses stress response [14,15]. Glucocorticoids have also systemic metabolic effects beyond the central nervous system, in organs, such as skeletal muscle and adipose tissue [27]. *FKBP5* is expressed in peripheral and central tissues with its highest expression in adipose and skeletal muscle [28]. Specifically, the functional variant of the gene analyzed in the present study (rs1360780) has been associated with higher levels of the FKBP5 protein and a prolonged cortisol response to stress measured by reduced cortisol suppression after different tests [29–31]. Unfortunately, we could not measure cortisol levels in our cohort, which is a limitation of the present study.

Given the polygenic nature of obesity, cumulative minor effects of different genes expressed in metabolic active tissues, either regulating *FKBP5* or other related pathways, could be implicated in the observed weight loss [32]. In our study, we have only analyzed a genetic variant in the *FKBP5* gene. However, weight loss after surgery can be attributed not only to the variability of this gene but also to other factors that could contribute to the outcome. One interesting strategy in future genetic studies should be to estimate polygenic risk scores based on biologically meaningful gene sets, which can represent functional pathways associated to weight loss, including *FKBP5* gene.

Additionally, other biological factors, such as age, sex, and hormones play an important role in both phenotype and response after the surgery procedure. On the other hand, environmental factors, such as perceived stress, which tends to increase in obese patients, should be considered a key variable in the phenotype of obesity and the study of the weight loss after bariatric surgery [33].

The findings of this study have to be taken in light of some limitations. We did not measure cortisol levels that would be interesting to correlate with genotypes. As we only evaluate a single polymorphism, we cannot discard the effect of other genetic markers given the polygenic nature of obesity. Finally, the present study performed an exhaustive clinical assessment to discard cases of monogenic obesity. However, a genetic screening for the mutations in genes of the leptin/melanocortin pathway associated with these early and severe forms of obesity was not performed.

Future longitudinal studies with larger sample sizes, as well as a longer follow-up period, might shed some light on the role of *FKBP5* variability and its interaction with variables, such as surgery, sex, and stress. It might be worth using two well-differentiated samples in terms of age (i.e., young and old sample) like in previous studies [26]. The identification of potential predictors of success after bariatric surgery will be relevant in the near future for improving patients' quality of life.

Conclusions

In summary, in our longitudinal study comparing 2 different bariatric surgery procedures (RYGB and SG) and considering the effect of *FKBP5* variability, age, and sex on the surgical outcome, we report better results for RYGB in men with the CC genotype. Our results show how age, sex, and genotype have a different impact on weight loss depending on the surgical technique used. These findings provide a basis for further studies, which could include as procedure selection criteria not only BMI but also sex, age, or different specific genetic variants that could have a significant impact on the surgery outcome.

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Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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Supervisor's report on the contribution of the PhD candidate to the article.

Dr. Araceli Rosa de la Cruz, Associate Professor at the Departament de Biologia Evolutiva, Ecologia i Ciències Ambientals of the Facultat de Biologia (Universitat de Barcelona) and supervisor of the present doctoral thesis by Elionora Peña, hereby certifies that none of the co-authors of the article "Role of *FKBP5* polymorphism rs1360780, age, sex and type of surgery in weight loss after bariatric surgery: a follow-up study," have used this publications for a doctoral thesis, and that the participation of the applicant in this article included the following tasks:

- Participation in the conception and design of the study.
- Experimental work
- Statistical analyses and interpretation of data.
- Writing of the manuscript.
- Critical revision of the article for intellectual content.

Signed by Dr. Araceli Rosa

Barcelona, September 2020

3.2. Response to the letter to the editor: FKBP5 polymorphism rs1360780 and weight loss after bariatric surgery

Elionora Peña, Assumpta Caixàs, Concepción Arenas, Mercedes Rigla, Sara Crivillés, Narcís Cardoner, Araceli Rosa.

Surgery of Obesity And Related Disease, 2020 Jul;16(7):974-975.

DOI: 10.1016/j.soard.2020.03.026.

Resum

En aquest article responem a la letter de Yasri and Wiwanitkit 2020, on comentaven el nostre treball previ "*Role of FKBP5 polymorphism rs1360780, age, sex and type of surgery in weight loss after bariatric surgery: a follow-up study*". En aquest estudi havíem trobat un efecte del genotip, l'edat i el tipus de cirurgia en la variabilitat de la pèrdua de pes post cirurgia. Els autors semblaven suggerir que la variabilitat en aquest gen no podia explicar la pèrdua de pes post-cirurgia. La nostra letter dona resposta a Yasri i Wiwanitkit, reprenent el concepte d'obesitat com a malaltia poligènica i multifactorial, on múltiples gens d'un efecte menor, factors ambientals i la interacció entre aquest, donaria lloc al desenvolupament de la patologia. També assenyalem que tot i el nombre de *loci* associats amb l'obesitat en els *Genome-Wide Association Studies*, la major part de la variabilitat fenotípica de l'obesitat encara no ha estat explicada. En aquest sentit, i donada la naturalesa de la malaltia, proposem que els estudis futurs haurien de considerar '*polygenic risk scores'* que pugin capturar el risc conferit per múltiples variants genètiques que serien de gran utilitat per predir, de manera més acurada, l'evolució dels pacients amb obesitat després de sotmetre's a una cirurgia bariàtrica.

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Response to the letter to the editor: *FKBP5* polymorphism rs1360780 and weight loss after bariatric surgery

We have read with attention the letter of Yasri and Wiwanitkit. According to our recent paper [1], as stated by the authors, our results suggest how age, sex, and *FKBP5* genotype have a different impact on weight loss depending on the surgical technique used. These factors could contribute to understand the interindividual variation in surgery outcomes, especially in relation to weight loss suffered by the patients in the postoperative period.

Obesity is a polygenic multifactorial trait, influenced by multiple genetic variants of minor effect and environmental factors. Recent genome-wide association studies have identified a number of common loci associated with obesity-related phenotypes (e.g., body mass index or waist circumference), although most of the genetic variability for body mass index remains unexplained [2]. However, the association of these variants with weight loss after bariatric surgery has been less examined. In this regard, Hartman's work and our paper [1,3], published in this journal, analyzed a single functional polymorphism (rs1360780) and reported the possible contribution of the protein encoded by *FKBP5* gene in metabolic regulation.

Kops et al. [4], cited by Yasri and Wiwanitkit, also analyzed the variability in 4 obesity-related genes (*LEP223*, *LEP656*, *FTO*, and *FABP2*) in relation to their effects on weight loss after bariatric surgery. They found a different change on weight loss in those patients with AA genotype in the *LEP223* gene (rs1137101). These studies are contributing to understand how the biological background, among other factors, impact in the outcomes after bariatric surgery.

As commented in our paper, we only studied a candidate gene and we cannot discard the effect of other genetic markers via complex interactions with environmental factors. Future studies should consider polygenic scores taking into account the variation and risk conferred by multiple genetic variants. These scores could have a better predictive power in relation to the evolution of the obese patients after surgery.

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Supervisor's report on the contribution of the PhD candidate to the article.

Dr. Araceli Rosa de la Cruz, Associate Professor at the Departament de Biologia Evolutiva, Ecologia i Ciències Ambientals of the Facultat de Biologia (Universitat de Barcelona) and supervisor of the present doctoral thesis by Elionora Peña, hereby certifies that none of the co-authors of the article "Response to the letter to the editor: *FKBP5* polymorphism rs1360780 and weight loss after bariatric surgery" have used this publications for a doctoral thesis, and that the participation of the PhD applicant in this article included the following tasks:

- Participation in the conception and design of the study.
- Experimental work
- Statistical analyses and interpretation of data.
- Writing of the manuscript.
- Critical revision of the article for intellectual content.

Signed by Dr. Araceli Rosa

Barcelona, September 2020

3.3. Influence of the *BDNF* Val66Met polymorphism on weight loss after bariatric surgery: a 24-month follow-up

Elionora Peña, Assumpta Caixàs, Concepción Arenas, Rocio Pareja, Josep León-Mengíbar, Mercedes Rigla, Timothy R Powell, Narcís Cardoner, Araceli Rosa.

Surgery of Obesity And Related Disesases (In press)

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Resum

Diversos estudis han posat de manifest que la variabilitat del gen que codifica pel *BDNF* pot influenciar la quantitat de BDNF a nivell hipotalàmic que alhora, por tenir una repercussió en el balanç energètic de l'individu, podent estar implicat en el fenotip de l'obesitat.

L'objectiu d'aquest estudi va ser examinar el paper del polimorfisme Val66Met (rs6265) del gen *BDNF* i la influència de la diabetis tipus 2 (T2D) en la pèrdua de pes post-cirurgia bariàtrica en una cohort de pacients amb obesitat severa. Es van avaluar 158 pacients sotmesos a cirurgia bariàtrica (*Roux-en-Y Gastric Bypa*ss o *Sleeve Gastrectomy*) amb un seguiment a 24 mesos post-cirurgia on el BMI, i el % d'EWL i TWL van ser avaluats.

Les anàlisis longitudinals van mostrar un efecte del genotip del *BDNF* en el BMI ($P = 0.0073$) així com una tendència pel %EWL ($P = 0.0564$). Aquests resultats semblaven indicar que els pacients portadors de l'al·lel Met responien millor a la cirurgia bariàtrica que els que presenten el genotip Val/Val.

Pel que respecta a la T2D, d'acord amb les nostres dades, els pacients que presentaven diabetis tipus 2 en el moment de la intervenció tenien una pitjor resposta a la cirurgia presentant una menor pèrdua de BMI ($P = 0.015$).

Addicionalment, vam trobar una interacció entre el genotip del *BDNF* i la T2D en el %EWL i el BMI ($P = 0.027$ i $P = 0.010$, respectivament), de manera que els individus portadors de l'al·lel Met que no presentaven T2D a t_0 mostraven un major %EWL així com un BMI més baix a t_{12m} i t_{24m}. que els seus homòlegs amb T2D o que els pacients amb genotip Val/Val amb i sense T2D.

ELSEVIER

Surgery for Obesity and Related Diseases ■ (2020) 1–8

SURGERY FOR OBESITY AND RELATED DISEASES

Original article

Influence of the *BDNF* Val66Met polymorphism on weight loss after bariatric surgery: a 24-month follow-up

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Abstract

Background: Bariatric surgery is currently the most effective long-term treatment for severe obesity. However, interindividual variation in surgery outcome has been observed, and research suggests a moderating effect of several factors including baseline co-morbidities (e.g., type 2 diabetes [T2D] and genetic factors). No data are currently available on the interaction between T2D and variants in brain derived neurotrophic factor (*BDNF*) and its effect on weight loss after surgery.

Objectives: To examine the role of the *BDNF* Val66Met polymorphism (rs6265) and the influence of T2D and their interaction on weight loss after bariatric surgery in a cohort of patients with severe obesity.

Setting: University hospital in Spain.

Methods: The present study evaluated a cohort of 158 patients with obesity submitted to bariatric surgery (Roux-en-Y gastric bypass or sleeve gastrectomy) followed up for 24 months (loss to follow-up: 0%). During the postoperative period, percentage of excess body mass index loss (%EBMIL), percentage of excess weight loss (%EWL), and total weight loss (%TWL) were evaluated.

Results: Longitudinal analyses showed a suggestive effect of *BDNF* genotype on the %EWL ($P = .056$) and indicated that individuals carrying the methionine (Met) allele may experience a better outcome after bariatric surgery than those with the valine/valine (Val/Val) genotype. We found a negative effect of a T2D diagnosis at baseline on %EBMIL ($P = .004$). Additionally, we found an interaction between *BDNF* genotype and T2D on %EWL and %EBMIL ($P = .027$ and $P = .0004$,

Elionora Peña and Assumpta Caixàs contributed equally to this study

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respectively), whereby individuals with the Met allele without T2D before surgery displayed a greater %EWL and greater %EBMIL at 12 months and 24 months than their counterparts with T2D or patients with the Val/Val genotype with or without T2D.

Conclusion: Our data showed an association between the Met variant and greater weight loss after bariatric surgery in patients without T2D. The presence of T2D seems to counteract this positive effect. (Surg Obes Relat Dis 2020;■:1–8.)

Key words: Obesity; Bariatric surgery; Weight loss; BMI; Follow-up; Type 2 diabetes; *BDNF* Val66Met; rs6265

Obesity is a major health problem in developing countries, leading to associated conditions such as type 2 diabetes (T2D), cardiovascular problems, liver disease, and some forms of cancer [1], impairing quality of life [2]. Therapeutic strategies used to induce weight loss range from dietary restriction to surgical procedures. In this regard, bariatric surgery results in significant excess weight loss and health benefits [3–5], solidifying this procedure as the most effective current treatment for patients with severe obesity [6,7]. However, studies reveal considerable interindividual variation in surgery outcome, particularly in relation to the percentage of total weight loss (%TWL) [8,9]. Studies to date have suggested a variety of complex factors potentially moderating weight loss outcomes, such as age, sex, baseline co-morbidities, and body mass index (BMI) among others, and the identification of robust predictors is one of the top priorities in this field [10,11]. Regarding co-morbidities, although benefits are still observed among T2D patients, it may be more difficult for this patient group to lose weight after bariatric surgery, especially in those previously and concurrently treated with insulin or oral agents (e.g., sulfonylureas) [12].

In addition, biological factors should be considered when studying weight loss outcomes after surgery [13]. Obesity has a strong genetic component, with heritability estimates ranging from 50% to 75% [14]. However, only a small proportion of obesity cases are monogenic or syndromic. These cases are usually severe and have an early onset and are primarily caused by mutations in genes implicated in the leptin-melanocortin pathway. Most obesity cases are attributed to the influence of multiple genetic variants of minor effect and to environmental factors [15]. In relation to genetic variants, genome-wide association studies (GWAS) have identified different common loci associated with obesity-related anthropometric measures (e.g., BMI) although a large proportion of the heritability remains unexplained [16].

Many of the variants identified by GWAS are near to genes that are highly expressed in the brain and/or have previously been shown to have a function in neuronal development or activity. One of these genes is the brain derived neurotrophic factor (*BDNF*), which regulates energy balance downstream of *MC4-R* in the leptin-melanocortin pathway [17]. It plays a critical role in nervous system development and function and in particular exerts an anorexigenic function in the brain. It is hypothesized that genetic variability in the *BDNF* gene could alter hypothalamic BDNF expression that would influence energy balance and may lead to the manifestation of the obese phenotype. Plasma BDNF tends to be lower in prepubertal children with obesity than in lean controls and increases after lifestyle intervention [18]. Furthermore, in syndromic obesity (e.g., Prader-Willi syndrome), patients exhibit alterations in their hypothalamus and exaggerated hyperphagia, as well as low fasting plasma BDNF levels and a lack of postprandial peak that can predict the odds of being hungry [19].

In addition, the secretion of BDNF is affected by a common functional polymorphism (rs6265, C > T) that results in valine (Val) to methionine (Met) substitution at codon 66 (Val66Met). This polymorphism has been associated with several clinical traits such as early seizures, bipolar affective disorders, obsessive-compulsive disorders, eating disorders, BMI, and obesity [20,21]. In this regard, a meta-analysis involving over 10,109 women found that Met homozygotes had lower BMI than individuals with the other genotypes (i.e., Val/Met or Val/Val) [22]. This association has been later confirmed by a large-scale GWAS in populations of European origin [23]. However, it is unclear whether the variability of this gene is involved in weight loss after bariatric surgery.

The present study was undertaken to examine the role of a *BDNF* polymorphism (rs6265) on weight loss in a cohort of 158 patients with obesity submitted to Roux-en-Y-gastric bypass (RYGB) or sleeve gastrectomy (SG) and followed-up for 24 months. We also sought to investigate the effect of T2D on the changes in weight loss of these patients. The ultimate aim is the identification of specific baseline biomarkers (e.g., genetic polymorphisms) and clinical factors (e.g., presence of co-morbidities such as T2D) that are capable of predicting long-term outcomes in bariatric surgery.

Methods

Participants

The present sample has previously been described in detail [24]. In brief, the present study consisted of a prospective cohort of 158 patients with severe obesity submitted to bariatric surgery at the Hospital Universitari Parc Taulí (Sabadell, Spain), who were followed up for 24 months. Inclusion criteria were BMI $\geq$35 kg/m^2 with co-morbidities or BMI $\geq$40 kg/m^2, and older than 18 years. Clinicians performed an exhaustive clinical assessment to discard cases of monogenic obesity. Surgical treatment included either RYGB (n = 99) or SG (n = 59).

This cohort was evaluated pre-, peri- and postoperatively by a multidisciplinary team (endocrinologists, clinical nurses, surgeons, and dieticians) in consecutive visits over a 2-year timespan according to the local protocol. This period was divided as follows: before surgery (t_0), 1 month after surgery ($t_{1\ m}$), 3 months after surgery ($t_{3\ m}$), 6 months after surgery ($t_{6\ m}$), 12 months after surgery ($t_{12\ m}$), and 24 months after surgery ($t_{24\ m}$).

Anthropometric assessment

Measurements of weight, height, and waist circumference were obtained from physical examination along the evaluated period. BMI was calculated in kg/m^2 according to the formula: weight (kg) / height (m^2).

To report weight loss, we calculated for all the assessments (from t_0 to $t_{24\ m}$): percentage of excess BMI loss (%EBMIL), percentage of excess weight loss (%EWL), and percentage of total weight loss (%TWL). The 158 patients completed all the assessments (loss of follow-up at $t_{24\ m}$ = 0%).

The %EBMIL was calculated as [(BMI at t_0) – (Postoperative BMI) / (BMI at t_0 – 24.9)] x 100. The %EWL was calculated as [(Weight at t_0) – (Postoperative Weight)] / [(Weight at t_0) – (Ideal Weight)], where ideal weight was taken as the weight in kilograms above the weight corresponding to the BMI for 24.9 kg/m^2. The %TWL was calculated as [(Weight at t_0) – (Postoperative Weight)] / [(Weight at t_0)] x 100.

Ethics

All patients were informed about our study and invited to participate in this prospective cohort. Informed consent was obtained from all participants included in the study. The Institutional Ethics Committee of Hospital Universitari Parc Taulí approved the protocol, and all investigations complied with the Declaration of Helsinki [25].

Laboratory analysis

Blood samples were collected from all patients and genomic DNA from buffy coat was extracted using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Genotyping of the *BDNF* Val66Met polymorphism (rs6265) was performed using TaqMan allelic discrimination assay from Life Technologies (Thermo Fisher Scientific). The assay was run in a 384-well plate on the ABI PRISM 7900 HT Fast Real-Time PCR System (Applied Biosystems) using standard conditions. The final volume of each well was 5 μL, which contained 5 ng of genomic DNA, 2.5 μL of TaqMan Master Mix, and .125 of 40 x genotyping assay. SDS v.2.4 (Applied Biosystems) software was used for the data analysis of the genotypes. Testing for validity and accuracy of genotyping, we retested a 20% random sample. In all cases, genotypes were reproducible.

Statistical analysis

All the statistical analyses were performed using RStudio 1.1.463 software (RStudio, Boston, MA) and $P < .05$ were considered statistically significant. Hardy-Weinberg equilibrium was tested by comparing observed and expected genotype frequencies in the sample using Hardy-Weinberg calculator (available at: https://genepop.curtin.edu.au/).

Variables were reported as mean ± standard deviation (SD) or percentages. The baseline characteristics of the sample were analyzed using the Pearson χ^2 test for contingency tables or the nonparametric Mann-Whitney *U* test for continuous variables.

Generalized estimating equation (GEE) models were used for the prospective analysis of the variation of % EBMIL, %EWL, and %TWL in a follow-up of 24 months after bariatric surgery. In these models we included some possible confounding variables as explanatory variables. Thus, the variables included in the models were time, age, sex, type of surgery, *BDNF* genotype, T2D, and the interaction of the *BDNF* genotype with T2D.

Four groups of patients were generated according to their *BDNF* genotype and T2D status at baseline. The comparison between groups was performed using the Kruskal-Wallis test followed by the Benjamini-Hochberg (False Discovery Rate) post hoc correction.

Results

Baseline assessment

A total of 158 patients with obesity, mainly women (77.2%) between 21–61 years were included in the study. All of them underwent bariatric surgery, either RYGB or SG. A description of the sample at baseline is shown in Table 1.

The *BDNF* genotype frequencies were: 104 Val/Val (65.82%), 46 Val/Met (29.11%), and 8 Met/Met (5.07%). Compliance with the Hardy-Weinberg equilibrium was confirmed (χ^2 = 1.06, P = .30). Based on previous studies and due to the low frequency of the Met allele, we assumed

Table 1
Baseline (t_0) characteristics of the sample (t_0) according to *BDNF* genotype

Variables	Total Sample (n = 158)	Val/Val (n = 104)	Met carriers (n = 54)	*P* value
Sex, n (%)				
Male	36 (22.8)	21 (20.2)	15 (27.8)	.379
Female	122 (77.2)	83 (79.8)	39 (72.2)	
Surgery, n (%)				
RYGB	99 (62.7)	66 (63.5)	33 (61.1)	.907
SG	59 (37.3)	38 (36.5)	21 (38.9)	
T2D, n (%)				
Non-T2D	103 (65)	67 (64.4)	36 (66.7)	.979
Yes-T2D	54 (35)	36 (34.6)	18 (33.3)	
Age (yr)	46.12 ± 9.89	46.97 ± 9.62	44.48 ± 10.28	.135
BMI	44.75 ± 7.20	45.46 ± 6.11	43.39 ± 8.86	.068
EW	47.93 ± 16.49	48.46 ± 15.43	46.90 ± 18.46	.297
FPG (mg/dL)	110.08 ± 37.21	112.03 ± 36.01	106.42 ± 39.43	.094
HbA1C (%)	6.24 ± 1.18	6.25 ± 1.11	6.21 ± 1.32	.457

RYGB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy; T2D = type 2 diabetes; BMI = body mass index; EW = excess weight; FPG = fasting plasma glucose; HbA1C = hemoglobin A1 c.
Pearson χ^2 test for sex, surgery and T2D; Mann-Whitney *U* test for the other variables.

a dominant model and patients were classified into 2 genotype groups according to whether or not they carried the Met allele (i.e., Val/Val and Val/Met or Met/Met genotypes, respectively). No differences were observed between genotype groups and the baseline characteristics considered (Table 1).

Fifty-four patients suffered T2D at t_0 according to American Diabetes Association criteria [26]. Nine out of 54 were treated with diet only; 32 with diet and oral agents and/or GLP1 analogs; 11 with diet, oral agents/GLP1 analogs and insulin; and 2 with diet and insulin. Patients with normal glucose tolerance, impaired fasting glucose, or impaired glucose tolerance were considered to not have T2D. Patients with and without T2D differed on age, BMI, Fasting Plasma Glucose (FPG), and Hemoglobin A1 c (HbA1C) (Table 2).

Table 2
Baseline (t_0) characteristics of the sample according to type-2-diabetes

Variables	T2D (n = 54)	Non-T2D (n = 103)	*P* value
Sex, n (%)			
Male	16 (29.6)	19 (18.4)	.162
Female	38 (70.4)	84 (81.6)	
Surgery, n (%)			
RYGB	29 (53.7)	69 (67)	.144
SG	25 (46.3)	34 (33)	
Age (yr)	51.00 ± 6.96	43.54 ± 10.30	1.34 e-05
BMI	42.48 ± 7.85	45.93 ± 6.62	.007
EW	45.49 ± 15.69	49.09 ± 16.87	.122
FPG (mg/dL)	140.48 ± 46.89	93.83 ± 14.19	4.47 e-13
HbA1C (%)	7.34 ± 1.39	5.65 ± .36	< 2.2 e-16

RYGB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy; T2D = type 2 diabetes; BMI = body mass index; EW = excess weight; FPG = Fasting Plasma Glucose; HbA1C = hemoglobin A1 c.
Pearson χ^2 test for sex, surgery; Mann-Whitney *U* test for the other variables.

Longitudinal assessment

All the participants completed the 2-year follow-up (loss to follow-up: 0%). We studied the effects of bariatric surgery on the variation of 3 anthropometrical variables: %EBMIL, %EWL, and %TWL. To this aim we used GEE models to consider the correlation between repeated measures in the same individual. Thus, using t_0 as a reference time point, we analyzed all repeated measurements included after bariatric surgery (i.e., $t_{1\ m}$, $t_{3\ m}$, $t_{6\ m}$, $t_{12\ m}$ and $t_{24\ m}$). The GEE model included the variables: age, sex, type of surgery, *BDNF* genotype, and T2D.

The model revealed an effect of time on the variation of all the variables analyzed ($P < 2.2$ e-16 for %EBMIL, %EWL, and %TWL). An effect of age was found on the %EBMIL, %EWL, and %TWL ($P = 7.81$ e-06, 5.84 e-09, and 4.48 e-14, respectively). Additionally, we found a suggestive effect of *BDNF* genotype on the %EWL ($P = .056$) and a trend on the %EBMIL ($P = .082$). These results seem to point to a better progress in weight loss after bariatric surgery for those patients carrying the Met allele than those carrying Val/Val genotype (Fig. 1a and 1b).

Furthermore, our analysis reported an association between T2D on %EBMIL ($P = .004$). Individuals without T2D at t_0 reported a higher %EBMIL after bariatric surgery than those patients with T2D (Fig. 1d). Regarding %EWL, although the effect of T2D on the model was not statistically significant, individuals without T2D lost on average 10.9% more %EWL than individuals with T2D at $t_{24\ m}$ (Fig. 1c).

Given the main effects found for *BDNF* genotype and T2D, we used the GEE model to explore the interaction between these 2 variables. We included in the model the previously mentioned variables (i.e., time, age, sex, type of surgery, *BDNF* genotype, T2D) and the interaction between *BDNF* genotype with T2D. The test of model effects

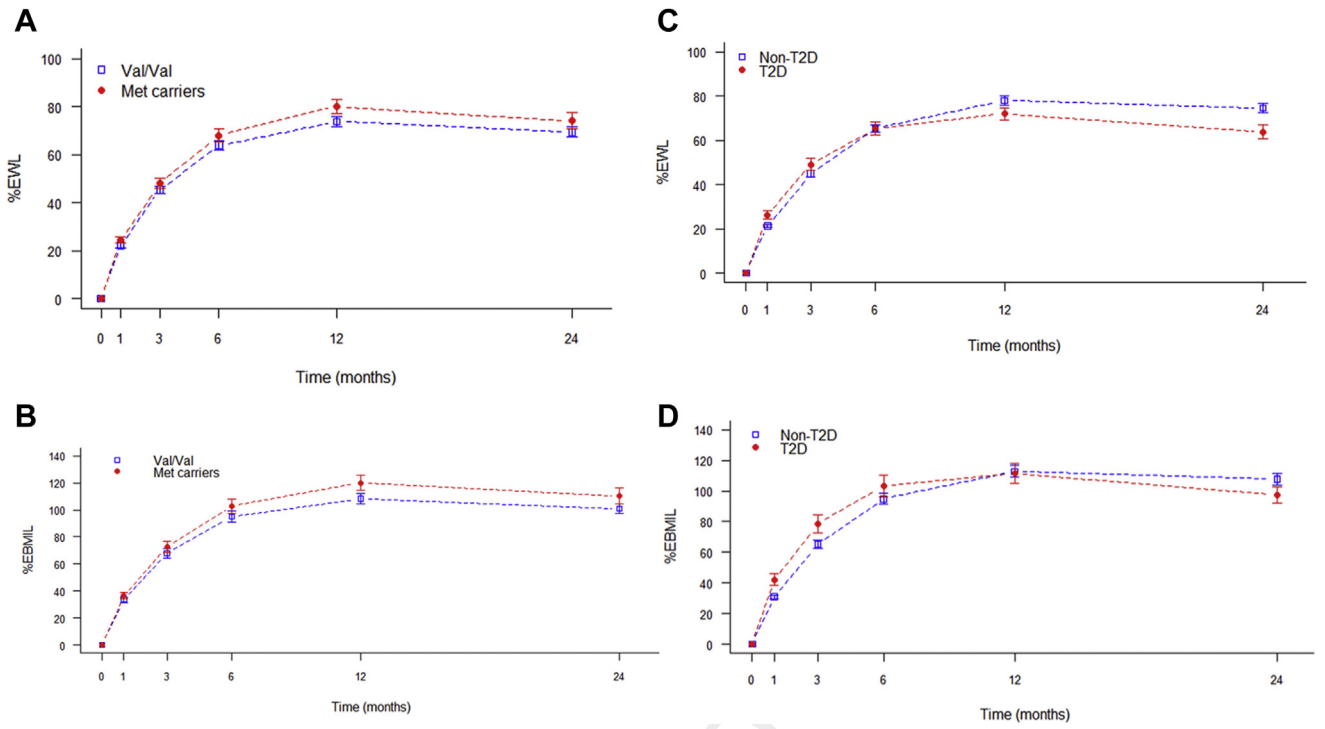

Fig. 1. Changes in the percentage of excess weight loss (%EWL) and percentage of excess body mass index loss (%EBMIL) over time stratified by *BDNF* genotype (a, b) and T2D status (c, d).

reported a significant interaction of these 2 variables on the %EBMIL and %EWL, (P = .027 and .004, respectively).

To better understand this interaction, we divided the patients into the following 4 groups: group 1: Met carrier individuals without T2D at baseline (n = 36); group 2: Val/Val individuals without T2D (n = 67); group 3: Val/Val individuals with T2D (n = 36); and group 4: Met carriers with T2D (n = 18). The Kruskal-Wallis test revealed differences for the %EBMIL at $t_{12\ m}$ and $t_{24\ m}$ (P = .027 and P = .047, respectively) and for the %EWL between groups at $t_{12\ m}$ (P = .033) and $t_{24\ m}$ months (P = .015) (Table 3).

The post hoc Benjamini-Hochberg correction for %EWL reported a trend for differences at $t_{12\ m}$, between groups 1 and 2, between groups 1 and 3, and between group 1 and 4 (adjusted P = .052, for all the comparisons). Concretely, individuals in group 1 reported 10.48%, 12.34%, and 13.96% more %EWL than individuals in group 2, 3, and 4, respectively. Differences on %EWL were also found at $t_{24\ m}$ between groups 1 and 3 and between groups 1 and 4 (adjusted P = .038 and .038, respectively). More specifically, individuals in group 1 reported 15.43% and 17.63% more %EWL compared to group 3 and 4, respectively (Fig. 2a). Regarding %EBMIL, multiple testing corrections confirmed differences between group 1 and 2 at $t_{12\ m}$ (adjusted P = .014). These results indicated that at $t_{12\ m}$ individuals in group 1 reported 22.61% more %EBMIL than individuals from group 2. These differences on %EBMIL were also found at $t_{24\ m}$ between groups 1 and 2, and between groups 1 and 4 (adjusted P = .055 and .055, respectively) (Fig. 2b). Individuals in group 1 displayed 19.39%

Table 3
Mean and standard deviation for %EWL and %EBMIL at $t_{12\ m}$ and $t_{24\ m}$ for the 4 groups based on *BDNF* genotype and presence or absence of T2 D at baseline

	Group 1 Met carriers – No T2 D	Group 2 Val/Val – No T2 D	Group 3 Val/Val – T2 D	Group 4 Met carriers – T2 D	*P* value
t_{12}					
%EBMIL	127.5 ± 42.89	104.89 ± 32.58	114.95 ± 51.70	105.58 ± 31.17	.027
%EWL	84.83 ± 22.29	74.35 ± 17.41	72.49 ± 22.69	70.87 ± 14.58	.033
t_{24}					
%EBMIL	120.19 ± 43.81	100.80 ± 33.25	101.13 ± 43.28	90.72 ± 31.39	.047
%EWL	79.99 ± 24.00	71.79 ± 20.06	64.56 ± 23.11	62.36 ± 22.34	.015

%EBMIL = percentage of excess body mass index loss; %EWL = percentage of excess weight loss.
Kruskal-Wallis test used.

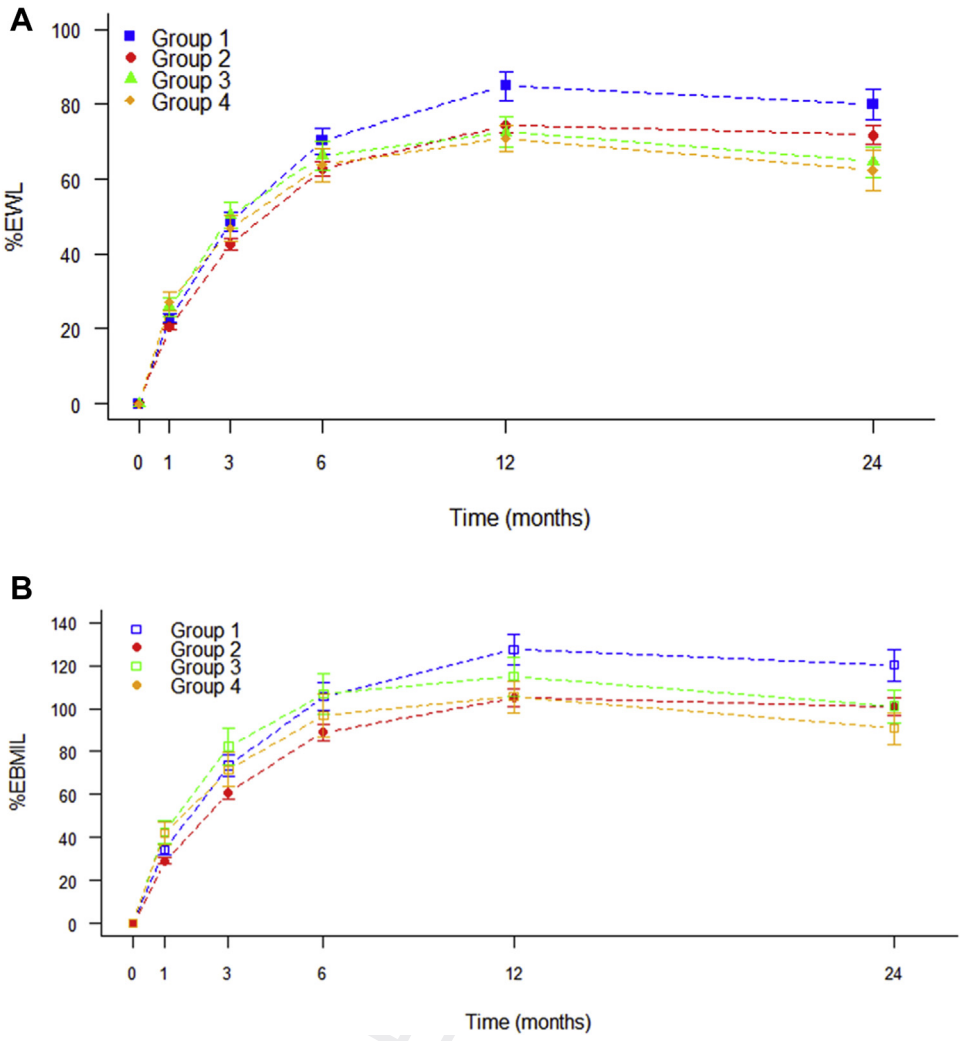

Fig. 2. Changes in the percentage of excess weight loss (%EWL) and excess body mass index loss (%EBMIL) over time in relation to groups stratified by *BDNF* genotype and T2D status (i.e., group 1: Met carriers – No T2D; group 2: Val/Val – No T2D, group 3: Val/Val – T2D and group 4: Met carriers – T2D).

and 29.47% more %EBMIL than patients from groups 2 and 4, respectively.

These results revealed that individuals carrying the Met allele (i.e., Val/Met or Met/Met genotypes) in the absence of T2D at baseline (i.e., individuals in group 1) had a better outcome after bariatric surgery for the variables %EBMIL and %EWL. However, it is a limitation that in this interaction study with 4 groups, we did not adjust for sex, age, or other possible confounding variables, as the sample size of our study did not support it.

Finally, we examined the statistical power inherent in this analysis. For the baseline comparison, we had 80% power to detect large effect sizes $f > .48$ in a sample of 158 patients, as part of a Mann-Whitney *U* test, with group sizes 104 and 54, and an error rate of $\alpha = .05$. For the longitudinal analysis, we had 80% power to detect medium changes in the analyzed variables over time, with an effect size of $f > .30$, given a sample size of $n = 158$, a correlation across timepoint of $r = .7$, and an error rate of $\alpha = .05$.

Discussion

Bariatric surgery is the most effective treatment for patients with severe obesity. Despite the beneficial effects of bariatric surgery, a heterogeneous response to surgery is evident. A variety of complex factors have been reported as moderators of postoperative weight loss, including age, sex, preoperative weight, BMI, physical activity, and T2D among others [10,27]. More recently, other underlying factors such as genetic background have emerged as potentially relevant for bariatric surgery outcomes. For instance, studies have reported that single nucleotide polymorphisms in

known obesity genes (e.g., Leptin receptor) differentially affect weight loss [24,28–30].

The present study first sought to investigate the role of the *BDNF* Val66Met polymorphism on weight loss in a cohort of patients with obesity who were submitted to bariatric surgery (RYGB or SG) and followed up for 2 years. Our data suggests a trend between the *BDNF* Val66Met genotype and %EWL and %EBMIL, with better outcomes in patients carrying the Met allele. The involvement of the *BDNF* gene in obesity and BMI has been reported in different GWAS from different populations [31,32]. However, to the best of our knowledge, this is the first study to analyze the effect of this *BDNF* variant on bariatric surgery outcomes. Physiologic and animal models have found that BDNF induces appetite suppression and weight reduction acting through melanocortin/leptin, dopamine, and serotonin neurotransmitter systems [33,34]. Genetic variation which affects BDNF levels has been implicated in conditions which affect weight, including eating disorders [35].

The Val66Met polymorphism has been one of the most extensively studied genetic markers because one of its variants affects BDNF activity and has been related to clinical traits associated with BMI and obesity. In this regard, previous studies in healthy populations have shown that individuals carrying the Met allele have lower BMI [36,37].

In the present study we also studied the effect of T2D at baseline on the outcome after the surgical procedure. We found that patients with T2D reported worse %EBMIL than patients without T2D. This is in agreement with another study showing that, in spite of less weight loss, people with diabetes still show an improvement in diabetes control and hypertension after bariatric surgery [12].

Interestingly, the present study also reports that the main effect of *BNDF* genotype and T2D at baseline could not be independent to explain weight loss after bariatric surgery. In this regard, we investigated the interactive effect of *BDNF* rs6265 genotype and T2D status. We found that individuals carrying the Met allele (either as homozygotes or heterozygotes) without T2D at baseline reported better outcomes in terms of %EWL and %EBMIL, especially at $t_{12\ m}$ and $t_{24\ m}$ (Fig. 2). A biological interaction between these 2 factors might suggest their co-participation in the same causal mechanism [38]. To our knowledge, no previous studies have studied the interaction between *BDNF* genotype and T2D in relation to bariatric surgery. However, considering the role of BDNF in the regulation of food intake and energy metabolism, different studies have analyzed its association with metabolic parameters related to T2D. For instance, animal models have shown that after subcutaneous administration of BDNF, high glucose levels are ameliorated in obese mice and glucose use is enhanced [39]. Furthermore, Kalenda et al. reported that healthy individuals carrying the *BDNF* Met allele had lower postprandial glucose levels and lower HbA1C [37]. Similarly, in human patients with T2D, a negative correlation between BDNF serum levels and blood glucose has been found [40].

Taking into account the role of BDNF and the exonic location of the variant, one may expect different serum levels of BDNF between carriers and noncarriers of the Met allele, although its functional effect has been largely discussed and remains unclear. Unfortunately, we were not able to directly measure circulating BDNF levels in our cohort, which is a limitation of our study.

Given the multifactorial, polygenic nature of obesity, another limitation is the evaluation of only a single-genetic marker, and the effects of other polymorphisms cannot be excluded [41]. In this regard, future longitudinal studies should incorporate data from multiple candidate genes, and also environmental factors, to try to predict surgical outcomes. Additionally, our analyses may have been underpowered to detect small effect sizes, given the relatively small sample size.

The reasons for the high variability in weight loss in response to bariatric surgery are still unknown, and according to the literature, the failure of surgical techniques may be attributed to different factors including presurgical BMI, type of surgery, genetic predisposition to resistant weight loss, and the co-morbidities suffered by patients, among others.

Conclusion

The results of our longitudinal study suggest that the BDNF Val166Met genotype, and the presence of T2D before surgery could have an interactive effect on weight loss after surgery. Future work is now needed to replicate our findings in larger samples and to continue to identify clin-ically meaningful predictors of bariatric surgery outcome, to improve the quality of life of patients with obesity.

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Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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Supervisor's report on the contribution of the PhD candidate to the article.

Dr. Araceli Rosa de la Cruz, Associate Professor at the Departament de Biologia Evolutiva, Ecologia i Ciències Ambientals of the Facultat de Biologia (Universitat de Barcelona) and supervisor of the present doctoral thesis by Elionora Peña, hereby certifies that none of the co-authors of the article "Influence of the *BDNF* Val66Met polymorphism on weight loss after bariatric surgery: a 24-month follow-up" have used this publications for a doctoral thesis, and that the participation of the PhD applicant in this article included the following tasks:

- Participation in the conception and design of the study.
- Experimental work
- Statistical analyses and interpretation of data.
- Writing of the manuscript.
- Critical revision of the article for intellectual content.

Signed by Dr. Araceli Rosa

Barcelona, September 2020

Section II: Telomere length in obesity and bariatric surgery and depression.

3.4. Longitudinal changes in telomere length in a cohort of obese patients submitted to bariatric surgery: a 2-year follow-up

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Resum

La longitud telomèrica (LT) és un biomarcador d'envelliment cel·lular emprat per explorar els efectes de l'ambient en les patologies relacionades amb l'edat. L'obesitat i un índex de massa corporal elevats han estat identificats com a factors de risc per a l'escurçament dels telòmers. L'objectiu del present estudi va ser avaluar la LT en diferents subtipus de pacients amb obesitat, així com avaluar els canvis el la LT en relació amb el pes perdut després de una intervenció per cirurgia bariàtrica.

Aquest estudi es va dur a terme en una cohort de 94 pacients que es van sotmetre a cirurgia bariàtrica i que s'havien seguit al llarg de 2 anys. A tots els pacients se'ls va avaluar el *Body Mass Index* (BMI) així com diferents variables metabòliques abans de la cirurgia (t_0) i durant el període post-operatori (t_{6m}, t_{12m} i t_{24m}). La LT va ser avaluada per tots els pacients a cadascun dels temps mitjançant PCR quantitativa.

Els nostres resultats van posar de manifest com, a nivell basal, els pacients amb obesitat classe III (més severs) presentaven una LT més curta que els pacients amb obesitat classe II (P = 0.027). La LT a nivell basal no diferia entre els pacients amb o sense diabetis tipus 2 (T2D) o síndrome metabòlica (MetS).

Quan vam avaluar la variació de la LT als dos anys posteriors a la intervenció, vam trobar que per tot el període avaluat, la LT era més curta en els pacients amb obesitat de classe III (P = 0.008). Les comparacions estadístiques entre els pacients amb obesitat classe II i classe III mostraven diferències en la LT a t_{6m} (P ajustada = 0.024) de manera que els pacients amb obesitat de classe II tenen una LT més llarga.

D'acord amb els nostres resultats, la severitat de la obesitat té un efecte negatiu sobre la LT independentment de la presència o no de T2D i MetS tot i que la LT és significativament més llarga en els pacients amb obesitat classe II que en els classe III 6 mesos després de la intervenció, aquestes diferències no semblen mantenir-se 24 mesos després de la cirurgia.

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SURGERY FOR OBESITY AND RELATED DISEASES

Original articles

Longitudinal changes in telomere length in a cohort of obese patients submitted to bariatric surgery: a 2-year follow-up

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Abstract

Background: Telomere length (TL) is one biomarker of cell aging used to explore the effects of the environment on age-related pathologies. Obesity and high body mass index have been identified as a risk factors for shortened TL.

Objective: To evaluate TL in different subtypes of obese patients, and to examine changes in TL in relation to weight loss after bariatric surgery.

Setting: University Hospital in Spain.

Methods: A cohort of 94 patients submitted to bariatric surgery were followed-up during 24 months (t_{24m}: lost to follow-up = 0%). All patients were evaluated before surgery (t_0) and during the post-operative period (t_{6m}, t_{12m}, and t_{24m}) for body mass index and metabolic variables. We assessed TL at each timepoint using quantitative polymerase chain reactions and the telomere sequence to single-copy gene sequence ratio method.

Results: Patients with class III obesity showed significantly shorter TL at baseline than those patients with class II obesity ($P = .027$). No differences in TL were found between patients with or without

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type 2 diabetes or metabolic syndrome. Longitudinal analysis did not show an effect of time, type of surgery, age, or sex on TL. However, a generalized estimating equation model showed that TL was shorter amongst class III obesity patients across the time course ($P = .008$). Comparison between patients with obesity class II and class III showed differences in TL at t_{6m} (adjusted $P = .024$), whereby class II patients had longer TL. However, no difference was observed at the other evaluated times.

Conclusion: Obesity severity may have negative effects on TL independently of type 2 diabetes or metabolic syndrome. Although TL is significantly longer in class II obesity patients relative to class III 6 months after bariatric surgery. This difference is not apparent after 24 months. (Surg Obes Relat Dis 2020;■:1–8.)

Key words: Relative telomere length; Obesity; Bariatric surgery; Weight loss; T2D; Metabolic syndrome; Follow-up

Telomere length (TL) is one biomarker of cell ageing that has been used to explore the effects of the environment on premature cell ageing and age-related pathology. Telomeres are specialized structures that consist of repetitive nucleotide sequences (TTAGGG) that cap the ends of linear chromosomes [1]. Their main function is to maintain the integrity of chromosomes, preserving genomic information, and in preventing interchromosomal fusion [1]. As cells divide, TL shortens as a result of the incomplete replication of chromosome ends during DNA replication (the "end-replication problem"). When TL reaches a critical length, the cell stops dividing and becomes senescent [2]. A reduction in the ability of cells to replace old and damaged cells contributes to tissue-level pathology (e.g., coronary plaque formation), risk for age-related disease, and an increased risk of mortality. Of note, TL shortening can be reversed, to an extent, by the initiation of specific environmental activities and lifestyle changes that activate endogenous telomere-lengthening mechanisms, such as the enzyme telomerase [3]. Consequently, a better understanding of what factors affect TL and promote TL restoration over time, may help people to live healthier lives for longer [3].

Obesity and high body mass index (BMI) have been identified as risk factors for shortened TL, alongside risk for chronic diseases, such as hypertension, type 2 diabetes (T2D), and dyslipidemia [4,5]. The excess of adiposity increases the production of a range of adipokines, including immunologic factors, cytokines, and hormones that exhibit proinflammatory actions [6]. Indeed, a recent, large meta-analysis using cross-sectional data from 146,114 people reported an inverse relationship between BMI and TL, whereby TL is shorter in individuals with higher BMI [7]. The proposed drivers of this association include suboptimal diets (e.g., those with high sugar, and with high levels of reactive oxygen species) and maladaptive bodily responses to high levels of adipose tissue (e.g., inflammatory adipokines) [8,9].

The realization that BMI may be intrinsically linked to premature ageing has prompted obesity intervention studies to consider the subsequent effects that weight loss has on TL and age-related traits. Bariatric surgery is one highly effective weight loss intervention for obesity, where diet and exercise prove ineffective. The two most common bariatric surgeries include the Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) [10].

Although, there is considerable interindividual variation in bariatric surgery outcome and particularly in relation to weight loss, clinical benefits in terms of reductions in morbidity and mortality have been reported [11]. Regarding TL, Laimer et al. [12] reported that weight loss and obesity-related indicators were positively correlated with TL elongation in the long term post surgery. However, studies evaluating short-term benefits of weight loss after bariatric surgery on TL do not seem to report the recovery of TL [13].

Here, we extend previous research in the field by comparing TL in subsets of obese patients; those with obesity class II and class III; with and without metabolic syndrome (MetS); and with and without T2D. Where we observed baseline differences between patient groups, we then compared longitudinal changes to TL after bariatric surgery over a 2-year period, to test for persistent and differential changes to TL trajectories. The ultimate hope is that by studying TL in this fashion, we can better understand both transient and persistent differences in subsets of obese patients, and better comprehend how efficacious bariatric surgery is as an intervention to promote TL restoration.

Methods

Participants

The study recruited 94 morbidly obese patients of Caucasian origin awaiting bariatric surgery in the Hospital Universitari Parc Taulí, Sabadell, Spain. The present sample has previously been described in detail [14]. The participants were mainly women (n = 71, 75.5%) and all of whom were aged between 23 and 61 years (mean age = 46.92, standard deviation [SD] = 9.89). All the participants showed a BMI >35 kg/m^2 and underwent either RYGB or

Table 1
Characteristics of the whole sample and by sex at baseline (t_0)

	Total sample (n = 94)	Men (n = 23)	Women (n = 71)	*P* value*
Age, yr	46.92 ± 9.89	43.17 ± 10.46	48.14 ± 9.46	.053
TL	−.078 ± .645	−.053 ± .740	−.085 ± .61	.9511
BMI, kg/m^2	43.16 ± 7.20	43.51 ± 9.09	43.05 ± 6.55	.702
EW, %	48.49 ± 19.32	55.43 ± 25.72	46.24 ± 16.34	.083
TBF, %	47.95 ± 6.57	38.95 ± 4.74	50.15 ± 4.41	2.025^{e-10}
Glucose, mg/dL	104.95 ± 30.70	114.40 ± 47.21	101.94 ± 22.83	.823
Insulin, mU/mL	23.67 ± 17.52	31.28 ± 19.81	21.29 ± 16.19	.012
HbA1C, %	6.12 ± 1.04	6.36 ± 1.34	6.04 ± .92	.6709
Surgery, n (%)				
RYGB	56 (60)	14 (61)	42 (59)	>.999
SG	38 (40)	9 (39)	29 (41)	
T2D, n (%)				
Yes	31 (33)	9 (39)	22 (31)	.6406
No	63 (67)	14 (61)	49 (69)	

BMI = body mass index; EW = excess weight; TBF = total body fat; HbA1C = glycosylated hemoglobin; RYGB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy; T2D = type 2 diabetes; TL = telomere Length.

Data are presented as mean ± standard deviation unless otherwise stated.

* Pearson X^2 test for surgery and T2D; Mann-Whitney *U* test for the other variables.

SG bariatric surgery between 2008 and 2015. RYGB was assigned to patients with BMI between 40 and 55 kg/m^2 and SG for those patients with a BMI between 35 and 40 and >55 (waiting for a possible second surgery in the future). The whole cohort was evaluated pre-, peri-, and postoperatively by a multidisciplinary team (endocrinologists, clinical nurses, surgeons, and dieticians) in consecutive visits over a 24-month timespan, according to the local protocol. This period was divided as follows: t_0: before surgery; t_{6m}: 6 months after surgery; t_{12m}: 12 months after surgery, and t_{24m}: 24 months after surgery. All patients fulfilled the eligibility criteria for bariatric surgery and the type of technique was chosen according to European guidelines [15]. Further details are reported in Table 1.

Anthropometric assessment

Measurements of weight and height were obtained from physical examinations at baseline, and weight was also measured at each follow-up. BMI was calculated in kilograms per millimeter squared according to the following formula: weight (kg) / height (m^2). Excess weight at baseline for each patient was taken as the weight in kilograms above the weight corresponding to the BMI for 24.9 kg/m^2. Total body fat was determined at baseline by bioelectrical impedance analysis (TANITA, body composition analyzer BC-418 MA Biologica Tecnologia Medica SL-BCN, Tokyo, Japan).

Clinical subtypes

According to World Health Organization criteria [16], we subcategorized individuals into 3 types of obesity as follows: (1) class I, BMI: 30 to 34.9, (n = 0); (2) class II, BMI: 35 to 39.9, (n = 34), and (3) class III, BMI ≥40, (n = 60). According to ATP III criteria [17], 46 of our patients can be characterized as having a MetS and 31 with T2D at baseline (Table 2).

Ethics

Informed consent was obtained from all the participants included in the study. The Institutional Ethics Committee of Hospital Universitari Parc Taulí approved the protocol, and all investigations complied with the Helsinki Declaration [18].

Laboratory analysis

Blood samples were collected from all the patients in blood collection tubes containing ethylenediaminetetraacetic acid. Genomic DNA was extracted from buffy coat using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). The purity and the quality of the samples were measured using the Nanodrop D1000 (Thermoscientific, Wilmington, DE, USA).

To assess relative TL, we performed a modified version of a quantitative polymerase reaction (qPCR) protocol by Cawthon et al. [19], as previously described [20,21]. The protocol involves 2 separate qPCRs performed on separate 384-well plates with DNA samples pipetted into identical wells on each plate. In the first reaction, we assayed the telomere repeat region (TTAGGG). In the second reaction, we assayed a single copy gene, albumin, which we used as an internal control to correct for minor differences in DNA concentration between samples [19]. The telomere/albumin ratio was used to calculate TL.

On each plate, 6 negative controls consisting of RNase-free water were used to screen for any DNA contamination, and 5 positive controls were used to confirm successful

Table 2
Baseline characteristics of the sample according to class of obesity (II or III) and co-morbidities (T2D and MetS)

	Class II (n = 34)	Class III (n = 60)	*P* value*	T2D (n = 31)	No T2D (n = 63)	*P* value*	MetS (n = 46)	Non-MetS (n = 48)	*P* value*
Age	43.4 ± 9.93	48.43 ± 9.68	.0202	51.09 ± 10.36	44.87 ± 10.36	.005	51.58 ± 7.19	42.45 ± 10.13	1.149^{e-05}
TL	.09 ± .60	−.19 ± .63	.0271	−.07 ± .68	−.08 ± .63	.882	−.023 ± .66	−.14 ± .63	.3387
BMI, kg/m^2	37.63 ± 1.49	46.49 ± 6.98	1.369^{e-14}	41.54 ±6.47	43.96 ±7.45	.049	42.35 ± 6.74	43.94 ± 7.61	.1831
TBF, %	44.04 ± 5.97	49.47 ± 6.09	8.353^{e-05}	46.37 ± 6.46	48.00 ± 6.61	.28	47.74 ± 6.56	47.14 ± 6.64	.7478
Glucose, mg/dL	101.16 ± 32.35	105.28 ± 27.38	.251	129.29 ± 37.78	92.38 ± 15.50	2.591^{e-08}	117.79 ± 36.77	92.93 ± 16.6	8.818^{e-05}
Insulin, mU/mL	19.15 ± 11.08	25.90 ± 19.80	.0652	30.63 ± 22.17	19.99 ± 13.31	.0040	27.24 ± 19.38	20.09 ± 14.84	.0089
HbA1C, %	6.05 ± 1.21	6.05 ± .77	.2237	7.02 ± 1.30	5.66 ± .4	1.214^{e-09}	6.63 ± 1.25	5.63 ± .38	1.747^{e-07}
Surgery, n (%)									
RYGB	15 (44.1)	41 (68.3)	.0375	16 (51.6)	40 (63.5)	.379	22 (48)	34 (70)	.0392
SG	19 (55.9)	19 (31.7)		15 (48.3)	23 (36.5)		24 (52)	14 (30)	

T2D = type 2 diabetes; MetS = metabolic syndrome; TL = telomere length; BMI = body mass index; TBF = total body fat; HbA1C glycosylated hemoglobin; RYGB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy.

Data are presented as mean ± SD unless otherwise stated.

* Pearson X^2 test for surgery; Mann-Whitney *U* test for the other variables.

amplification. An 8-point dilution series using human leukocyte genomic DNA (.47, .94, 1.88, 3.75, 7.5, 15, 30, and 60 ng) was used on each plate to allow for absolute quantification of each sample and to account for any differences in efficiency between the telomere and albumin reactions. All reactions were performed in triplicates. Each qPCR mix for the telomere reactions consisted of 12 μL of PrecisionPLUS qPCR Master Mix (SYBR green) with ROX (Primer Design, Southampton, UK), 12 ng of DNA, 3 uL of RNase-free water, 1000 nM of telg, 5-'ACACTAAGGTTTGGGTT TGGGTTTGGGTTTGGGTTAGTGT-3 and 800 nM of telc, 5-TGTTAGGTATCCCTATCCCTATCCCTATCCCTATCCC TAACA-3. Four stages made up the thermocycling conditions as follows: stage 1: 95°C for 15 minutes, stage 2: 2 cycles for 15 seconds at 94°C and 49°C, stage 3: 25 cycles at 94°C for 15 seconds, 10 seconds at 62°C, and 15 seconds at 73°C (data collection), and stage 4: dissociation curve (primer specificity detection). The same reagents and quantities were used for the albumin reactions, apart from the albumin forward and reverse primers replaced the telomere primers. Quantities of the albumin forward and reverse primers were adjusted to 765 nM for the forward primer albu, 50-CGGCGGCGGGCGGCGCGG GCTGGGCGGAAATGCTGCACAGAATCCTT-30 and 930 nM for the reverse primer albd, 50-GCCCGGCCCGCCGC GCCCGTCCCGCCGGAAAAGCATGGTCGCCTGTT-30. The thermocycling conditions for the albumin reaction consisted of 4 stages as follows: stage 1: 95°C for 15 minutes, stage 2: 2 cycles for 15 seconds at 94°C and 49°C, stage 3: 33 cycles at 94°C for 15 seconds, 10 seconds at 62°C, and 15 seconds at 88°C (data collection) and stage 4: dissociation curve (primer specificity detection). Reactions were performed using the QuantStudio 5 Real-Time PCR System (Thermo Fisher Scientific, California, CA, USA).

Initial quality control was performed using the QuantStudio Design and Analysis Software. We checked that melting curves on every plate demonstrated a single clear peak, and that all standard curves produced strong positive correlations between genomic input and levels of fluorescence ($R^2 \geq .99$). PCR efficiencies were all between 90% and 110%.

TL calculation

A standard deviation of <.5 was required for at least 2 of the 3 cycle threshold (C_t) technical triplicates for a sample to be included in downstream analysis. C_q values were then created from the remaining C_t values by relating them to absolute quantities as part of the standard curve. TL was then calculated by dividing each sample's mean C_q value from the telomere reaction by each sample's mean C_q value from the albumin reaction. Data were then adjusted for plate batch by taking the standardized residuals (z scores). Outliers were identified as those data points greater than 2 standard deviations from the mean and subsequently removed.

Statistical analysis

Variables are reported as mean ± SD or percentages. The baseline characteristics of the sample was analyzed using the Pearson X^2 test for contingency tables or the nonparametric Mann-Whitney *U* test for continuous variables (i.e., age, TL, BMI, excess weight, insulin, and glycosylated hemoglobin). Correlation analysis between baseline TL, age, and the anthropometric and metabolic parameters in bariatric patients was performed using Spearman correlation.

As the present study consisted of a prospective analysis of the variation of TL in a follow-up of 24 months after bariatric surgery, generalized estimating equation models were considered for the longitudinal analysis. Loss to follow-up was 0%. The variables included in the model were time, age, type of surgery, sex, and class of obesity. The comparisons between groups depending on obesity class were performed using the Mann-Whitney *U* test. For the initial exploratory analyses at baseline, we deemed a nominal $P < .05$ as significant, which we used to inform our

Table 3
Comparison of TL between patients according to obesity class at 0, 3, 12, and 24 months after bariatric surgery

	TL (mean ± SD)			
	t_0	$t_{6\ m}$	$t_{12\ m}$	$t_{24\ m}$
Obesity class II	.0896 ± .5988	.281 ± .809	−.0240 ± .7056	−.2381 ± .7676
Obesity class III	−.19 ± .6349	−.241 ± .5869	−.1289 ± .5980	−.2064 ± .6906
Adjusted *P* value*	.0540	.0240	.5333	.7000

TL = telomere length.
* Mann-Whitney *U* test and Benjamini & Hochberg procedure for correction.

longitudinal analysis. Subsequently, the *P* values were corrected using Benjamini & Hochberg false-discovery rate method, where adjusted $P < .05$ was deemed significant.

All analysis were performed using RStudio 1.1463 (Boston, MA, USA).

Results

Baseline analyses

Before carrying out our analyses we explored the potentially confounding/contributory baseline effects of age, glucose, total body fat, insulin, and glycosylated hemoglobin status on TL. Our analyses revealed no effect of any of these variables in the whole cohort ($P > .05$) (see Supplementary information). There was also no significant effect of BMI on TL at baseline, though it did trend toward significance (Spearman's $r = -.192$, $P = .0759$).

TL does not differ between patients with MetS and those without MetS (mean = −.024, SD = .66 and mean = −.14, SD = .63, respectively, $P = .3387$), neither between patients with T2D or without T2D (mean = −.08, SD = .63 and Mean = −.069, SD = .68, respectively, $P = .89$). These results are in accordance with the results described above which revealed no clear effects of insulin and glucose on TL.

TL was, however, significantly shorter ($P = .0271$) in patients with obesity class III (mean = −.19, SD = .63) compared with obesity class II patients (mean = .09, SD = .60). Consequently, for the purposes of our longitudinal analysis we tested whether this baseline difference corresponded to persistent or differential TL trajectories in response to bariatric surgery.

Longitudinal assessment

To evaluate longitudinal changes in TL over the 24 months after bariatric surgery, we used the generalized estimating equation model. The model included the variables time, age, type of surgery, sex, and class of obesity. Despite drastic reductions in BMI postsurgery, the generalized estimating equation model did not reveal an effect of time on the variation of TL in patients ($P = .5475$ and $P > .05$ for all comparisons between times) (Fig. 1a), or an effect of the type of surgery, age, or sex ($P > .05$). However, our model did reveal an effect of the class of obesity on the variability of TL over time ($P = .0080$). This result revealed persistent mean differences in TL between patients with different class of obesity over the course of the study (Fig. 1b). To better understand these differences, we plotted TL trajectories (Fig. 1b), and compared TL between class II and class III patients at each evaluated time (t_0, t_{6m}, t_{12m}, and t_{24m}) using Mann-Whitney *U* test and Benjamini & Hochberg procedure for correction. The analysis revealed that class II patients presented 52.2% longer telomeres at t_{6m}

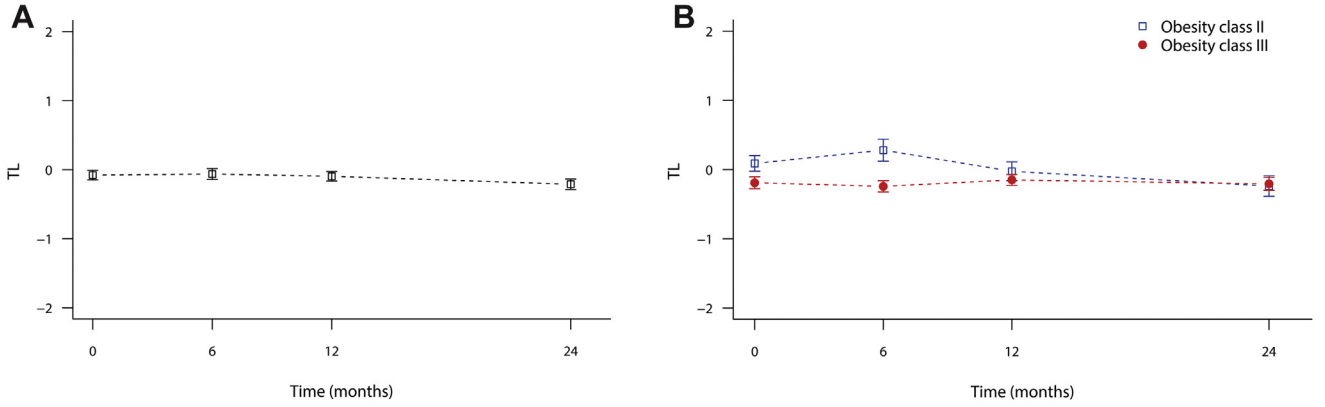

Fig. 1. Change on telomere length (LT) along time from t0 to t_{24m} in (a) all the patients submitted to bariatric surgery (n = 94) and (b) in patients depending on class of obesity (class II or class III).

compared with class III, this difference was statistically significant (adjusted $P = .024$). However, this difference was not apparent at 2 years (t_{24m}) (adjusted $P = .700$). (Table 3).

Finally, we examined the statistical power inherent in these analyses. For the baseline comparison, we had 80% power to detect large effect sizes $f > .62$ in a sample of 94, as part of a Mann-Whitney U test, with group sizes 34 and 60, and an error rate of $\alpha = .05$. For the longitudinal analysis, we have 80% power to detect medium to large changes to telomere length over time, with an effect size of $f > .39$, given a sample size of $n = 94$, a correlation across timepoint of $r = .7$ and an error rate of $\alpha = .05$.

Discussion

Telomere shortening is a natural process associated with aging although health conditions modulated by oxidative stress and inflammation, such as obesity, could accelerate the process. Given that age-related diseases are more prevalent in young obese patients, it is hypothesized that obesity could accelerate telomere shortening and in some way a state of premature aging [22].

On that basis, our study first sought to investigate relative TL in a cohort of obese patients awaiting bariatric surgery. At baseline, we found no associations between TL and measures of glycemic status, co-morbidities, such as MetS, T2D, or BMI. However, we did find significant differences relating to the overall severity of the obesity, whereby class III obesity patients had shorter telomeres than class II patients. This probably reflects the chronic long-term differences between these patient subtypes, and suggests that among obese patients, obesity class may be more informative than BMI when considering TL. Indeed, two previous meta-analysis reported weak-to-moderate inverse associations between BMI and TL in primarily overweight populations (BMI range = 24.5–30.4 kg/m^2) [7,23]. By contrast, our study and previous work by Formichi et al. [13], consisted of severely obese patients (BMI Range = 34.18–73.53 and 33.3–78.7 kg/m^2, respectively) and did not reveal significant relationship between BMI and TL.

Our second aim was to evaluate which factors influence TL across a 2-year period as part of our prospective cohort study of patients with severe obesity submitted to bariatric surgery, and to identify clinical and biological predictors of TL change. Different studies have reported the benefits that healthy lifestyles, such as physical activity, reduction of stress, and good nutrition could have in the elongation of telomeres [24,25]. Bariatric surgery is currently the most effective treatment for obesity that results in a substantial weight loss, reduces the risk of co-morbidities associated with excess weight, and improves quality of life [11]. Subsequently, we hypothesized that the reduction in weight (mainly adipose tissue) and consequently in oxidative stress and inflammation, would help to restore telomere length after surgery in a progressive way. However, despite the huge reduction in weight experienced by patients in our study [14], we did not find any significant change in TL two years after surgery. This finding is in accordance with previous studies on weight loss after bariatric surgery unable to identify a recovery of TL in the short-term, despite the numerous beneficial effects described after surgery [13]. This could be explained by the negative effects of some postoperative situations. For instance, the catabolic state that is generated during the first years after surgery is supposed to increase the production of reactive oxygen species that can induce toxic effects via damage of cellular structures including lipids, proteins, and nucleic acids [26]. Telomeres are highly sensitive to oxidative stress given their high content of guanines [27]. In addition, the adaptation to dietary changes, the appearance of postoperative complications, and unmet expectations may contribute to elevated rates of anxiety and depressive disorders described in these patients [28]. Unfortunately, we did not report depressive symptoms in our cohort, but previous studies suggest its association with increased telomere erosion [29,30].

Surprisingly, in our longitudinal model we observed an effect of class of obesity (class II or class III) on TL at follow-up. The subsetting of obese patients into class, as suggested by Formichi et al. [13], allowed us to explore the differential changes to TL in the postoperative period. Our results showed that across the time course, those with a less severe class of obesity showed longer TL in general. However, despite these significant differences, which were most apparent at 6 months, there were no clear differences by the end of the study at 24 months. The negative effects of oxidative stress in the first months following bariatric surgery may outweigh the positive effects of weight loss on TL. More studies are needed to corroborate our hypothesis, monitoring oxidative stress and TL during the follow-up.

According to our findings and previous reports, TL recovery is difficult to capture at short periods, possibly because the chronicity of the pathology is more important than the positive effects of weight change [13,31]. As reviewed by Epel [3], an ideal window of 3 to 6 years might be required to observe variation in TL in different clinical conditions. In this regard, in a previous study Laimer et al. [12] studied long-term effects of weight loss after bariatric surgery on TL. They found increased TL in patients submitted to bariatric surgery after 10 years in comparison to an age- and sex-matched cohort population [12]. Similar results were found by Dersham et al. [32] in patients evaluated 3 and 5 years after gastric bypass. The restoration of telomeres could be related to the decrease of psychological and metabolic stress linked to the weight loss of these patients many years after the surgery. These factors would increase the activity of telomerase contributing to telomere elongation.

The findings of this study must be taken in the light of some limitations. First, we did not measure metabolic stress parameters, such as cortisol and catecholamine levels, or other metabolic intermediate products indicators of stress, catabolism, or related to the undernourishment situation that occurs during the first year after bariatric surgery, namely plasma-free fatty acids, ketone bodies or moreover, cytokines, or reactive oxygen species. Second, the lack of information about inflammatory state of patients and telomerase activity in the sample hinders our ability to interpret which mechanisms contribute to associations. Furthermore, we can only assume that individuals are following the dietary recommendations after bariatric surgery, but it is still possible that patients were eating in an unhealthy way, just in a reduced quantity. In addition, we do not have information on physical activity, and other health-related parameters. Furthermore, our analyses may have been underpowered to detect small effect sizes, given the relatively small sample size. Finally, a longer follow-up of the sample would be necessary to understand not only short-term effects of surgery but also to evaluate the oscillating variations on TL in the long term.

Conclusion

Our study reports longer TL in class II obese patients in comparison with class III patients, despite the lack of association between BMI and TL before surgery. We also report a lack of effect of MetS or T2D on TL in morbidly obese patients. We found a lack of TL improvement at 2 years after surgery in both class II and class III obese patients. The temporary improvement of TL in class II patients at 6 months after surgery needs further studies to draw firm conclusion. Future studies should investigate whether additional environmental interventions (e.g., diets and physical exercise) can be useful in improving telomere recovery after bariatric surgery.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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E. Peña and T.R. Powell contributed equally to this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.soard.2020.06.027.

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Supervisor's report on the contribution of the PhD candidate to the article.

Dr. Araceli Rosa de la Cruz, Associate Professor at the Departament de Biologia Evolutiva, Ecologia i Ciències Ambientals of the Facultat de Biologia (Universitat de Barcelona) and supervisor of the present doctoral thesis by Elionora Peña, hereby certifies that none of the co-authors of the article "Longitudinal changes in telomere length in a cohort of obese patients submitted to bariatric surgery: a 2-year follow-up " have used this publications for a doctoral thesis, and that the participation of the PhD applicant in this article included the following tasks:

- Participation in the conception and design of the study.
- Experimental work
- Stay at the King's College London
- Statistical analyses and interpretation of data.
- Wrigint of the manuscript.
- Critical revision of the article for intellectual content.

Signed by Dr. Araceli Rosa

Barcelona, September 2020

3.5. Leukocyte telomere length in obese patients submitted to bariatric surgery: a systematic review

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Submitted to European Eating Disorders Reviews

Resum

Els pacients amb obesitat mostren nivells més elevats d'inflamació i estrès oxidatiu que han estat associats amb un envelliment prematur. La longitud telomèrica (LT) és un marcador clau de l'envelliment cel·lular i biològic. En aquest sentit, l'obesitat ha estat associada amb una LT més curta. La cirurgia bariàtrica és avui en dia el tractament més efectiu per la pèrdua de pes i per la millora de les patologies associades a l'obesitat.

L'objectiu de la present revisió sistemàtica és examinar la relació entre cirurgia bariàtrica i LT.

Per assolir aquest objectiu s'ha dut a terme una cerca bibliogràfica a tres bases de dades diferents (*MEDLINE, Web of Knowledge i SCOPUS*). Els estudis inclosos en la revisió avaluen la TL en pacients adults que s'han sotmès a una L*aparoscopic-Adjusted Gastric Banding*' (LAGB), *Roux-en-Y Gastric Bypass* (RYGB), i S*leeve Gastrectomy* (SG).

Els termes emprats per la cerca bibliogràfica en les tres bases de dades van ser 'telomer/*' i 'bariatric surgery*' i es van identificar 50 articles. Després d'eliminar els duplicats i aplicar els criteris d'exclusió 7 estudis es van incloure en la nostra revisió sistemàtica. Les nostres anàlisis van posar de manifest que tot i l'efectivitat de la cirurgia bariàtrica en la pèrdua de pes i la recuperació de l'estat de salut dels pacients, a curt termini és difícil observar recuperació telomèrica. En canvi, els estudis longitudinals amb seguiments més llargs mostren una elongació d'aquestes regions en aquests pacients.

Leukocyte telomere length in obese patients submitted to bariatric surgery: a systematic review

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ABSTRACT

BACKGROUND: Obese patients show increased levels of inflammation and oxidative stress that have been associated with premature ageing. Telomere length (TL) is a key marker of cellular and biological ageing, and patients with seem to present shorter TL. Bariatric surgery (BS) is currently the most effective treatment for weight loss and the improvement of the metabolic unhealthy conditions linked to obesity. The aim of this systematic review was to examine the relationship between BS and TL.

METHODS: A systematic search of three databases was conducted (MEDLINE, Web of Knowledge and SCOPUS). Studies included reported TL evaluated in leukocyte in adult patients who had undergone laparoscopic-adjusted gastric banding (LAGB), Roux-en-Y gastric bypass (RYGB), and sleeve gastrectomy (SG) procedures. Data were extracted to determine changes in telomere length after surgery.

RESULTS: Seven paper encompassing 19 studies based on independent samples fulfilled our inclusion criteria. Changes in TL after bariatric surgery were analysed depending on time, metabolic syndrome, weight change, dyslipidemia, diabetes, inflammation, gender and age. The analysed studies reported divergent results regarding the effect of bariatric surgery in TL.

CONCLUSION: Current evidence suggest that, despite the strong effect of BS on weight loss and improvement of comorbidities secondary to obesity, the impact of this intervention on TL only seems evident in long-term studies, with a weak and inconsistent effect on short-term follow-up.

KEYWORDS: Bariatric surgery, Leukocyte telomere length, obesity, oxidative stress, review.

INTRODUCTION

Obesity is considered as a global epidemic and a leading cause of premature death, characterized by an excessive storage of adipose tissue. Adipose tissue is an important endocrine organ that communicates with the brain and peripheral tissues, regulating appetite and metabolism [1].

Obesity is a major risk factor for many metabolic disturbances and other comorbid conditions, including osteoarthritis, type 2 diabetes (T2D), hypertension, dyslipidemia, cardiovascular disease and many cancers [2]. Furthermore, it has been suggested that obesity not only increases the onset of metabolic imbalances, but also decreases life span and influences cellular processes in a manner similar to ageing [3].

Telomeres are key markers of cellular and biological aging. Telomeres are non-coding double-stranded repetitive structures (TTAGGG) at the end of chromosomes. Their main function is to maintain the integrity of chromosomes, preserving genomic information, and in preventing inter-chromosomal fusion. Typically, human TL range from 10 to 15 kilobases. Telomeric DNA shortens upon each cell replication, at a rate of 50-200 base pair from the loss of DNA as a result of the 'end-replication problem', as well as degradation by nucleases. When TL reaches a critical length, the cell stops dividing leading to senescence or apoptotic cell death [4]. A reduction in the ability of cells to replace old and damaged cells contributes to tissue-level pathology (e.g. coronary plaque formation), risk for age-related disease, and an increased risk of mortality. Despite aging and TL shortens are natural process, different pathological conditions have been associated with an accelerated attrition of this chromosomal regions [5].

Obesity and high body mass index (BMI) have been identified as risk factors for shortened of TL [6,7]. Regarding this, oxidative stress and inflammation have been suggested as the underlying mechanisms for the association between obesity and shorter telomeres [8]. The G triplets in telomeres are particularly vulnerable to oxidative stress and inflammatory processes which promote an accelerated telomere loss [9,10]. Interestingly, TL shortening can be reversed, to an extent, by the initiation of specific environmental activities and lifestyle changes such as reduction of stress, practice exercise and having a good nutrition, among others [11,12]. Lifestyle changes may contribute to decrease the erosion of TL or to promote the activation of endogenous telomere-lengthening mechanisms, such as the telomerase enzyme [13].

Many potential therapeutic interventions have been proposed for patients with obesity (diet, physical activity, behavior modifications and pharmacological interventions). However, bariatric surgery has been described as the most effective treatment for weight loss and the improvement of comorbidities [14]. Laparoscopic-adjusted gastric banding (LAGB), Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most common bariatric procedures undertaken globally, inducing weight loss and metabolic improvement by mechanisms other than restriction and malabsorption [15]. However, there is considerable interindividual variation in post-operative outcomes and particularly in relation to weight loss, clinical benefits in terms of reductions of morbidity and mortality [16]. Furthermore, studies evaluating oxidative stress after surgery have shown a decrease in cellular oxidation and proinflammatory markers and increased levels of antioxidants [17,18].

The current literature examining TL after bariatric surgery has reported controversial results, with no clear understanding about the role of TL as a biomarker of BS outcome. With this scenario, we conducted a systematic review of the published studies, specifically focusing on studies exploring the association between TL and obesity patients submitted to bariatric surgery. Our aim is to better understand how the beneficial health effects of the bariatric surgery in obese patients can be reflected in the restoration of telomere length. As a

secondary objective, we evaluated the relationship between TL and other pre and post BS parameters.

Methods:

Protocol and registration

A review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number ID: 197711) and conceptualized in July 2020. This systematic review was designed, executed and reported using the Preferred Reporting Items for Systematic Reviews and Meta- Analysis (PRISMA) Statement [19].

Eligibility criteria

Human studies of obese patients submitted to bariatric surgery (i.e.: sleeve gastrectomy, gastric banding, gastric by-passes, biliopancreatic diversion or gastric plications) followed up at least for two years, were included. Only studies using defined techniques to measure an analyze telomeres in leukocytes were included.

Information Sources and Search strategy

A comprehensive search strategy in July 2020 identified studies indexed in PubMed Online (Ovid Technologies, New York, NY, USA), Scopus (Elsevier, Amsterdam, Netherlands) and Web of Knowledge (Thomson Scientific Technical Support, New York, NY, USA). The search was performed by two of the investigators with clinical and research experience in the topic of interest (EP and JL); both researchers reviewed titles, abstracts and articles, and disagreements were settled by consensus. The search strategy included terms for telomeres (telomeres, telomerase, and 'telomer/*' and 'bariatric surgery*' in all the three databases. Studies were appraised for inclusion or exclusion using the a priori criteria described above. Mendeley software was used to merge all the publications. Duplicates were removed.

Study selection

The publications were selected independently by EP and JL. These authors were not blinded to the study results, authors, or institutions, inter-rater reliability was high (>95%). In an initial step, titles and abstracts were screened for potentially eligible studies, which subsequently underwent full-text review. Cross referencing of selected studies was employed to complete identification of eligible studies.

Results

The comprehensive literature search identified 50 studies. After de-duplication and eligibility exclusions, 7 studies were included in the systematic review (Figure 1). All of them were prospective cohort studies. Five lacked a control group, two had a control group at baseline and one during follow-up. The characteristics of the included studies are reported in Table 1. Detailed information about patients and metabolic and anthropometrical characteristics are reported in Table 1. The studies investigated the effect of bariatric surgery on TL before and after bariatric surgery. Included studies were conducted between 2014 and 2020.

In the present review, we analyze changes on TL depending on: time, metabolic syndrome, weight change, dyslipidemia, diabetes, inflammation, gender and age.

Time:

Those studies no longer than 12 months did not find an increase in TL after the operation [20–22]. Notwithstanding, Jongbloed et al. found an increase the first 6 months with a decrease at month 12 resulting in an overall decrease throughout the first year after surgery ($P = 0.017$).

For those studies with a follow-up of 24 months, Hohensinner et al. found that TL doubled from initially ($P < 0.001$), whilst Peña et al. found an effect of class of obesity on the variability of TL. Class II patients presented longer telomeres at 6 months after surgery compared to class III ($P = 0.024$), however, this difference was not apparent at 2 years of follow-up ($P = 0.7$) [23].

After a follow-up of 3-5 years Dersham et al. found that in the overall group, the median TL from baseline to follow-up increased without being significant (P = 0.167). However, when they split the sample by baseline TL, a significant lengthening was observed for those with the shortest baseline TL (P = 0.0011), but not for those with intermediate baseline TL (P = 0.411) or longest baseline TL (P = 0.207) [20]. Finally, Laimer et al., with a follow-up of ten years, found that TL increased in bariatric patients after surgery (P = 0.047) [24].

Metabolic syndrome (MetS):

Jongbloed et al. found that at baseline TL was significantly shorter in the MetS group compared with the no MetS group (P = 0.02) in patients < 50 years, whilst in patients with > 50 years, no significant differences were observed. Throughout the follow-up in patients with MetS there was a steady increase in TL within the first 6 months, whilst in the no MetS group there was a decrease between 3 and 6 months [22]. Formichi et al. and Peña et al. did not find differences in TL depending on the presence of MetS (P = 0.194; P = 0.3387 respectively) [21,23].

Weight change:

At baseline Formichi et al. found that TL was significantly shorter in obese patients compared to normal-weight subjects (P < 0.001). Whilst, Dersham et al. and Peña et al. did not find a significant correlation between BMI and TL at baseline. However, Peña et al. found that TL was significantly shorter (P = 0.0271) in patients with obesity class III compared to obesity class II patients at baseline.

Throughout the follow-up, the analysis revealed that three studies found a positive relationship between weight loss and TL (Hohensinner, Jongbloed, Morton). However, Morton et al. only found this relationship in patients who had an adverse cardiometabolic state before surgery.

The other studies observed that there was not any significant correlation between the percent change in TL and the percent change in BMI [20,21,23,24]. Notwithstanding, Peña et al. found that there was an effect of the class of obesity on the variability of TL over time (P = 0.0080). Class II patients presented 52.2% longer telomeres at 6 months compared to class III (P = 0.024). Albeit, this difference was not apparent at 2 years (P = 0.7) [23].

Dyslipidemia:

The relationship between hypercholesterolemia and TL was trailed in four studies [20,21,24,25]. Two of them did not find any relationship between TL and hypercholesterolemia [20,21]. Laimer et al. found that baseline TL was negatively associated with baseline cholesterol (r = -0.194; P = 0.043).

Taking into consideration LDL, Dersham et al. did not find any association between LDL and TL, whilst, Morton et al. observed that patients with a preoperative LDL-C level higher than 140 mg/dl had significant telomere lengthening compared with patients with low LDL-C levels preoperatively (P = 0.04). About HDL, Dersham et al. did not find any correlation between HDL and TL, however, Laimer et al. and Morton et al. found that the increase in TL was positively correlated with HDL (r = 0.256, P = 0.006; r = 0.842, P = 0.02 respectively). Finally, about triglycerides (TG) Dersham et al. found that TG were positively correlated with baseline TL (P = 0.41; P = 0.033) and negatively correlated with change in TL after surgery (r = -0.32; P = 0.026), whilst, Laimer et al. found a negative correlation at baseline between TL and TG (r = -0.277; P =0.005).

Diabetes:

Most of the studies did not find a significant correlation between TL and glycaemia, insulin, HbA1c or insulin resistance at baseline or after surgery (Formichi, Peña, Dersham). However, Laimer et al. found that the increase in TL was negatively correlated with baseline glucose concentration (r = -0.277; P = 0.005).

Inflammation:

Most of the studies did not include markers of oxidative stress or inflammation, so they could not evaluate the relationship with TL [20–24]. Hohensinner et al. found that 2 years after surgery

TL increased significantly whilst there was a drop of telomere oxidation (r = -0.458; P < 0.001). The main markers studied were C-reactive protein (CRP), interleukin-6 (IL-6) and the protease inhibitor plasminogen activator inhibitor-1 (PAI-1) who decreased significantly throughout the follow-up (P <0.001, P <0.001 and, P = 0.007 respectively) [26]. Weight difference did not correlate with IL6 and CRP after surgery, but correlated slightly with PAI (r = 0.261; P = 0.047). Finally, Morton et al. found that patients with a preoperative CRP level higher than 7mg/dl had significant telomere lengthening compared with patients with low CRP levels preoperatively (P = 0.005) [25].

Gender:

Laimer et al. is the only study who analyze the role of gender in TL. They found that after a follow-up of 10 years with pronounced and sustained weight loss TL increased significantly in female bariatric patients (0.023 +/- 0.14; P = 0.044; n = 121) but not in male bariatric patients (0.025 +-0.13; P = 0.454; n = 21). Baseline TL did not differ significantly between female and male bariatric patients (P = 0.0415). However, in the control group TL differed at baseline significantly between sex categories with women having longer TL compared with men (P = 0.016). In the control group during the follow-up TL shortened in female (-0.049 +-0.19; P = 0.004 n = 93) and male participants (-0.101+-0.13; P = 0.019, n = 17) [24].

Age:

At baseline Dersham et al. described a positive correlation between age and TL (r = 0.32; P = 0.022), however, after surgery there was a negative correlation (r = -0.31; P = 0.027) [20]. Formichi et al. and Laimer et al. found that in the control group TL decreased with ageing (P = 0.0003; P =0.039 respectively), albeit, in the bariatric patients' group Formichi did not find this association (P = 0.642), whilst Lamier et al. found a proportional association between age and TL (P = 0.049). Finally, Jongbloed et al. and Peña et al. did not find any correlation between age and TL [21,24].

DISCUSSION

To our knowledge, this is the first comprehensive systematic review to deeply analyse the change in TL in obese patients after bariatric surgery.

Several studies have studied the relationship between the size of telomeres and obesity versus different types of weight loss' treatments such as dietary or physical activity [27,28]. Most of the studies report a significant effect of caloric restriction and significant weight loss in TL [29,30]. Indeed, these changes seem to be seen in short and long term [28,31]. Additionally, these changes in TL were inversely associated with changes in anthropometric parameters [31]. In fact, there are some studies that reported an association between consumption of specific foods and TL [32,33]. For example, Leung et al.[33] suggested that a diet rich in fruits, vegetables, whole grains, dairy, vegetable proteins, and low in red and processes meats, sodium and sugar is related to higher TL. However, the different authors who analysed the effect of bariatric surgery in TL show several divergent results.

Time:

When we analyse the effect on TL depending on time, we observed that those studies with a short follow-up, no longer than 12 months [21,22,25], did not find an increase in TL after bariatric surgery whereas those studies with a longer follow-up did find a change in TL after bariatric surgery [20,23,24,26]. The lack of improvement of TL after surgery-induced weight loss is consistent with previous reports evaluating the effect of dietary on weight loss on TL [31,34]. That results could be explain for several reasons.

On one hand, the short follow-up window may negatively influence TL because in such a short period, several parameters known to influence TL are not stabilized yet, particularly weight loss and the catabolic state after surgery. The catabolic state that is generated during the firsts years after surgery is supposed to increase the production of reactive oxygen species that can induce toxic effects via damage structures including lipids, proteins and nucleic acids [35]. Indeed, in a review by Epel et al, an ideal window of 2-6 years to observe telomere

lengthening is outlined in order to overcome oscillating variations in TL [13].

On the other hand, other factors may affect TL independently from follow-up. TL is a complex trait that is modulated by a combination of genetic, epigenetic and environmental determinants, such as psychological stress, low physical activity levels, smoking and socioeconomic status; however, the range of factors that influence telomere dynamics is not fully established [36]. Whilst in those studies with a longer follow-up the lengthening in TL may derive from the greater variation in metabolic disturbances and the decrease in the inflammation and oxidative stress. This amelioration may compensate the influence of both, age and baseline TL in telomere attrition [24].

Metabolic syndrome (MetS):

It seems reasonable that the presence of MetS could have a role in TL attrition. Many recent studies have associated shorter telomeres with several metabolic disorders, such as type 2 diabetes (T2D) and hypercholesterolemia [37,38] or even with active smoking [39,40].

In our revision we find that Formichi et al. and Peña et al. did not find any difference in TL depending on MetS. The lack of this association might be due to the selection of patient with severe obesity (BMI>35) in both studies. It is possible that in this category of severe obesity, even in the absence of MetS, the inflammatory status is enough to influence in TL. Jongbloed et al. found that at baseline those patients under 50 years with MetS had significantly shorter TL compared with those patients without MetS, these differences disappeared in those patients >50. It might be because under 50, the age had a lower role on TL. Finally, Morton et al showed that weight loss was associated with lengthening of TL in patients who has adverse cardiometabolic state before surgery. It suggests that the greatest potential benefit for lengthening TL is in patients with the most comorbidity before surgery.

We consider that the effect of metabolic traits related to obesity may be possible determining factor for telomere elongation in patients undergoing bariatric surgery, which has been already shown in studies performed by Huzen et al [39] and Zhao et al [40]. Thus, the missing correlation between baseline TL and its elongation may arise from the variation in metabolic traits at follow-up, which are present by some but not all bariatric patients.

Weight change:

When we analyse the role of weight change and BMI on TL, we observe that the results of the different studies are not fair-minded.

In our review we show that at baseline Formichi et al. found an inverse relationship between TL and BMI, whilst Peña et al found that TL was significantly shorter in patients with obesity class III compare to class II. Throughout the follow-up three studies found a direct relationship between TL and weight loss (Hohensinner, Jongbloed, Morton), whilst the other studies (Dersham, Formichi, Lamier, Peña) did not find this relationship.

In literature, there are several large studies that have shown that shorter telomeres are associated with obesity [41,42] and with several anthropometric measures of obesity such as BMI and waist and hip circumferences [8,42]. What is more, some authors suggest an additional 8.8 years of ageing in obese patients compare with lean subjects [8]. Furthermore, an inverse correlation of TL and BMI has already been described [39,43,44].

In contrast, other studies of comparable size found no association between TL and BMI, adiposity measures or adipokine levels [45]. Also, only a few studies have shown the recovery of TL in obese adults who has lost weight through caloric restriction [28].

If we focus on the weight lost after bariatric surgery, weight loss has been shown to significantly diminish metabolic traits and to increase telomere length, although with a considerable delay of 5 post-operative years [28]. Nevertheless, the impact of body weight on telomere attrition is not

clarified. Muezzinler et al. conclude that on the one hand increased body weight most likely promote telomere attrition, but on the other hand the heterogeneity of and the small number in relevant studies limit the understanding of adiposity in telomere dynamics [46].

In addition, actual weight loss itself seems less important than the metabolic amelioration after bariatric surgery. Albeit, in the long-term, bariatric patients benefit from weight loss facilitating TL protective mechanisms, which are then able to maintain or even restore TL [24].

Thus, substantial weight loss promotes improvement of chronic inflammation and adipose tissue oxidative stress and can lead to shorter telomeric attrition, promoting TL conservation and DNA repair. It being most important the role of weight loss on TL in those patients with a lower metabolic burden.

In our opinion, the reason of these different results may be because of the role or confusion factors such as the improvement of metabolic traits after surgery, the decrease in the inflammation rate, the heterogeneity of the studies, the small number of patients, the different surgical techniques and the lack of a control group. However, despite the recruitment of a sufficient control cohort is desperately needed in prospective studies investigating the effect of bariatric surgery, withholding surgery from patients with a medical indication for bariatric intervention for years goes against the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Dyslipidaemia and Diabetes:

As we have already mention before there are several studies that have reported a relationship between TL attrition and hypercholesterolemia and T2D [37,38]. However, mean differences in HDL-C, LDL or fasting plasma glucose did not correlate to changes in TL in most of the studies that we analysed. This may be caused by the relatively small sample size of bariatric patients and as some metabolic parameters changed in both directions, a small size may reduce statistical power and distort correlation between changes in TL and metabolic parameters.

Inflammation:

In this review, we have previously analysed that the main mechanism explaining the telomere dysfunction by chronic inflammation seems to be oxidative stress and the inflammatory processes that accompany this disease. Now, we would like to focus on the different parameters of inflammation that may have a role in the attrition of TL.

In literature, is widely known that there is a relationship between obesity and inflammation [47]. Indeed, adipose tissue is an extensive source of proinflammatory cytokines and growth factors [48]. This proinflammatory state appears to be associated with adipocyte hyperplasia and hypertrophy, which may be correlated with adipose tissue hypoxia [49]. These characteristics contribute to a chronic low-grade inflammatory state and, consequently, to the appearance of metabolic imbalances beyond the acceleration of ageing and the propensity for age-related diseases [50]. In addition, adipose tissue from obese individuals contain higher number of senescent cells compared to lean age-matched controls. These cells are characterized by the production of senescent-associated secretory proteins (SASP) such as, interleukin 6 (Il-6), tumour necrosis factor-α (TNF-α), several matrixmetalloproteases (MMPs), and the protease plasminogen activator inhibitor-1 (PAI-1), which taken together support the inflammatory state of ageing [26]. Furthermore, adipose tissue may promote inflammation through directly secreting leptin [51].

In our review, only two studies analyse the role of the different parameters of inflammation in TL after bariatric surgery (Hohensiner, Morton et al.). Hohensinner et al. shows that dramatic weight loss in morbidly obese patients two years after bariatric surgery is accompanied by a reduction of the SASP IL-6 and PA1-1, and the inflammatory marker and acute phase reactant (PCR) confirming previous data. Furthermore, this weight loss is directly

associated with the increase in TL. Hohensinner et al. also shows that PAI-1 reduction correlated with weight loss, which may be a considerable factor for the decrease in PAI-1 plasma levels, ad adipose tissue is considered to be the main source of increased PAI-1 in obese individuals [26]. It would be tempting to speculate that at least part of this reduction in PAI-1 originates from the loss of aged cells in the adipose tissue. That hypothesis would be supported by the notion that adipose tissue is a site of considerable senescent cell accumulation [26], which would vanish after bariatric surgery.

Gender:

Regarding gender, women outlive men in every age group in nearly every population. This sexual inequality in lifespan is mirrored in the telomers. At birth, there are no sex differences in TL, but thereafter, males tend to have shorter telomeres than females, indicating that males' telomeres shorten faster [52]. Concerning bariatric surgery, it is well known that men and women differ in terms of fat storage and metabolism [53] and studies indicate that BS may be more effective in men than women [54,55]. Despite the evidences suggesting differences between sex, only one of the reviewed studies explores the role of gender in TL changes after BS [24]. Laimer and colleagues reported differences between sex, whereby women had longer TL than men in the control group. This difference was not replicated in the group of patients with obesity. However, 10 years after surgery, a significant increase in TL was found in women but not in males.

Age:

In our review, Formichi et al. and Laimer et al. found an inverse relationship between age and TL in the control group. However, in the bariatric patients group the results are not equally between the studies that we analyse at baseline or after surgery.

TL is a proposed marker of biological ageing, and several cross-sectional and epidemiological studies support this hypothesis [24]. Indeed, most of the studies illustrated an inverse relationship between age and TL. However, we can also find some articles as the study from Garcia-Calzon et al, that found that TL was independent of age, notwithstanding, the study was performed with a follow-up of 6 months, whereas age-related change in TL was not expected.

One possible explanation for the divergent results between age and TL in bariatric patients may be the amelioration of metabolic traits induced by weight loss with the reduction of the inflammation burden and oxidative stress that may overrule the effect of ageing on TL.

Limitations:

This review has several limitations. The major weaknesses for this review is the small amount of studies that we have analysed. Probably, the lack of the studies is because the interest in TL in obese patients undergoing bariatric surgery has emerged in the last years. Also, most of the studies include a relatively small sample size and the heterogeneity among the studies difficulties the opportunity of doing statistical analysis. Another important issue is the lack of a control group in most of the studies that would have helped to know if the results are explained by regression to the mean. Regression to the mean can frequently be observed when measurements are performed in the same subject repeatedly. Relatively high and low observations are likely to be followed by less extreme measurements, which is caused by a non-systematic variation in observed values, deriving from, for example, random measurement error or fluctuations in a subject [24].

Finally, in the studies, the demographic distribution of those undergoing bariatric surgery should be viewed through a greater social context. Social contexts surrounding bariatric surgery eligibility and TL are unequally distributed along socioeconomic and racial/ethnic minority lines. One study from the National Health and Nutrition Examination Survey found that the total bariatric surgery-eligible population demonstrated significantly skewed racial/ethnic and socioeconomic distributions, with a greater percentage of non-white race, lower educational level, and low incomes [56]. A 2012 study based in

Canada concluded that notable differences in sociodemographic profiles and comorbidities are present amongst individuals that are eligible for compared with those actually receiving bariatric surgery. Likewise, another study found that TL was sensitive to the addition of socioeconomic, psychological, coping and biobehavioural variables. Furthermore, previous studies suggest that there is an association between depressive symptoms and telomere erosion, notwithstanding, in the studies that we have analysed there is any report of the depression symptoms. Also, it has been shown that dietary restraint, especially in combination with a strong tendency to overeat, is related to perceived stress and to shorter TL, independent of BMI. Additionally, the adaptation to dietary changes, the appearance of post-operative complications and unmet expectations may contribute to erase elevated rates of anxiety and depressive disorders in these patients [23]. Thus, a properly report of the psychological state of patients should be reported.

Conclusions:

The different articles that we have analysed provide a solid information that after bariatric surgery there is an attrition in TL due to the catabolic situation and the enhance of oxidative stress that seems to drop gradually because of the amelioration of metabolic traits, which is associated with weight loss. Thus, producing an amelioration of TL at long-term and may compensate age and baseline TL on telomere attrition. Because of numerous confounding factors, future prospective intervention studies with both, a considerable sample size and follow-up period are required to identify the main contributors to changes in TL after bariatric surgery. In addition, demographic differences of the population and phycological state should be reported.

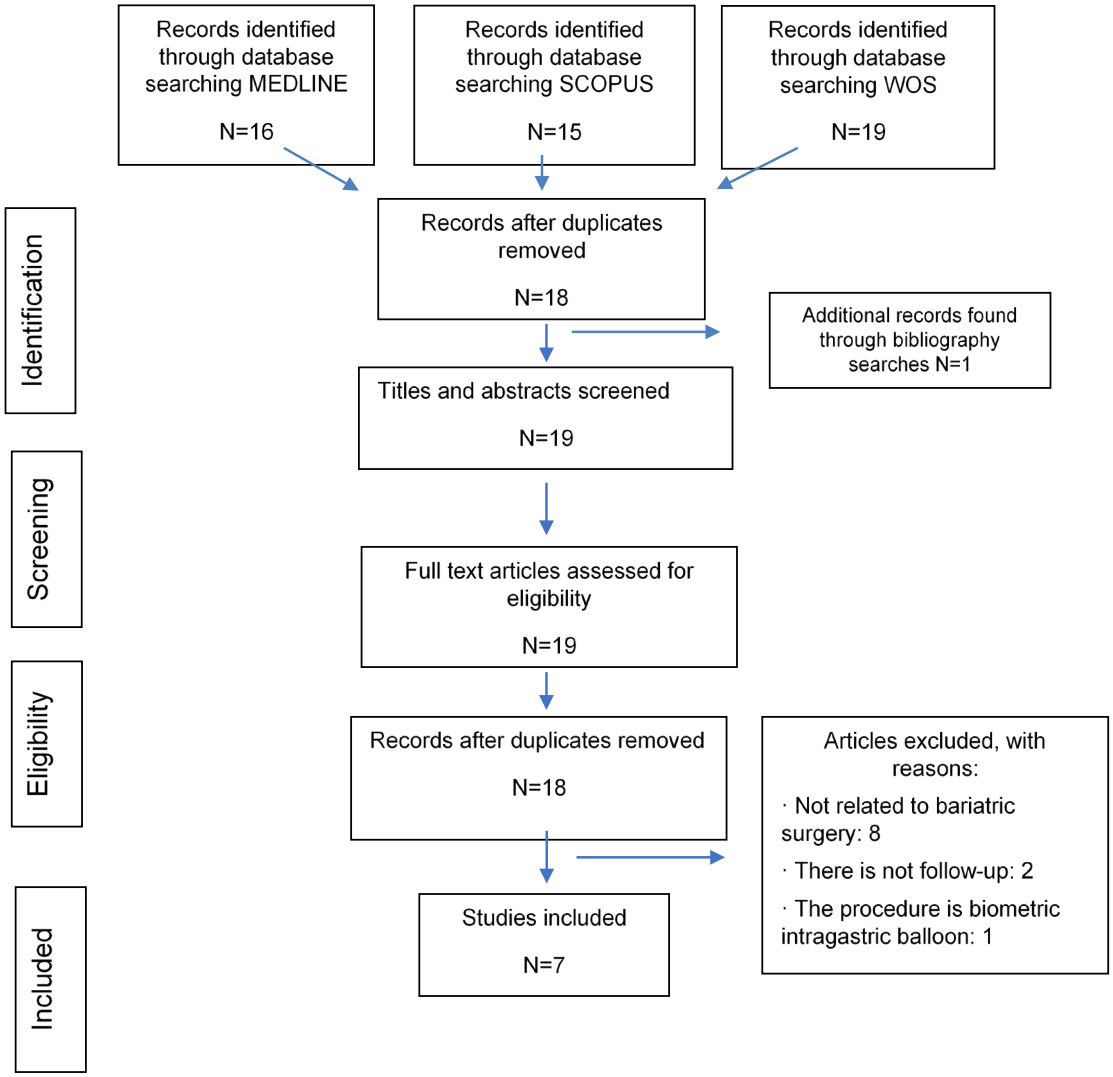

Figure 1. PRISMA diagram illustrating the selection process for included studies

Table 1. Characteristics of the included studies and patients with obesity in pre-operative time.

Authors	n	Surgery	Follow-up (years)	Mean age (SD)	Gender (female)	Mean BMI (SD)	Mean weight (SD)	Mean glucose (SD)	Mean HbA1c (SD)	Mean TC (SD)	Mean TG (SD)	Mean HDL (SD)	Mean LDL (SD)	TL Change after BS
Formichi et al. 2014	93	39 SG 25 RYGB 29 others	1	45.8 (8.8)	79	47.9 (8.6)	NA	125.2 (54.5)	NA	NA	189.9 (113)	42.7 (10.6)	NA	↓
Laimer et al. 2016	142	128 GB 14 RYGB	10	51.99 (10.74)	88	41.35 (6.73)	117.07 (21.54)	102.65 (23.80)	NA	196.36 (40.24)	143.79 (95.99)	52.99 (13.47)	114.36 (30.50)	↑
Dersham et al. 2017	50	RYGB	3-5	46.8 (10.3)	82	50.3 (11.2)	138.2 (35.9)	93.9 (22.0)	6.1 (1.1)	185.9 (32.7)	145.2 (60.9)	48.4 (10.9)	108.5 (28.4)	↑
Jongbloed et al. 2018	107	RYGB	1	39.55 (NA)	77	43.38 (NA)	127.85 (NA)	NA	NA	NA	NA	NA	NA	↓
Hohensinner et al. 2018	58	RYGB	2	41.9 (11.2)	70	43.98(3.55)	127.36 (17.19)	NA	NA	178.57 (37.61)	156.71 (144.38)	NA	NA	↑
Morton et al. 2018	51	RYGB	1	48.6 (NA)	76	NA	NA	NA	NA	NA	NA	45.3 (NA)	96.8 (NA)	=
Peña et al. 2020	94	56 RYGB 38 SG	2	46.92 (9.89)	71	43.16 (7.20)	NA	104.95 (30.70)	6.12 (1.04)	NA	NA	NA	NA	=

Sleeve Gastrectomy (SG), Gastric Banding (GB), RYGB: Roux-en Y gastric bypass, Others: biliopancreatic diversion and gastric applications, BMI: Body mass index, HbA1c: Glycosylated Hemoglobin A1c, TC: Total cholesterol, TG: Triglycerides, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, NA: Not available.

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Supervisor's report on the contribution of the PhD candidate to the article.

Dr. Araceli Rosa de la Cruz, Associate Professor at the Departament de Biologia Evolutiva, Ecologia i Ciències Ambientals of the Facultat de Biologia (Universitat de Barcelona) and supervisor of the present doctoral thesis by Elionora Peña, hereby certifies that none of the co-authors of the article "Leukocyte telomere length in obese patients submitted to bariatric surgery: a systematic review" have used this publications for a doctoral thesis, and that the participation of the PhD applicant in this article included the following tasks:

- Participation in the conception and design of the study.
- Identification and selection of the papers.
- Writing of the manuscript.
- Critical revision of the article for intellectual content.

Signed by Dr. Araceli Rosa

Barcelona, September 2020

3.6. Depresión y envejecimiento prematuro: implicación de los telómeros

Elionora Peña. E., Marta de Castro-Catala, Margarita Rivera, Blanca Gutiérrez., Sara Crivillés, Narcís Cardoner, Araceli Rosa

La antopologia física en la era de la genómica

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Resum

L'envelliment humà és un procés evolutiu gradual i multidimensional. Un dels marcadors biològics de l'envelliment analitzats clàssicament ha estat la longitud telomèrica (LT). Els telòmers són complexes nucleics situats als extrems dels cromosomes i la seva funció és protegir-los contribuint així a la estabilitat genòmica. El seu escurçament és un procés natural, no patològic, tot i que clàssicament ha estat relacionat amb el càncer i més recentment amb patologies mentals.

Les persones que pateixen depressió major (DM) presenten una reducció de la seva qualitat de vida i funcionalitat, en molts casos associada a l'aparició de patologies somàtiques que acaben disminuint la seva esperança de vida, així com un escurçament telomèrica. No obstant, la direccionalitat d'aquest fenomen és molt discutida.

L'objectiu del nostre estudi va ser revisar la literatura sobre DM i LT, així com dels possibles mecanismes associats en aquest relació. Es va realitzar una revisió sistemàtica de la literatura en les bases de dades PubMed/Medline i 13 estudis complien els criteris establerts. Els estudis revisats semblaven posar de manifest una associació dosi-efecte entre la DM i la LT disminuïda. De manera que, com major era la durada dels símptomes i la seva severitat, major era l'erosió dels telòmers i major era el seu escurçament. Els mecanismes subjacents a aquesta associació semblen ser l'estrès i els processos inflamatoris als que es troben exposats aquests pacients.

Els resultats semblen mostrar que l'escurçament telomèrica descrit en trastorns mentals, com la DM, podria ajudar-nos també a explicar tant les elevades co-morbiditats com l'envelliment prematur observat en aquest pacients.

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DEPRESIÓN Y ENVEJECIMIENTO PREMATURO: IMPLICACIÓN DE LOS TELÓMEROS

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RESUMEN

El envejecimiento humano es un proceso evolutivo gradual y multidimensional. Uno de los marcadores biológicos de envejecimiento analizados clásicamente ha sido la longitud telomérica (LT). Los telómeros son complejos nucleicos situados en los extremos de los cromosomas cuya función es protegerlos contribuyendo a la estabilidad genómica. Su acortamiento es un proceso natural, no patológico, aunque clásicamente ha sido relacionado con cáncer y más recientemente con enfermedades mentales.

Las personas que padecen depresión mayor (DM) presentan una reducción de su calidad de vida y funcionalidad, en muchos casos asociada a la aparición de patologías somáticas que acaban disminuyendo su esperanza de vida, así como acortamiento telomérico. No obstante, la direccionalidad de este fenómeno es discutida.

El objetivo de nuestro estudio fue revisar la literatura sobre DM y LT, así como los posibles mecanismos asociados en esta relación.

Se realizó una revisión sistemática de la literatura en las bases de datos electrónicas PubMed/Medline y 13 estudios cumplieron los criterios establecidos.

Los 13 estudios revisados parecían poner de manifiesto una asociación dosis-efecto entre DM y LT disminuida. De esta manera, cuanto mayor era la duración de los síntomas y su severidad, mayor era la erosión telomérica, y mayor su acortamiento. Los mecanismos subyacentes a esta asociación parecen ser el estrés y los factores inflamatorios a los que están expuestos estos pacientes.

Estos resultados parecen mostrar que el acortamiento telomérico descrito en trastornos mentales, como la DM, podría ayudarnos también a explicar tanto las elevadas co-morbilidades como el envejecimiento prematuro observado en estos pacientes.

Palabras clave: telómeros, depresión, envejecimiento prematuro, estrés, inflamación

ABSTRACT

Human aging is an evolutive and multidimensional process. Telomere length (TL) has classically been the biomarkers for aging. Telomeres are DNA-protein complexes that cap the chromosomes and are involved in their genomic stability. However, this length will be reduced as a normal and non-pathological biological aging process, although they have been related to cancer and more recently to mental illness.

Individuals with major mental disorders, such as major depression (MD) have shorter life expectancy and higher rates of chronic medical conditions such as cardiovascular disease, metabolic disorders, cognitive decline, obesity and chronic pain conditions. For this reason, most of these patients have a "decreased" functionality and quality of life, compared to the rest of people. Thus, it has been speculated that MD is associated with accelerated aging-related biological and functional decline. One of the biomarkers used to examine the accelerated aging hypothesis is leukocyte telomeres length and telomerase activity.

This review aims to integrate findings from studies analyzing these biomarkers and to discuss its interest in the etiology and prognostic of depression.

A systematic revision of the literature in PubMed/Medline was made and 13 studies comply the established criteria.

The reviewed studies suggest a relation between major depression and a shortening of the telomeric regions. This seems to point toward telomere length as a predictor of physical health and processes associated with aging. Leukocyte telomeres are relatively short in psychiatric disorders such as depression; this result may help to understand the excess of medical morbidity associated with the disease.

Key words: telomeres, depression, accelerated aging, stress, inflammation.

INTRODUCCIÓN

La vulnerabilidad del ser humano para la enfermedad mental debe ser contemplada desde su condición biológicamente mediada (genes) y en el contexto del medio social con el que interactúa. La vulnerabilidad para sufrir un trastorno mental se sustentaría en la propia complejidad de la naturaleza humana, vinculada a la complejidad de su cerebro, y sería fruto de un proceso evolutivo que ha dado lugar a una especie con un cerebro esencialmente preparado para la relación compleja con la realidad (Fañanás, 2003).

En este sentido, una de las patologías con mayor afectación en la población mundial es la depresión mayor (DM), así como uno de los trastornos con mayor carga de enfermedad. Este trastorno presenta una prevalencia alrededor del 15%, afectando a uno de cada seis adultos a lo largo de su vida (Josine E Verhoeven *et al.,* 2014). Asimismo, constituye una condición multifactorial y poligénica, donde una combinación de factores genéticos de riesgo interactúan entre sí y con factores ambientales, predisponiendo al individuo al desarrollo del trastorno (Lopizzo *et al.*, 2015).

Los estudios epidemiológicos han puesto de manifiesto la existencia de diversos factores ambientales de riesgo implicados en la etiología de la depresión, como los acontecimientos vitales estresantes, la desventaja social, el abuso físico o emocional en la infancia y el consumo de drogas. Muchos de estos factores de riesgo se relacionan con situaciones de estrés que pueden impactar en el desarrollo cerebral, dando lugar a cambios estructurales y funcionales que pueden mantenerse a lo largo de la vida del individuo (Otte *et al.,* 2016).

A pesar del gran avance farmacológico, alrededor de un 40% de los pacientes con DM no responden al tratamiento o lo hacen con una remisión parcial de los síntomas (Rush *et al.,* 2008), lo

cual supone una reducción significativa de su calidad de vida y funcionalidad. Este hecho, no es causado solo por la propia sintomatología de la depresión, sino también por una disminución de su salud somática, que viene dada por una mayor presencia de enfermedades crónicas como la diabetes tipo 2, enfermedades cardiovasculares, obesidad, demencia y cáncer en estos pacientes. Esta elevada comorbilidad explicaría, en parte, la pérdida de esperanza de vida de estos pacientes respecto a la población general (Verhoeven *et al.,* 2014). Por esta razón, se especula que la depresión estaría relacionada con un mayor envejecimiento prematuro o acelerado, que se podría relacionar con la aparición de estas patologías somáticas.

El envejecimiento humano puede ser considerado como un proceso evolutivo dinámico y multidimensional que conduce a una adaptación continua del cuerpo a los cambios y al deterioro que ocurre a lo largo de la vida y que por tanto es un proceso biológico normal que va asociado al propio fenómeno de la vida. Uno de los biomarcadores clásicamente utilizados para explorar el envejecimiento es el estudio de los telómeros, y más específicamente su longitud. Adicionalmente, dada la pérdida de esperanza de vida de los pacientes con DM, el estudio de los telómeros también constituye una nueva aproximación que puede ayudarnos a entender las correlaciones descritas entre factores genéticos y ambientales de riesgo y su relación con la salud física y mental de los pacientes (Zhang *et al.,* 2015).

Los telómeros están situados en los extremos de los cromosomas de las células y están constituidos por ADN no codificante formado por un elevado número de repeticiones de 6 nucleótidos (TTAGGG) (Fig 1). La función de estas regiones es proteger los extremos de los cromosomas, evitando así la erosión asociada a cada replicación de las células y en última instancia contribuyendo a la estabilidad genómica. En el momento del nacimiento, nuestros telómeros presentan una longitud que oscila entre las 10-15 kilobases (kb: unidad de medida de un fragmento de ADN que contiene 1000 nucleótidos). Sin embargo, el acortamiento de estas regiones es un proceso biológico que ocurre de manera natural con la edad. En este sentido, en cada división celular se pierden aproximadamente entre 40-200 nucleótidos, de manera que a medida que se replican las células, el tamaño de los telómeros va disminuyendo (Notaro *et al.,* 1997). Durante los primeros años de vida hay una rápida pérdida de repeticiones teloméricas, que va reduciéndose, siendo de hasta 20-60 nucleótidos por año en la vida adulta (Frenck *et al.,* 1998). El correcto mantenimiento de los telómeros es crucial para que éstos no alcancen una longitud crítica que los lleve a ser disfuncionales. Este mantenimiento requiere de una enzima, la telomerasa, que añade ADN telomérico, preservando tanto la longitud como la función celular de estas regiones (Blackburn 2001). No obstante, algunos factores como la exposición crónica a estrés oxidativo, moléculas inflamatorias u hormonas relacionadas con el estrés (p.ej. el cortisol o las catecolaminas) – clásicamente asociados con algunas condiciones psiquiátricas graves como la DM – podrían acelerar el acortamiento de las regiones teloméricas. Cuando los telómeros llegan a longitudes críticas, la célula deja de dividirse o pasa a ser altamente inestable, siendo muy probables los reordenamientos cromosómicos, es decir, cambios en la estructura normal de los cromosomas individuales (Von Zglinicki, 2002) (Figura 1).

El interés de estos marcadores en el campo de la depresión vendría dado no solo por la asociación entre DM y envejecimiento acelerado, sino también por el estudio de aquellos mecanismos biológicos que conectarían ambos fenómenos. En este sentido, el mayor estado oxidativo e inflamatorio descrito en los pacientes podría contribuir a una mayor erosión de los telómeros en depresión, del mismo modo que se cree que lo haría en ciertas enfermedades médicas (Zhang *et al.,* 2016; Wolkowitz *et al.,* 2011). A pesar del interés que despiertan estos marcadores por su importancia sobre el estado celular, el estudio de la dinámica telomérica en las enfermedades mentales es un campo relativamente nuevo, aunque con una gran potencialidad dado que integra la importancia del estrés en la etiología de la depresión, explica la marcada morbi-mortalidad en esta patología, así como la calidad de vida de los pacientes.

En la literatura de los últimos años han aparecido numerosos estudios que, aunque parecen poner de manifiesto la asociación entre depresión y este biomarcador, presentan unos resultados

muy heterogéneos. El objetivo de la presente revisión es recopilar los estudios publicados hasta el momento que han evaluado la asociación entre depresión y longitud telomérica leucocitaria y discutir tanto su relevancia etiológica y pronóstica, así como las diversas limitaciones inherentes a ellos.

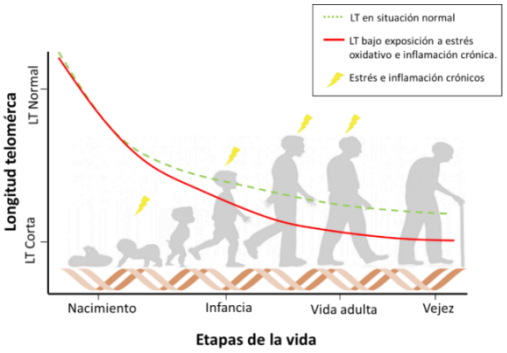

Figura 1. Variación de la longitud telomérica (LT) a lo largo de la vida. Evolución de la LT a lo largo de las diferentes etapas de la vida en situación normal (línea discontinua verde) y evolución de la LT bajo la exposición a estrés e inflamación (línea continua roja).

MATERIAL Y MÉTODOS

Siguiendo la metodología propuesta por la declaración PRISMA (Liberati *et al.,* 2009) se llevó a cabo una búsqueda general en las bases de datos electrónicas PubMed/Medlinede artículos cuyos títulos contuvieran los términos telomer* y depres*. Como resultado de esta búsqueda, se obtuvieron 35 artículos, a partir de los cuales se realizó una criba seleccionando los artículos escritos en inglés que cumplieran los siguientes criterios: i) trabajos de investigación llevados a cabo en humanos; ii) que incluyeran pacientes que cumplieran criterios de trastorno depresivo mayor o episodio depresivo mayor, iii) que informaran de forma clara de las características de la muestra, las variables e instrumentos utilizados, así como el método experimental utilizado para llevar a cabo la medida de la longitud telomérica leucocitaria. La búsqueda se completó utilizando referencias de publicaciones previas de interés y artículos de revisión. La Fig. 2 representa el proceso de selección de la literatura. Finalmente, delimitando los criterios comentados, se identificaron 13 estudios que se han incluido en el presente trabajo y que se resumen por orden cronológico.

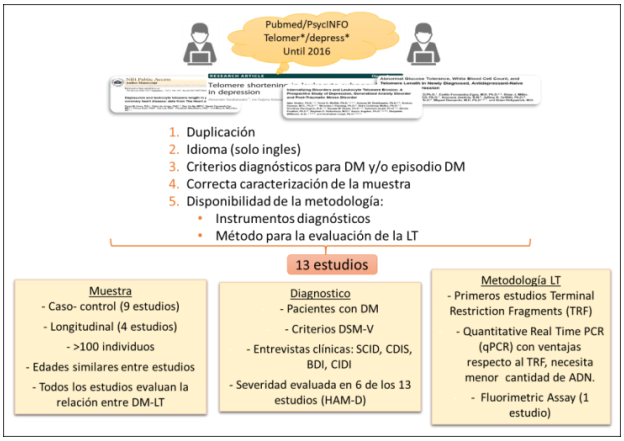

Figura 2. Diagrama de flujo. Representación gráfica del proceso llevado a cabo por los investigadores para la obtención de los artículos seleccionados en el presente estudio.

RESULTADOS

En la Tabla 1 se numeran y detallan los 13 estudios revisados señalándose el tipo de diseño (principalmente caso-control o longitudinal), los tamaños muestrales de los casos y controles incluidos, el tipo de pacientes, instrumento diagnóstico utilizado, la edad media de los participantes, la metodología utilizada para la medida de la longitud telomérica (LT), así como las longitudes reportadas en pacientes y controles y el resultado global del estudio.

Diez de los trece estudios eran de tipo caso-control. Por lo que respecta al tamaño muestral, en la mayoría de trabajos se analizan muestras con un tamaño superior a cien sujetos (n=1095 en el caso de Verhoeven *et al.* 2014), excepto en los estudios 1, 3, 5 7 y 8, donde se incluye un número muy bajo de sujetos tanto para casos como para controles. Dada la correlación positiva descrita entre edad de los participantes y la LT, la mayoría de estudios incluyen pacientes y controles con edades similares. Los rangos de edades de las muestras son similares en los diferentes estudios, a excepción del realizado por Schaakxs y colaboradores en 2014 donde la muestra está formada por población anciana (Schaakxs *et al.,* 2014).

En todos los estudios el diagnóstico de depresión se basó en criterios DSM-IV o versiones anteriores (Shalev *et al.,* 2014). Adicionalmente, la mayoría de estudios emplearon entrevistas como el SCID (*Stuctured Clinical Interview for DSM Disorders*), el CDIS (*Computerized Diagnostic Interview Schedule*), el BDI (*Beck Depression inventory*) o el CIDI (*Composite Internacional Diagnostic Interview 2.1*). El estudio de Simon y colaboradores (2006) incluye, además a los pacientes con depresión, una muestra de 29 pacientes diagnosticados de trastorno bipolar. De forma similar, el estudio de Shalev y colaboradores (2014) incluye también pacientes con ansiedad generalizada y pacientes con estrés post-traumático. El estudio de Hoen *et al.* es el único trabajo que estudia la asociación entre depresión y LT en pacientes con una patología sistémica (enfermedad coronaria) (Hoen *et al.,* 2011).

Otro de los aspectos que puede tener relevancia en la valoración de la longitud de los telómeros son los años de evolución de la enfermedad, así como el estado de remisión de los síntomas en los pacientes. Sólo algunos de los trabajos revisados detallaron si se trataba de pacientes de larga evolución, en remisión o primeros episodios.

Respecto a la metodología utilizada para el análisis de la longitud telomérica, los primeros estudios utilizaron *Southern blot*, con el cual, mediante el análisis de fragmentos de restricción, reportan la LT en kb (Simon *et al.,* 2006; Lung, Chen y Shu, 2007; Hartmann *et al.,* 2010).Los estudios más recientes analizaron la LT de forma cuantitativa mediante fluorescencia o mediante PCR a tiempo real (RT-qPCR) y reportan la LT mediante el parámetro Ct o un ratio T/S, que en algunos casos los autores convierten a kb. El estudio de García Rizo y colaboradores empleó flurometría para el análisis de los telómeros y reportó la LT como "contenido telomérico", medida que correlaciona (r=0.9) con el número de kb proporcionado en un trabajo previo (Garcia-Rizo *et al.,* 2013; Fernandez-Egea *et al.,* 2009).

(a) Depresión y Longitud Telomérica (LT)

En total, en siete de los trabajos revisados los pacientes con DM presentaban LT significativamente más cortas respecto a los individuos control (Lung, Chen y Shu 2007; Hartmann *et al.,* 2010; Hoen *et al.,* 2011; Wikgren *et al.,* 2012; Garcia-Rizo *et al.,* 2013; J E Verhoeven *et al.,* 2014; Shalev *et al.,* 2014). Sin embargo, en seis de los estudios no se encontraron diferencias significativas entre la LT de pacientes y controles (Simon *et al.,* 2006; Wolkowitz *et al.,* 2011; Teyssier *et al.,* 2012; Needham *et al.,* 2015; Schaakxs *et al.,* 2014; Simon *et al.,* 2015). La mayoría de los estudios (cuatro de los seis) que no reportaron ninguna asociación presentan tamaños muestrales pequeños. En el estudio de Simon y colaboradores, la muestra está formada por 15 pacientes con depresión y 29 con trastorno bipolar, se encontraron longitudes teloméricas menores en los pacientes respecto a los controles. Sin embargo, estas diferencias no se asociaban de manera concreta a ninguno de los

diagnósticos (depresión y trastorno bipolar), quizás por los tamaños muestrales reducidos que incluidos en el estudio (Simon *et al.,* 2006). No obstante, en el estudio longitudinal llevado a cabo en la cohorte de Dunedin (Shalev *et al.,* 2014), se pone de manifiesto como los hombres que entre los 11 y 38 años han sufrido de manera persistente trastornos de internalización (depresión, trastorno de ansiedad generalizada y trastorno por estrés post-traumático) presentaban una longitud telomérica disminuida. Este fenómeno era independiente de otros posibles factores confusores como el tabaco o la dependencia a sustancias o el maltrato en la infancia y era especialmente significativo en los hombres que habían sufrido depresión y trastorno de ansiedad generalizado entre los 26 y los 38 años.

(b) Severidad, carga de la enfermad y LT

Los estudios revisados parecen poner de manifiesto una relación dosis-efecto entre la carga de la enfermedad y la LT. Así pues, cuanto mayor era la pérdida de salud y la severidad, mayor erosión sufrían sus telómeros. Así lo evidencia el trabajo de Verhoeven y colaboradores en el cual se estudiaron las longitudes teloméricas en tres grupos de pacientes: (1) episodio depresivo en curso, (2) episodio depresivo remitido y (3) controles. Ambos grupos de pacientes no diferían en las longitudes teloméricas pero sí lo hacían con el grupo control que presentaba unas LT mayores. Cuando se realizó un análisis más exhaustivo del grupo 1 teniendo en cuenta: i) la severidad de los síntomas depresivos (leves, moderados, severos) y ii) la duración de los síntomas (entre 1-9 meses, entre 10-23 meses, 24 o más meses) se mostró que los individuos con un episodio depresivo en curso que presentaban síntomas severos y mayor duración de la enfermedad, eran aquellos que a su vez también mostraban unas regiones teloméricas más cortas. Estos resultados, apoyarían el trabajo de Wikgreen *et al* donde se ponía de manifiesto que los pacientes de larga evolución presentaban una disminución de la longitud telomérica respecto a los controles (Wikgren *et al.,* 2012). Cabe destacar que el único estudio que evaluó la longitud de los telómeros en un grupo reducido de pacientes con primeros episodios de depresión no encontró asociaciones destacables (Teyssier *et al.,* 2012).

(c) Inflamación, estrés oxidativo y LT

Son muchas las evidencias que apoyan la asociación entre la DM y anormalidades en sistemas biológicos relacionados con el estrés, como el eje hipotálamo-hipofisario adrenal (HPA, del inglés *hypothalamic–pituitary–adrenal axis*) y la respuesta inflamatoria. La desregulación de estos sistemas podría subyacer a las bases del acortamiento de los telómeros y del envejecimiento acelerado. Sin embargo, a pesar de la importancia de estos factores en la DM, solo el estudio llevado a cabo por Wolkowitz *et al.,* analiza la implicación de la inflamación y el estrés oxidativo en la longitud telomérica de los pacientes con depresión. En este estudio, el estrés oxidativo se evaluó mediante un balance entre productos oxidantes y anti-oxidantes. De manera concreta, se definió el estrés oxidativo como un ratio entre F2-isoprostanos (derivados de la oxidación de radicales libres) y el ácido ascórbico (Vitamina C). Respecto a los niveles de inflamación, se evaluaron mediante la cuantificación de la concentración de Interleucina-6 (IL-6). En ambos casos, se observó una relación inversa con la longitud telomérica, es decir, cuanto mayor era el ratio de factores oxidantes/antioxidantes y los niveles de IL6, mayor era el acortamiento de las regiones teloméricas (Wolkowitz *et al.,* 2011).

DISCUSIÓN

Los resultados de esta revisión sugieren que existiría una relación entre la depresión mayor (DM) y un acortamiento en las regiones teloméricas situadas en los extremos de los cromosomas

humanos. También sugieren una relación dosis-efecto, es decir, que cuanto mayor es la duración y la severidad de la enfermedad, mayor sería el acortamiento que observamos. Asimismo, estudios preliminares parecen poner de manifiesto cómo inflamación y estrés oxidativo podrían ser factores subyacentes a la asociación entre la erosión de los telómeros y la depresión.

La LT constituiría un biomarcador de la enfermedad, pero que también podría asociarse a diferentes condiciones patológicas, a la edad biológica del individuo y a los eventos estresantes sufridos, aunque esta última hipótesis no ha sido ampliamente estudiada (O'Donovan *et al.,* 2011). En este sentido, sería interesante señalar que probablemente no se trata de un biomarcador exclusivo de depresión, dado que el acortamiento telomérico acelerado también ha sido descrito en otras patologías psiquiátricas como la esquizofrenia, el trastorno bipolar o el trastorno por estrés post-traumático, entre otros (Pawelczyk *et al.,* 2015; Elvsåshagen *et al.,* 2011; Malan *et al.,* 2011).

Los resultados encontrados en las diferentes condiciones psiquiátricas parecen poner de manifiesto una relación dosis-efecto. Para explorar esta hipótesis, algunos estudios recientes han evaluado la longitud telomérica así como su relación con la cronicidad y severidad de los síntomas. Pawelczyk y colaboradores estudiaron pacientes crónicos (más de dos años de evolución) y con esquizofrenia temprana (menos de dos años de evolución) y observaron cómo la recurrencia de la sintomatología psicótica, así como su intensidad y cronicidad, correlacionaba con la erosión telomérica, que estaría implicada en la activación de procesos degenerativos, senescencia celular y apoptosis (Pawelczyk *et al.,* 2015). La conexión entre severidad, cronicidad de los episodios psiquiátricos y la disminución de la longitud telomérica podría estar condicionada por el estrés oxidativo. Éste, constituiría un desequilibrio entre la producción de las especies reactivas al oxígeno (ROS), representada básicamente por la actividad de radicales libres y los factores antioxidantes. El ADN telomérico, rico en guaninas, sería particularmente sensible a los efectos nocivos del estrés oxidativo, pudiéndose producir roturas de los fragmentos distales de los cromosomas y su consiguiente acortamiento (Kawanishi y Oikawa, 2004), así como procesos relacionados con la edad como la apoptosis o una capacidad disminuida de respuesta al estrés. Estos mecanismos podrían estar implicados en el exceso de mortalidad observado en los pacientes psiquiátricos, incluidos los pacientes con depresión, en los que se ha descrito un estado "acelerado de envejecimiento" con un aumento de la incidencia de enfermedades relacionadas con la edad. En este sentido, la depresión mayor ha sido asociada con un riesgo incrementado para desarrollar problemas médicos propios de la edad avanzada, como diabetes, enfermedades cardiovasculares y del sistema inmunitario, demencia, osteoporosis, síndrome metabólico (Musselman, Evans y Nemeroff, 1998), así como con una muerte prematura. En todas estas patologías, aparte del daño celular oxidativo, hay implicados factores como el sexo y mecanismos inflamatorios. Estos factores contribuirían al envejecimiento fisiológico, el cual se refleja a nivel cromosómico en la erosión de sus telómeros (marcador de envejecimiento precoz), y confiriendo un peor pronóstico para estas patologías. Actualmente, la etiología del envejecimiento no ha sido comprendida por completo, aunque parecería que la acumulación de cambios lesivos, tanto a nivel molecular como celular, sería lo que conduciría finalmente a una disminución en el nivel funcional de tejidos y órganos (Zhang *et al.,* 2015). El desgaste de los telómeros y la inflamación crónica, han sido consideradas como los principales mecanismos implicados en el envejecimiento(Perry, Cunningham y Holmes, 2007).

Dado que las modificaciones oxidativas y la erosión de los telómeros estarían inducidas por ROS, sería de esperar que factores antioxidantes pudieran prevenir esta erosión. En este sentido, diversos estudios han realizado ensayos adicionando factores antioxidantes y sus resultados sugieren que una reducción del estrés oxidativo mediante un tratamiento antioxidante podría ayudar al mantenimiento de la longitud telomérica (Furumoto *et al.,* 1998). A pesar de los resultados controvertidos, los estudios parecen señalar como los tratamientos antidepresivos podrían mejorar diversos indicadores de estrés oxidativo que se encuentran alterados en los pacientes con depresión (Jimenez-Fernandez *et al.,* 2015). Asimismo, algunos estudios ponen de manifiesto que un tratamiento antidepresivo efectivo podría conducir a una normalización de los telómeros, por un

incremento de la actividad de la telomerasa y por la normalización de la respuesta inflamatoria (Lindqvist *et al.,* 2015). Estas evidencias señalan la necesidad de contemplar la medicación que reciben los pacientes como un posible factor de confusión, así como llevar a cabo los análisis en función de las dosis y los tratamientos recibidos por los pacientes (Hartmann *et al.,* 2010). Adicionalmente a la medicación, otras variables circunscritas a nivel individual como la edad, el sexo, la vulnerabilidad genética, la historia vital de cada individuo, la dieta o el fenotipo depresivo propio de cada paciente, podrían estar afectando la longitud telomérica de manera independiente al proceso de la enfermedad propiamente estudiada en cada caso.

La heterogeneidad de resultados en este campo, hasta día de hoy, sugiere la necesidad de realizar estudios futuros con nuevas aproximaciones que nos permitan elucidar cuál es, realmente, la importancia de estas regiones cromosómicas en las enfermedades somáticas, pero también, en las enfermedades psiquiátricas. Asimismo, es necesario estudiar más en profundidad los mecanismos que subyacen a la erosión aumentada de los telómeros en estos pacientes. Dado que uno de los factores limitantes parece ser el tamaño muestral analizado, los estudios futuros deberían incorporar un número de participantes que permita tener mayor poder estadístico para detectar el efecto y reducir la posibilidad de encontrar falsos positivos. Asimismo, la evaluación de muestras amplias nos permitirá estratificar a los pacientes según diferentes criterios y evaluar si el aumento de la erosión telomérica caracteriza a determinados subtipos de pacientes en función de fenotipos clínicos, curso de la enfermedad o respuesta terapéutica. Por otro lado, muchos de los estudios que se incluyen en esta revisión son transversales (*cross-sectional*) lo cual es un es un factor limitante a la hora de determinar la relación causa-efecto. Por ello, estudios longitudinales con pacientes con primeros episodios y controles altamente similares, en lo que respecta a factores de confusión comentados anteriormente, nos permitirían evaluar de manera más precisa la evolución que siguen los telómeros con el paso del tiempo en estos pacientes respecto a los controles.

Por último, señalar que son pocos los estudios que, a pesar del interés de la telomerasa, han investigado tanto su actividad como la variabilidad genética del gen que codifica para esta enzima responsable del mantenimiento de la longitud de los telómeros y por consiguiente de su funcionalidad. Un estudio exhaustivo del gen de la telomerasa, así como de otros genes relacionados, podría ayudar a esclarecer si el aumento de la erosión de los telómeros podría asociarse a algunas variantes del gen que codificaran para una enzima telomerasa con una actividad diferencial.

CONCLUSIONES

Los resultados de nuestra revisión parecen poner de manifiesto:

- Una relación entre DM y el acortamiento de las regiones teloméricas.
- Esta relación parece ser dosis-respuesta, de modo que como mayor es la severidad y la cronicidad de los síntomas, mayor es el acortamiento de los telómeros.
- La inflamación y el estrés parecen ser los mecanismos subyacentes a la erosión de los telómeros.
- El eje hipotálamo-hipofisario-adrenal como principal sistema regulador del estrés.

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TABLA 1. Estudios revisados donde se examina la longitud telomérica (LT) en depresión mayor (DM).

	REFERENCIA	TIPO DE ESTUDIO	TAMAÑO MUESTRA (PACIENTES/ CONTROLES)	PACIENTES	METODOLOGÍA	LONGITUD TELOMÉRICA (PACIENTES/CONTROL)	RESULTADO	
1	Simon *et al.*, 2006 Pubmed	Caso-control	44/44	Crónicos con DM (n= 15) y TB (n=29) con o sin ansiedad	*Southern blot*	6.87 /7.64(kb)	-	No se encontraron diferencias en la LT entre pacientes con DM vs controles. La LT está disminuida en los pacientes (DM+TB) vs controles
2	Lung *et al.*, 2007 Pubmed	Caso-control	253/411	DM	*Southern blot*	8.17/9.13 (kb)	+	La LT está disminuida en los pacientes con DM vs controles
3	Hartmann *et al.,* 2010 Pubmed	Caso-control	54/20	DM	*Southern blot*	7.20/7.55 (kb)	+	La LT está disminuida en los pacientes con DM vs controles
4	Hoen *et al.*, 2011 Pubmed	Longitudinal	206/746	DM y enfermedad coronaria	RT-qPCR	0.86/0.90 (t/s)	+	La LT está disminuida en los pacientes con DM vs controles
5	Wolkowitz *et al.*, 2011 Pubmed	Longitudinal	18/17	DM sin medicar	RT-qPCR	5.10/5.14 (kb)	-	No se encontraron diferencias en la LT entre pacientes con DM vs controles
6	Wikgren *et al,*, 2012 Pubmed	Caso-control	91/451	DM	RT-qPCR	5.26/5.53 (kb)	+	La LT está disminuida en los pacientes con DM vs controles
7	Teyssier *et al.*, 2012 Pubmed	Caso-control	17/16	Primer episodio de DM (n=12) y DM recurrente (n=5)	RT-qPCR	13.42/13.60 (mean Ct)	-	No se encontraron diferencias en la LT entre pacientes con DM vs controles
8	Garcia-Rizo *et al.,* 2013 Pubmed	Caso-control	9/48	DM sin medicar	Flurometría	89.0/103.7 (telomere content)	+	La LT está disminuida en los pacientes con DM vs controles
9	Verhoeven *et al.,* 2013 Pubmed	Longitudinal (NESDA)	1897/510	DM actual (n=1095) y DM remitida (n=802)	RT-qPCR	5.46 (DM actual) /5.46 (DM remitida) 5.53 (controles) (kb)	+	La LT está disminuida tanto en los pacientes con MD actual como en aquellos con MD remitida vs controles. La LT no difiere entre MD actual y remitida
10	Pubmed	Longitudinal (DUNEDIN)	455/372	Trastorno de internalización (depresión, ansiedad y estrés post-traumático)	RT-qPCR	0.97 (DM), 0.94 (TAG), 0.98 (TEPT), 1.05 (controles) Valores para hombres en c/t	+	La LT está disminuida especialmente en hombres que padecen DM y TAG en el intervalo de los 26 a los 38 años vs controles.
11	Needham *et al.*, 2015 Pubmed	Caso-control	75/966	DM	RT-qPCR	1.12/1.14 (t/s)	-	No se encontraron diferencias en la LT entre pacientes con DM vs controles
12	Schaakxs *et al.*, 2015 Pubmed	Caso-control	355/128	DM en población anciana	RT-qPCR	5.03/5.05 (kb)	-	No se encontraron diferencias en la LT entre pacientes con DM vs controles
13	Simon *et al,*, 2015 Pubmed	Caso-control	166/166	DM	*Southern blot* y confirmación por RT-qPCR	9.1/8.9(kb) 0.65/0.64 (t/s)	-	No se encontraron diferencias en la LT entre pacientes con DM vs controles

c/t= *cycle threshold for telomeric signal relative to cycle threshold for single copy gene*, DM= Depresión Mayor, DSM= *Diagnostic and statistical manual of mental disorders*, FIGS= *Family interview for genetic studies*, TAG= Trastorno por estrés generalizado, , Kb= kilobases, LT= Longitud telomérica, RT-qPCR= *Real time Quantitative polymerase chain reaction*, S= Severidad, SCID= *The Structural Cliinical Interview for DSM, SD= standard deviation,* TB= trastorno bipolar, t/s= *Telomere to single copy gene ratio*

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Supervisor's report on the contribution of the PhD candidate to the article.

Dr. Araceli Rosa de la Cruz, Associate Professor at the Departament de Biologia Evolutiva, Ecologia i Ciències Ambientals of the Facultat de Biologia (Universitat de Barcelona) and supervisor of the present doctoral thesis by Elionora Peña, hereby certifies that none of the co-authors of the chapter "Depresión y envejecimiento premature: Implicación de los telómeros" have used this publications for a doctoral thesis, and that the participation of the applicant in this article included the following tasks:

- Participation in the conception and design of the review.
- Identification and selection of papers
- Summary of the evidence and interpretation of data.
- Writing of the book chapter
- Critical revision of the chapter for intellectual content.

Signed by Dr. Araceli Rosa

Barcelona, September 2020

4. Global Summary of Results

The specific objectives of **section I**, which aimed to explore the implication of the genes *FKBP5* and *BDNF* and other variables of interest (i.e. sex, age, type of surgery and comorbidities) in the response of bariatric surgery in patients with obesity, resulted in three publications:

1. **Peña et al., 2020**. *Role of the FKBP5 polymorphism rs1360780, age, sex, and type of surgery in weight loss after bariatric surgery: a follow-up study.* **Surgery of Obesity and Related Diseases;** 2020. 16(4):581-589. doi: 10.1016/j.soard.2019.12.002.

2. **Peña et al., 2020.** *Response to the letter to the editor: FKBP5 polymorphism rs1360780 and weight loss after bariatric surgery.* **Surgery of Obesity and Related Diseases;** 2020 1;S1550-7289(20)30167-2. doi: 10.1016/j.soard.2020.03.026.

3. **Peña et al., 2020.** *Influence of the BDNF Val66Met polymorphism on weight loss after bariatric surgery: a 24-month follow-up.* **Surgery of Obesity and Related Diseases;** 2020. EPub ahead August 2020. doi: 10.1016/j.soard.2020.08.012

The results obtained in these studies are the following:

In the first study, we explored the relation between the ***FKBP5*** rs1360780 genetic variability in weight loss in a sample of 151 patients with severe obesity submitted to Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) followed during 24-months (t_{24m}; loss to follow-up: 0%). During the postoperative period body mass index (BMI) and percentage of excess and total weight loss were evaluated (%EWL and %TWL). The BMI analysis showed an effect of the interaction *FKBP5* genotype by sex (P =.0004) and a tendency to the interaction genotype by surgery (P =.048), so that men carrying the T-allele had higher BMI at t_{24m} than those without the T-allele, and T-allele carriers that underwent SG had higher BMI at t_{24m} than the noncarriers. Additionally, we found an interaction between *FKBP5* and age for the %EWL and BMI (P = .0005 and P = 1.5e-7, respectively), whereby individuals older than 48 years with the T allele displayed significant differences for the analysed variables at t_{24m} compared with the homozygotes for the alternate C allele showing lower weight loss.

In the second publication, we answer the letter to the editor of Yasri and Wiwanitkit [105] where the authors commented that not only *FKBP5* gene can influence weight loss after bariatric surgery, and other genetic polymorphisms could influence the weight outcomes analysed in our previous paper. In our response, we argued that in our paper we only studied a candidate gene, but we cannot discard the effect of other genetic markers via complex interactions with environmental or genetic factors. We agreed with Yasri and Wiwanitkit that future studies should consider polygenic scores taking into account the variation and risk conferred by multiple genetic variants. These scores could have a better predictive power in relation to the progress of the patients with obesity after surgery.

In the third study, we analysed the genetic polymorphism ***BDNF*** Val66Met (rs6265), and the influence of type-2 diabetes (T2D), and their interaction on weight loss after bariatric surgery in a cohort of patients with severe obesity. We evaluated a cohort of 158 patients with obesity submitted to bariatric surgery (RYGB or SG) followed-up over 24 months (t_{24m}: loss to follow-

up: 0%). During the post-operative period, percentage of excess body mass index loss (%EBMIL), percentage of excess weight loss (%EWL) and total weight loss (%TWL) were evaluated.

Longitudinal analyses showed a suggestive effect of *BDNF* genotype on the %EWL ($P = 0.056$) and indicated that individuals carrying the Met allele may experience a better outcome after bariatric surgery than those with the Val/Val genotype. We found a negative effect of a T2D diagnosis at baseline on %EBMIL ($P = 0.004$). Additionally, we found an interaction between *BDNF* genotype and T2D on %EWL and %EBMIL ($P = 0.027$ and $P = 0.0004$, respectively), whereby individuals with the Met allele without T2D at t0 displayed a greater %EWL and more %EBMIL at t_{12m} and t_{24m} than their counterparts with T2D or patients with the Val/Val genotype with or without T2D. Our data showed an association between the Met variant, and greater weight loss after bariatric surgery in patients without T2D. The presence of T2D seems to counteract this positive effect.

The specific objectives of **section II** were to investigate telomere length (TL) in different subtypes of obese patients, in patients with depression, and to examine changes in TL in relation to weight loss after bariatric surgery. This section resulted in three publications, including one original research article, a systematic review and a chapter published in a conference book:

1. **Peña E et al., 2020.** *Longitudinal changes on telomere length in a cohort of obese patients submitted to bariatric surgery: A two-year follow-up***. Surgery of Obesity and Related Diseases; 2020** (in press).

2. **Peña E et al., 2020.** *Leukocyte telomere length in obese patients submitted to bariatric surgery: a systematic review* (submitted to European Eating Disorders Review).

3. **Peña E et al., 2018**. *Depresión y envejecimiento prematuro: implicación de los telómeros.* En: **Actas del XX Congreso de la Sociedad Española de Antropología Física**. **"La Antropología Física en la Era de la Genómica".** ISBN: 978-84-948252-4-8

The results obtained in these studies are the following:

In the first study of this section, we evaluated TL in different subtypes of obese patients, and we examined changes in TL in relation to weight loss after bariatric surgery. We studied a cohort of 94 patients submitted to bariatric surgery followed-up during 24th months. All patients were evaluated before surgery (t_0) and during the post-operative period (t_{6m}, t_{12m} and t_{24m}) for body mass index (BMI) and metabolic variables. We assessed TL at each timepoint using quantitative PCRs and telomere sequence to single copy gene sequence ratio method.

We found that patients with class III obesity showed significantly shorter TL at baseline than those patients with class II obesity ($P = 0.0271$). No differences in TL were found between patients with or without T2D or metabolic syndrome (MetS). Longitudinal analysis did not show an effect of time, type of surgery, age or sex on TL. However, a generalized estimating equation model showed that TL was shorter amongst class III obesity patients across the timecourse (*P*

= 0.0080). Comparison between patients with obesity class II and class III showed differences in TL at t6m (adjusted P = 0.024) whereby class II patients had longer TL. However, no difference was observed at the other evaluated times.

According to our results obesity severity may have negative effects on TL independently of T2D or MetS. Although TL is significantly longer in class II obesity patients relative to class III 6 months after bariatric surgery. This difference was not apparent after 24 months.

The second study included in this section aimed to review systematically all the studies examining the effects of weight loss after bariatric surgery in TL. A systematic search of three databases was conducted (MEDLINE, Web of Knowledge and SCOPUS). Seven papers fulfilled our inclusion criteria. The studies included reported TL evaluated in leukocyte in adult patients who had underwent laparoscopic-adjusted gastric banding (LAGB), Roux-en-Y gastric bypass (RYGB), and sleeve gastrectomy (SG) procedures.

Five of the studies explored changes in TL in a course time above 2 years. Two of them found changes between TL at baseline and 24 months later with a decreased in TL. Two studies reported no differences between baseline and at the end of follow-up. However, our study showed differences at baseline between obesity classes, whereby individuals of class II showed longer TL than those of class III. Only one of the studies with a follow-up above or equal of 2 years found a recovery on TL one of the studies found changes on TL at 2 years follow-up with an increase of doubled from initially.

On the other hand, two of the included studies in the review explored the changes in TL in longer follow-ups (>2 years). In the first study they divided the individuals according to the TL at baseline (i.e. short, intermediate, long). They found significant lengthening in those patients with the shortest TL at baseline but not for those with intermediate or longest baseline TL [106]. The second study explored changes in TL after 10 years surgery, they found an increase in TL that was not observed in a control sample. [107].

The third study included in this section consisted in a book chapter about TL in patients with major depression (MD) and the etiopathological mechanisms implicated. Thirteen articles encompassing 35 studies based on independent samples, fulfilled our inclusion criteria. Ten of them were case-control studies and most of them with sample size over one hundred subjects. Most of the studies included patients with MD, although some of them included individuals with internalizing disorders.

In total, seven studies found significantly shorter TL in patients with MD compared to controls. However, six of them found no significant differences in TL between MD patients and controls. The impact of severity and the duration of symptomatology on TL was only explored in two studies, which confirmed that shorter TL were associated with more severity and longer duration of the symptomatology in patients with MD. Regarding inflammation and oxidative stress, only one of the included studies assessed the implication of these mechanisms in TL change in patients with MD. The study reported that oxidative stress and inflammation were inversely correlated with TL in patients with MD. The reviewed studies suggest a negative association between depression and telomere length. This seems to point toward telomere length as a predictor of physical health and processes associated with ageing. Further studies are

needed to clarify potential causality underlying this association and to elucidate the biology linking depression and this cellular marker of stress exposure and ageing.

5. Discussion

The present thesis aims to explore the involvement of genetic variability in bariatric surgery (BS) outcomes. Furthermore, we seek to investigate the change in telomere length (TL) in patients with obesity after weight loss induced by BS and in patients with depression. This thesis resulted in three articles, one response to a letter, a systematic review and a book chapter.

One of the main assumptions of this thesis is the existence of a variety of complex factors moderating weight loss outcomes, including clinical, psychological, demographic, and biological factors. Specifically, previous studies have revealed age, sex, pre-operative weight and body mass index (BMI), physical activity, type 2 diabetes (T2D) and other obesity associated disorders (e.g.: anxiety or depression) as moderators of BS outcomes [100,108]. Recent studies have investigated the role of different genetic variants in BS outcomes, reporting different trajectories on weight loss depending on genotype [109,110].

In the present thesis we have collected a clinical sample of 158 patients, consisting in 36 men and 122 women, with different classes/types of obesity that underwent a BS and with 2-year follow-up. Individuals were evaluated before surgery for different anthropometrical variables (i.e. weight, height, BMI, excess weight, waist circumference and waist-hip ratio) and clinical variables (T2D, metabolic syndrome, hemoglobin A1c and fasting plasma glucose). These variables were evaluated in different post-operative periods (t_{1m}, t_{3m}, t_{6m}, t_{12m}, t_{24m}). Patients were submitted to two different procedures: Roux-en-Y gastric bypass (RYGB) and Sleeve gastrectomy (SG). RYGB was assigned to patients with BMI between 40 and 55 kg/m^2 (n = 99) and SG for those patients with a BMI between 35 and 40 kg/m^2 and more than 55 kg/m^2 (n = 59). To report weight loss, we calculated for all the assessments (from t_0 to t_{24m}): i) Body Mass Index (BMI), ii) percentage of excess weight loss (%EWL), iii) percentage of total weight loss (%TWL) and iv) percentage of excess BMI loss (%EBMIL). BMI was calculated in kg/m^2 according to the formula: weight (kg) / height (m^2). The %EWL was calculated as [(weight loss / excess weight) x 100], where excess weight was taken as the weight in kilograms above the weight corresponding to the BMI for 24.9 kg/m^2. The %TWL was calculated as [(weight loss / weight at t_0) x 100]. The %EBMIL was calculated as [(BMI at t_0) - (Postop BMI) / (BMI at t_0 – 24.9)] x 100.

Given the variability in weight loss between individuals submitted to the same surgical procedure, the current looking for specific genes and other factors affecting weight loss emerges as an important field to understand both, the complexity of obesity and weight loss variability. In line with previous investigations, the studies comprising this thesis are focused on genetic variability as an important modulator of weight loss and the benefits of BS in terms of quality of life on the patients.

Based on this, in the first section we explored the variability within two candidate genes and the associations with different outcomes in the above-mentioned sample of patients with severe obesity submitted to BS.

The first gene studied here was the *FKBP5*, given its role as a regulator of the hypothalamic–pituitary–adrenal (HPA) axis [111]. HPA axis has been described as an important mediator in the stress response. Stress is a challenge to the natural homeostasis of the individual. Although an acute short-term stress response is necessary for homeostasis recovery, chronic or prolonged

stress responses can be harmful and may cause several disease states and increase the risk for obesity and various metabolic diseases [28]. In this regard, studies in the past 15 years have demonstrated that cytokines produced by immune cells or adipocytes can stimulate the HPA axis, at the level of the hypothalamus, anterior pituitary gland, and the adrenal cortex [112]. Therefore, it is evident that it exists some crosstalk between the HPA axis and the inflammatory response; this may relate to the role of HPA axis alterations in the development of obesity.

The *FKBP5* is well known for its important role as a molecular co-chaperone that inhibits glucocorticoid receptors activity, and consequently suppresses stress response [113,114]. *FKBP5* is highly expressed in peripheral and central tissues with its highest expression in adipose and skeletal muscle [115]. Specifically, the functional variant of the gene analysed in the present study (rs1360780) has been associated with higher levels of the FKBP5 protein and a prolonged cortisol response to stress, measured by reduced cortisol suppression after different tests [116–118]. The rs1360780 variant was firstly studied in relation to BS response in patients with obesity by Hartmann and collegues [110]. In this work, the authors associated the T allele of this gene with lower weight loss after 26 months post-surgery in a cohort of forty-two obese patients. Our data on the variability of the *FKBP5* gene and its association with weight loss after bariatric surgery did not show a direct association between genotype and the analysed outcomes (BMI, %EWL and %TWL). However, our study has several strengths compared to Hartmann's study with a considerably bigger sample (n = 151 patients, loss of follow-up was 0%), and with a higher proportion of males. Furthermore, Hartman´s study only included patients submitted to RYGB whereas in our study 37.7% of patients underwent SG, allowing us to compare the effectiveness of both surgical methods. With an expanded sample size and considering age and type of surgery followed by the patients, we pointed out how these variables were not independent to explain the complexity of weight loss after BS. In this regard, males carrying the T allele of *FKBP5* rs1360780 and submitted to SG, displayed worse scores for %EWL, %TWL and BMI. Also, BS was less effective in older individuals (≥ 48 years).

In line with previous investigations, the type of surgery had an effect on weight loss during the post-operative period. In this regard, individuals submitted to RYGB seemed to have better outcomes 24 months after the surgery compared to those individuals submitted to SG. These two bariatric procedures are the most commonly used in severe obese patients and are effective at promoting weight loss. Several studies have compared whether the results of these two techniques are equivalent. A recent meta-analysis pointed out that both procedures result in similar %EWL and BMI reduction levels at 6 and 12 months. However, %EWL and BMI reduction were significantly greater in the RYGB group 24 months after surgery [119].

Regarding the role of age as a predictor of excess weight loss after bariatric surgery, controversial results are found in literature. Some studies report less %EWL among patients older than 60 years in comparison with younger subjects [120,121] while others do not show significant age differences [122,123]. In a previous publication, Contreras and colleagues (2013) found that patients younger than 45 years lose greater amount of weight after BS, as we found in our study [124]. The most plausible explanation for this effect of age could be the impaired metabolic capacity and decrease in energy requirements in the elderly compared to young individuals as well as hormonal factors, especially in women. Only one previous study has

reported a sex-specific effect of age on weight loss after bariatric surgery. In this study, Ochner and colleagues found that weight loss in the post-operative period was significantly reduced in women aged 55-65 years compared to women aged 20-45, but not in men [125].

Thus, pooling all these studies together, available data so far suggest that different types of bariatric surgery may have different effects on weight loss depending on sex and age, shedding some light on the etiological complexity of obesity.

The second gene studied in the present thesis was the *BDNF*. It is implicated in the regulation of energy balance downstream of *MC4R* in the leptin-melanocortin pathway [126]. It plays a critical role in nervous system development and function, and particularly, exerts an anorexigenic function in the brain. It is hypothesized that genetic variability in the *BDNF* gene could alter hypothalamic BDNF expression that would influence energy balance and may lead to the manifestation of the obese phenotype. It has been described that levels of plasma BDNF tend to be lower in obese prepubertal children than in lean controls, this is not related to any other metabolic syndrome component and increases after lifestyle intervention [127]. Furthermore, syndromic obesity such as Prader-Willi syndrome patients exhibit alterations in their hypothalamus and exaggerated hyperphagia, as well as low fasting plasma BDNF levels and a lack of postprandial peak that can predict the odds of being hungry [128]. The secretion of BDNF is affected by a common functional polymorphism (rs6265, C > T) that results in valine (Val) to methionine (Met) substitution at codon 66 (Val66Met). The Val66Met polymorphism has been one of the most extensively studied genetic markers because one of its variants affects BDNF activity and has been related to clinical traits associated with BMI and obesity. In this regard, previous studies in healthy population have shown that individuals carrying the Met allele had lower BMI [129]. This association has been confirmed in a meta-analysis involving 10.108 women and in a large-scale GWAS in populations of European origin where Met homozygotes individuals showed lower BMI than individuals with the other genotypes (i.e.: Val/Met or Val/Val) [130,131]. Our results in the whole sample seemed to be in the same direction of these previous studies, suggesting better outcomes for the %EWL and %EBMIL in patients carrying the Met allele than in those carrying the Val/Val genotype.

In our study we explored the effect of T2D status on patients before surgery on the outcome after the surgical procedure. We found that patients with T2D at baseline showed worse surgical results than patients without T2D on %EBMIL. This is in accordance with previous literature showing that although the patients with diabetes have an improvement in diabetes control and hypertension after BS, the surgery is less effective in terms of weight loss [132]. Furthermore, we also report an interaction effect between *BNDF* genotype and T2D at baseline to explain weight loss after surgery. Individuals carrying the Met allele (either as homozygotes or heterozygotes) without T2D at baseline showed better outcomes in terms of %EWL and %EBMI, especially twelve and twenty-four months after the surgery. A biological interaction between these two factors would suggest their co-participation in the same causal mechanism, that is, the absence of T2D drives the effect in Met allele carriers, and conversely, homozygosity for the Val allele had a worse effect on weight loss independently of the presence of T2D [133].

The above-mentioned studies support the existence of allelic variants in different genes coding for proteins involved in the pathophysiology of obesity that may impact in weight loss after BS.

Furthermore, the implication of different variables such as sex, age, type of surgery and the presence or absence of comorbidities, previously reported in clinical studies, is also supported in our sample. The fact that genetic variability and clinical and demographic factors are not independent, according to our findings, supports the idea of the complexity of weight loss. These factors, as well as their interaction, could contribute to understand the interindividual variation in surgery outcomes experienced by the patients in the postoperative period.

However, weight loss after surgery cannot be only attributed to the variability of the genes analysed in this thesis (i.e. *FKBP5* and *BDNF*). Our research has conducted a candidate gene approach that has provided some evidence that common genetic polymorphisms associated with obesity or related phenotypes, may be linked to the response to bariatric surgery. However, we are well aware that this approach should be criticized for being biased, limiting the search to few hypothesized candidates without the integration of the information given by multiple candidate genes. Groundbreaking advances in high-throughput genotyping techniques over the last years have provided the technological tool to tackle such limitations in genetic analysis. Genotyping microarrays are nowadays able to interrogate several millions of genetic variants across the genome in a single experiment. This technological advance leads the opportunity to develop genome-wide approaches or to integrate the variability of a high number of genetic markers with the aim to better explore and understand the intricacy of complex traits. For example, polygenic-risk scores (PRS) allow the joint analysis of a large number of SNPs, taking into account the relative risk associated to each one. PRS provide a score aggregating these risks that represent a genetic risk profile in each individual [134]. These PRS can be applied to: i) predict outcome after BS, ii) investigate potential intermediate phenotypes and iii) address more biologically-informed approaches by exploring variants in genes involved in particular biological pathways [135]. These PRS could potentially be included as a complementary tool in the presurgical assessment of patients with severe obesity. These approaches would allow not only to implement a more effective and personalised surgery, but also to optimise healthcare resources [136].

Other biological factors, such as age, sex, inflammation, and hormones play an important role in both, phenotype and response after the surgery procedure. Additionally, environmental factors, such as perceived stress, which tends to increase in obese patients, should be considered a key variable in the phenotype of obesity and the study of the weight loss after bariatric surgery [137].

Regarding this, obesity is characterised by a chronic inflammatory state and increased oxidative stress, which have been also described in several mental disorders such as depression. Cross-sectional epidemiological studies suggest that the relation between depression and obesity is bidirectional. Individuals with a history of a major depression (MD) have 58% increased risk of obesity when compared to the general population (McIntyre et al., 2006; Simon et al., 2006) and similarly, individuals with obesity are also more likely to suffer from MD compared to healthy weight individuals (55% increased risk) [140]. Several studies support the hypothesis that the co-occurrence of both disorders may be due to several factors, including the influence of each trait on the other [141], shared environmental determinants (e.g. childhood trauma) or shared genetic factors [85,142] . Disturbances in the HPA axis, immune functioning, and the serotonin/dopamine

pathways in both conditions, raise the possibility that both, depression and obesity, are influenced by gene-environment interactions. Environmental and behavioral factors such as emotional eating and physical inactivity also may play a role in the influence of one trait on the other [143].

Clearly, identifying modifiable environmental factors and examining the genetic, biological, environmental, social, and cultural mechanisms underlying the relationship between depression and obesity can lead to more effective prevention and treatment strategies for both conditions. In this regard, in both pathologies, individuals show lower life expectancy and an increase in early mortality. In addition, obese patients suffer from an increase in age-associated disease prevalence suggesting a premature ageing phenotype [144,145]. Taking this into account, and the fact that telomere length (TL) is a key marker of cellular and biological ageing used to explore the effects of the environment on premature cell ageing and age-related pathology, we found it interesting to study this marker in both phenotypes.

Previous investigations have associated shorter telomeres with increasing BMI, increased adiposity and, recently, with increased waist-hip ratio and visceral fat accumulation. Many of the metabolic imbalances of obesity (e.g. glycaemic, lipidemic, etc.) give rise to organ dysfunction in a way that resembles the accelerated ageing process [84]. Based on this, the studies included in section II aimed to explore changes in TL after BS in obese patients and in patients with depression.

The first article included in this section, sought to investigate relative TL in a cohort of obese patients submitted to BS. At baseline, we found no association between TL and measures of glycemic status, BMI or co-morbidities such as metabolic syndrome (MetS) and T2D. This result seemed to be in the same direction of previous studies, showing no association at baseline between TL and metabolic variables [146]. However, patients with class III obesity showed significantly shorter TL at baseline than those patients with class II obesity. Furthermore, like in a previous study, our longitudinal approach could not detect an improvement of TL in patients two years after the surgery [146]. Again, when we divided the patients according to obesity class (class II vs class III), we found that TL was shorter amongst class III obesity patients (i.e.: with higher BMI) across the time course. This finding pointed to the importance of severity of obesity in the evolution of patients after surgery. These significant differences, which were most apparent at 6 months, were not clear differences by the end of the study at 24 months.

Considering our previous findings, we found of great interest to review the literature regarding the effects of weight loss induced by BS in TL. Our systematic review pointed out that few studies analysed a longitudinal sample of obese patients after BS, and for this reason only seven studies were included.

The studies exploring the outcome of BS at short-term (≤12 months) reported shorter TL in the post-operative period compared to TL at baseline (Formichi and JOngloed), suggesting an overall decrease in relative TL throughout the first year after surgery. However, another study reported no differences in TL 12 months after surgery [147]. Nevertheless, when patients were categorised according to levels of inflammatory and lipidic markers, significant differences in TL emerged over time. Individuals with worse preoperative profile showed a greater elongation

of TL [147].

In our original study we reported differences on TL when we classified patients according to obesity class (i.e.: severity), whereby individuals with more sever forms of obesity at preoperative time, displayed worse outcomes after surgery. This probably reflects the chronic long-term differences between these patients' subtypes, and suggest that among obese patients, obesity class may be more informative than BMI when considering TL. Regarding this, our study is in line with previous studies with short follow-ups (i.e.: 12-24 months), where it is difficult to capture variations in TL. The analysis of TL according to anthropometrical variables (e.g.: BMI) or inflammatory variables allow us to capture subtle differences in TL between groups.

In contrast to short-term studies, cohorts with longer follow-ups (i.e.: >2 years) seem to be able to detect changes in TL. The study of Laimer and colleagues, with one the longest follow-up after bariatric surgery (10 years), found an increase in TL in the group of patients submitted to surgery. However, the control group experienced a reduction in the TL after this period. The comparison of TL after 10 years between patients and controls reported lower telomere erosion in patients compared to controls [107]. In the study of Dersham and colleagues (2018) no differences in TL was found in 50 patients submitted to BS and with 3-5 years follow-up. However, significant lengthening was observed for those individuals with shorter telomeres at baseline [106].

Despite the huge benefits of BS as promoting weight loss and improving associated comorbidities, surgical intervention per se induces an inflammatory response [148]. Oxidative stress is also involved in the surgical stress response and can be associated with complications such as sepsis, lung edema, and liver and kidney dysfunction, as well as increased mortality [149]. These problems may be further aggravated in the case of an obese patient because both, obesity and surgery, elicit oxidative stress and inflammatory processes. Given these observations, recovery of TL immediately after BS procedure is difficult to capture [146,150]. However, studies that report an elongation of TL have evaluated patients after 5 years. Future directions of this thesis included the re-evaluation of our patients that have submitted to BS 10 years ago. Given the costs and dangers surrounding BS, there is an urgent need to perform longitudinal studies with greater follow-ups will allow us to determine the efficacy of BS and the potentiality of TL not only as a biomarker of quality of life, also as an indicator of BS success.

Regarding TL and measures of glycemic status and co-morbidities, such as MetS and T2D in our article, we did not find statistically significant associations, supporting previous results [146]. Despite the high frequency of these co-morbidities in patients with obesity, few studies explored its implication in BS outcomes in relation to TL [107,151].

In the same way, despite the inflammation being one of the most important mechanisms underlying telomere erosion, most of the studies did not include markers of oxidative stress or inflammation. Only two of the reviewed studies analysed inflammatory markers in patients submitted to BS, suggesting that individuals with worse preoperative status had better recovery after surgery [147,152]. In this regard, the lack of information about inflammatory state and oxidative stress in patients hinders the ability to interpret which mechanisms contribute to the associations and TL erosion or recovery after surgery. Further studies including these parameters, as well as

other factors implicated in telomere erosion, could help to elucidate the clinical benefits of BS in telomere length recovery.

Regarding the association between depression and TL, as commented before, a large number of epidemiological studies and meta-analyses have confirmed the association between major depression (MD) and obesity as commonly co-occurring medical conditions [30,153]. The co-existence of both seems to underlie shared biological mechanisms such as inflammation, which have been described as mechanisms of accelerated biological ageing, indicated by a shorter TL [154].

Based on this, the book chapter included in the present thesis consisted in a review of the published articles exploring the relationship between depression and TL. Thirteen studies fulfilled our inclusion criteria. The studies included explored the effect of MD in TL considering several factors such as, the severity and duration of the symptomatology, and the role of inflammation and oxidative stress. Seven of the reviewed studies found significant shorter TL in patients with MD compared to controls [154–160], whereas six of them did not report any significant differences [161–166]. Those studies considering the severity and duration of the symptoms, found a dose-response relationship. In this regard, depressive patients with severe and chronic symptomatology showed shorter TL [154]. Wikgreen and colleagues support this results [158]. The recurrence of depressive symptomatology, as well as its intensity and chronicity were also correlated with telomeric erosion, that would be involved in the activation of degenerative process, cellular senescence and apoptosis [167].

Although it is well known that inflammation and oxidative stress are also implicated in MD [168], only one of the included studies explored its implication in TL in these patients [162]. In this study an inverse correlation was found between lifetime depression and TL, whereby patients with major exposure showed shorter telomeres, corresponding to approximately seven years of accelerated cell-ageing respect to controls. Several studies suggest that the reduction of oxidative stress caused by treatments adding antioxidant factors may contribute to the TL maintenance [169]. Despite the controversial results, studies point out that antidepressant treatments might improve oxidative stress indicators which are altered in depressive patients [170]. Additionally, other studies suggest that an effective antidepressant treatment will help to preserve TL by an increase of the telomerase activity and a normalization of the inflammatory response [171]. Furthermore, other therapies reducing levels of stress and increasing positive states of mind such as meditation or yoga have emerged as new therapies with salutary effect on TL on those patients [172].

However, the heterogeneity of the findings observed, suggest the need of future studies using new approaches that allow the elucidation of the real role of these chromosomal regions in somatic but also in psychiatric illnesses. Furthermore, the co-existence of different somatic and mental pathologies that accelerate ageing is a new field of research that need special attention. In relation to this, we plan to review the clinical psychiatric history of our sample of patients with obesity to know the presence of depressive symptoms before surgery and examine the evolution of these symptoms in relation to weight loss after bariatric surgery.

Limitations

Several limitations should be considered when considering the present work.

Regarding the papers included in the first section, we only explored the variability of a single-genetic marker in two genes. Given the multifactorial, polygenic nature of obesity and the involvement of multiple factors modulating weight loss, the evaluation of only a single-genetic marker may result insufficient, and the effects of other polymorphisms cannot be excluded. One interesting strategy in future genetic studies will be the calculation of polygenic-risk scores or pathway analyses, which may reflect better the multifactorial etiology of both, obesity and weight loss. We did not measure metabolic stress parameters such as cortisol and catecholamine levels, or other metabolic intermediate products indicators of stress, catabolism or related to the undernourishment situation that occurs during the first year after bariatric surgery namely plasma free fatty acids, ketone bodies or moreover, cytokines or reactive oxygen species (ROS). The lack of information about inflammatory state of patients and telomerase activity in the sample hinders our ability to interpret which mechanisms contribute to the erosion of telomeres in obese patients. Furthermore, we can only assume that individuals were following the dietary recommendations after bariatric surgery, but it is still possible that patients were eating in an unhealthy way, just in a reduced quantity. In addition, we do not have information on physical activity, and other healthrelated parameters.

Finally, a longer follow-up of the sample would be necessary to understand not only short-term effects of surgery but also to evaluate changes on TL in the long-term. The identification of potential predictors of success after bariatric surgery will be relevant in the near future for improving patients' quality of life.

6. Conclusions

The results of the studies presented in this thesis provide new and independent evidence of the involvement of genetic factors underlying weight loss in obese patients and changes in TL after bariatric surgery procedure and in patients with depression. Overall, the main conclusions are:

1. Genotype of *FKBP5*, age, sex and type of surgery have different impact on weight loss in patients with obesity after bariatric surgery intervention.

2. *BDNF* Val166Met genotype, and the presence of T2D before surgery could have a non-independent impact on weight loss after surgery.

3. Obesity is a polygenic multifactorial trait, influenced by multiple genetic variants of minor effect and environmental factors. The study of candidate genes contributes to understand how biological and environmental factors impact in bariatric surgery outcomes. However, the calculation of polygenic risk scores will help to understand and to predict the evolution of patients with obesity after surgery.

4. Patients with obesity class II report longer TL in comparison with class III patients before surgery. No effect of co-morbidities (i.e. MetS and T2S) was found in relation to TL. We found a lack of TL improvement at 2 years after surgery in both class II and class III obese patients. The temporary improvement of TL in class II patients at 6 months after surgery needs further studies to draw firm conclusions.

5. Despite the numerous beneficial effects of bariatric surgery, short-term studies are unable to detect benefits regarding TL. This could be explained by the negative effect of some postoperative situations and due to bariatric surgery being a stressful situation per se. Studies with longer follow-ups are able to capture changes in TL.

6. Depressive patients have shorter TL. This association is in a dose-response fashion, whereby individuals with higher chronicity and severity of depressive symptoms show shorter TL. The reduction of inflammation and oxidative stress via antidepressants or alternative therapies would have beneficial effects on TL.

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compared to healthy controls before and after antidepressant treatment: Results from a meta-analysis. *J Clin Psychiatry*. 2015;76(12):1658-1667. doi:10.4088/JCP.14r09179

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8. Curriculum vitae

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EDUCATION

2008 – 2013 BSc, Biomedical Science – Universitat de Barcelona
Final Project: "Association between the candidate gene for schizophrenia p250GAP and schizotypy: Study in healthy general population", supervised by Dr. Araceli Rosa. Mark: 9.5 (Award by the Societat Catalana de Biologia, see later in CV)

2013 – 2014 MSc interuniversity, Initiation to mental health research – Universidad de Cantabria
Final Project: "'"Is FKBP5 gene a modulator of the psychosis-inducing effects of childhood trauma?", supervised by Dr. Araceli Rosa. Mark: 10

2016 – present PhD in Biomedicine – Universitat de Barcelona

SCIENTIFIC ACTIVITY

2012 - present Collaboration in the project "Genetic Variability in Emotion Regulation, Social Bonding and Hypothesized Candidate Pathophysiological Mechanisms in Psychosis: Relationship with Daily-life Stress-Sensitivity and Expression of the Psychosis Continuum Phenotype" (PSI2011-30321-C02-02), IP: Dr. Araceli Rosa.

2016 - present Project "Connexion between obesity, depression, inflammation and accelerated ageing. Multimodal study in a cohort of patients with morbid obesity candidates for a bariatric surgery". Ajuts per incentivar la iniciació a la recerca, amb el projecte, CIR2016/034. IP: Dr. Sara Crivillés Mas. Hospital Universitari Parc Taulí

PUBLICATIONS

Articles published in scientific journals

1. Cristóbal-Narváez P, Sheinbaum T, Rosa A, Ballespí S, de Castro-Catala M, **Peña E**, Kwapil TR, Barrantes-Vidal N. *The Interaction between Childhood Bullying and the FKBP5 Gene on Psychotic-Like Experiences and Stress Reactivity in Real Life.* **PLoS ONE**; 2016; 11(7):e0158809. doi:10.1371/journal.pone.0158809
2. de Castro-Catala M, van Nierop M, Barrantes-Vidal N, Cristóbal-Narváez P, Sheinbaum T, Kwapil TR, **Peña E**, Jacobs N, Derom C, Thiery E, van Os J, van Winkel R, Rosa A. *Childhood trauma, BDNF Val66Met and subclinical psychotic experiences. Attempt at replication in*

two independent samples. **Journal of Psychiatric Research**; 2016; 83:121-129. doi: 10.1016/j.jpsychires.2016.08.014

3. de Castro-Catala M, **Peña E**, Cristóbal-Narváez P, Sheinbaum T, Kwapil TR, Barrantes-Vidal N, Rosa A. *RGS4 variants and psychosis proneness: association at the population level*. **European Archives of Psychiatry and Clinical Neuroscience**; 2017; 267(1):19-24. doi:10.1007/s00406-016-0676-7

4. de Castro-Catala M, **Peña E**, Kwapil TR, Papiol S, Sheinbaum T, Cristóbal-Narváez P, Ballespí S, Barrantes-Vidal N, Rosa A. *Interaction effect of FKBP5 gene and childhood trauma on psychosis, depression, and anxiety symptoms: study in a non-clinical sample*. **Psychoneuroendocrinology, 2017 85:200-209. doi: 10.1016/j.psyneuen.2017.08.024**.

5. Pérez-Pérez B, Cristóbal-Narváez P, Sheinbaum T, Kwapil TR, Ballespí S, **Peña E**, de Castro-Catala M, D. Riba M, Rosa A, Barrantes-Vidal N. *Interaction between FKBP5 Variability and Recent Life Events in the Anxiety Spectrum: Evidence for the Differential Susceptibility Model*. **PLoS One**, 2018 Feb 21;13(2):e0193044. doi: 10.1371/journal.pone.0193044.

6. **Peña E**, Caixàs A, Arenas C, Rigla M, Crivillés S, Cardoner N, Rosa A. *Role of the FKBP5 polymorphism rs1360780, age, sex, and type of surgery in weight loss after bariatric surgery: a follow-up study*. **Surgery of Obesity and Related Diseases;** 2020. 16(4):581-589. doi: 10.1016/j.soard.2019.12.002.

7. **Peña E**, Caixàs A, Arenas C, Rigla M, Crivillés S, Cardoner N, Rosa A. *Response to the letter to the editor: FKBP5 polymorphism rs1360780 and weight loss after bariatric surgery*. **Surgery of Obesity and Related Diseases;** 2020 1;S1550-7289(20)30167-2. doi: 10.1016/j.soard.2020.03.026.

8. **Peña E**, R Powell T, Arenas C, Cardoner N, Rebasa P, Luna A, Caixàs A, Rosa A. *Longitudinal changes on telomere length in a cohort of obese patients submitted to bariatric surgery: A two-year follow-up*. **Surgery of Obesity and Related Diseases;** 2020 Jun 27;S1550-7289(20)30347-6. doi: 10.1016/j.soard.2020.06.027

9. **Peña E**, Caixàs A, Arenas C, Pareja R, León-Mengíbar J, Rigla M, R Powell T, Cardoner N, Rosa A. *Influence of the BDNF Val66Met polymorphism on weight loss after bariatric surgery: a 24-month follow-up*. **Surgery of Obesity and Related Diseases;** 2020 Aug. DOI: 10.1016/j.soard.2020.08.012 (in press)

10. **Peña E**, León-Mengíbar J, R Powell T, Cardoner N, Caixàs A, Rosa A. *Leukocyte telomere length in obese patients submitted to bariatric surgery: a systematic review* (submitted to European Eating Disorders Review)

Publications in dissemination journals

1. **Peña E.** *Vulnerabilitat per psicosi mesurada en població sana catalana*. Treballs de la Societat Catalana de Biologia, volum 66 (2015), p66-67. ISSN: 2013-9802 (electronic edition); 0212-3037 (print edition).

Conference communications published on indexed journals

1. Rosa A, **Peña E**, de Castro-Català M, Kwapil TR, Cristóbal- Narváez P, Barrantes-Vidal N. *P250GAP a new candidate gene for schizophrenia and psychosis-proneness?* Schizophrenia

Research, 153: 249. 4th Schizophrenia International Research Society Conference (Florence, 5-9 April 2014). **Poster**

2. de Castro-Catala M, Barrantes-Vidal N, **Peña E**, Kwapil TR, Cristóbal-Narváez P, Rosa A. *Impact of the schizophrenia candidate gene RGS4 on psychosis-proneness.* Schizophrenia Research, 153: 146. 4th Schizophrenia International Research Society Conference (Florence, 5-9 April 2014). **Poster.**
3. de Castro-Català M, **Peña E**, Cristóbal-Narváez P, Kwapil TR, Barrantes-Vidal N, Rosa A. *Psychotic-like experiences in non clinical samples and its association with several candidate genes for psychosis.* American Journal of Medical Genetics (in press). XXIInd World Congress of Psychiatric Genetics (Copenhagen, 12-16 October 2014). **Poster.**
4. Cristóbal-Narváez P, Sheinbaum T, Rosa A, Ballespí S, Mitjavila M, de Castro-Catala M, **Peña E,** Kwapil TR, Barrantes-Vidal N. *The interaction between bullying and FKBP5 haplotype on psychotic-like experiences and reactivity to stress: Does it matter in real life?* Schizophrenia Research (in press). 5th Schizophrenia International Research Society Conference (Florence, 2-6 April 2016). **Poster**

Conference communications published in abstract books

1. **Peña E**, de Castro-Català M, Burela PA, Barrantes-Vidal N, Rosa A. *Association between the candidate gene for schizophrenia p250GAP and schizotypy: study in healthy population*. Abstract book from the IX Edició dels Premis Gemma Rossell Romero / V Setmana de la Recerca, organised by the Associació d'Estudiants de Ciències de la Salut (AECS). Facultat de Medicina, Universitat de Barcelona (May 7-9th, 2013). **Oral communication**
2. de Castro-Català M, Moreno A, Ros-Morente A, **Peña E**, Burela PA, Kwapil TR, Barrantes-Vidal N, Rosa A. *Estudio de la variabilidad del gen de la COMT y su asociación con rasgos esquizotípicos y síntomas psicóticos en población sana.* Abstract book from the XVIII Congreso Internacional de la Sociedad Española de Antropología Física: Una mirada al futuro (Bilbao, June 19-21st, 2013). **Oral communication**
3. de Castro-Catala M, **Peña E**, Mora A, Sheinbaum T, Cristóbal-Narváez P, Kwapil TR, Barrantes-Vidal N, Rosa A. *Efecto Moderador de los genes en la expresión del fenotipo humano bajo el efecto de factores ambientales estresantes.* Abstract book from the XIX Congreso de la Sociedad Española de Antropología Física "Poblaciones humanas, genética, ambiente y alimentación" (Madrid, June 23-26th, 2015). **Oral communication**
4. Rosa A, Samper B, Herranz M, de Castro-Catala M, Martín M, **Peña E**, Torche F. *Estudio de la asimetría fluctuante en niños sometidos a estrés prenatal: el terremoto de tarapacá.* Abstract book from the XIX Congreso de la Sociedad Española de Antropología Física "Poblaciones humanas, genética, ambiente y alimentación" (Madrid, June 23-26th, 2015). **Oral communication.**
5. de Castro-Catala M, **Peña E**, Sheinbaum T, Cristóbal-Narváez P, Kwapil TR, Barrantes-Vidal N, Rosa A. *The FKBP5 and its moderating role on the psychosis-inducing effects of childhood trauma: new evidences from GxE studies.* 5th European Conference on Schizophrenia Research (Berlin, September 24-26th, 2015). **Poster.**
6. **Peña E**, de Castro-Catala M, Cristóbal-Narváez P, Sheinbaum T, Kwapil TR, Barrantes-Vidal N, Rosa A. *Moderating effect of the candidate gene p250GAP in the association between childhood trauma and psychosis liability.* 5th European Conference on Schizophrenia Research (Berlin, September 24-26th, 2015). **Poster**

7. de Castro-Catala M, Mora-Solano A, **Peña E**, Cristóbal-Narváez P, Barrantes-Vidal N, Rosa A. *Uso de polygenic risk scores para el studio de factores genéticos implicados en fenotipos no clínicos* XX Congreso de la Sociedad Española de Antropología Física "La Antropología Física en la era de la Genómica" (Barcelona, July 12-14th, 2017). **Oral communication.**
8. de Castro-Catala M, Mora-Solano A, **Peña E**, Cristóbal-Narváez P, Barrantes-Vidal N, Rosa A. *Utilidad de los estudios de asociación del genoma complete para la comprensión de los fenotipos complejos en la población sana.* XX Congreso de la Sociedad Española de Antropología Física "La Antropología Física en la era de la Genómica" (Barcelona, July 12-14th, 2017). **Oral communication.**
9. Planas S, Martín M, de Castro-Catala M, **Peña E**, Bastons-Compta A, Vall O, García-Algar O, Rosa A. *Estudio de las alteraciones de la asimetría fluctuante en niños expuestos a alcohol dorante su desarrollo prenatal.* XX Congreso de la Sociedad Española de Antropología Física "La Antropología Física en la era de la Genómica" (Barcelona, July 12-14th, 2017). **Oral communication.**
10. **Peña E**, de Castro-Catala M, Rivera M, Gutiérrez B, Cardoner N, Rosas A. *Depresión y envejecimiento prematuro: implicación de los telómeros.* XX Congreso de la Sociedad Española de Antropología Física "La Antropología Física en la era de la Genómica" (Barcelona, July 12-14th, 2017). **Oral communication.**
11. Ibaceta-Guerra N, Rosa A, **Peña E**, Vásquez R.A. *Oxytocin receptor gene (OXTR), childhood trauma and personality differences in a women population.* 32nd International Congress of Psychology (Prague, July 2021). **Poster** (Submitted)
12. León-Mengíbar J, Caixàs A, **Peña E**, Arenas C, Pareja R, Rigla M, R. Powell T, Cardoner N, Rosa A. *Influencia del polimorfismo BDNF Val66Met en la pérdida de peso tras un seguimiento de 24 meses de la cirugía bariátrica.* 61 congreso de la Sociedad Española de Endocrinología y Nutrición (SEEN) (Online, 14 -16 October 2020) **Poster**
13. Caixàs A, **Peña E**, R. Powell T, Cardoner N, Pareja R, Rigla M, Arenas C, Rebasa P, Luna A, Rosa A. *Efecto de la cirugía bariátrica sobre la longitud de los telómeros en una cohorte de pacientes obesos sometidos a cirugía bariátrica: seguimiento durante 2 años.* 61 Congreso de la Sociedad Española de Endocrinología y Nutrición (SEEN) (Online, 14 -16 October 2020) **Poster**

Oral communications

1. **Peña E.** *Connexion between mental illness, stress, obesity, inflammation and accelerated ageing: implications of telomeric length*. Eurolife Winter school 2018. Structure and function of genomes in homeostasis and disease. Obergurgl, Austria, 15th of December – 21st of December 2018.
2. **Peña E**, de Castro-Catala M, Rivera M, Gutiérrez B, Cardoner N, Rosas A. *Depresión y envejecimiento prematuro: implicación de los telómeros.* XX Congreso de la Sociedad Española de Antropología Física "La Antropología Física en la era de la Genómica" (Barcelona, July 12-14th, 2017). **Oral communication.**

Book chapters

1. de Castro-Català M, Moreno-Fortuny A, Ros-Morente A, **Peña E**, Burela PA, Kwapil TR, Barrantes-Vidal N, Rosa A. *Estudio de la variabilidad del gen de la COMT y su asociación con rasgos*

esquizotípicos y síntomas psicóticos en población sana. La investigación en antropología física: una mirada al futuro, p. 239-255 (ISBN: 978-84-9082-034-6).

2. de Castro-Catala M, **Peña E**, Mora A, Sheinbaum T, Cristóbal-Narváez P, Kwapil TR, Barrantes-Vidal N, Rosa A. *Moderating effect of genes in the human phenotype expression under the effect of environmental stressors.* Poblaciones Humanas, genética, ambiente y alimentación, p. 238-252 (ISBN: 978-84-617-4098-7).
3. Rosa A, Samper B, Herranz M, Martín M, de Castro-Catala M, **Peña E**, Torche F. *Study of fluctuating asymmetry in children exposed to prenatal stress: The earthquake of Tarapacá.* Poblaciones Humanas, genética, ambiente y alimentación, p. 47-64 (ISBN: 978-84-617-4098-7).
4. **Peña E**, de Castro-Catala M, Rivera M, Gutiérrez B, Crivillés S, Cardoner N, Rosa A. 2018. *Depresión y envejecimiento prematuro: implicación de los telómeros.* 262-272. En: Actas del XX Congreso de la Sociedad Española de Antropología Física. "La Antropología Física en la Era de la Genómica". ISBN: 978-84-948252-4-8
5. Planas S, Martín M, de Castro-Catala M, **Peña E**, Bastons-Compta A, Vall O, García-Algar O, Rosa A. 2018. *Study of fluctuating asymmetry alterations in children exposed to alcohol during their prenatal development.*274-285. En: Actas del XX Congreso de la Sociedad Española de Antropología Física. "La Antropología Física en la Era de la Genómica". ISBN: 978-84-948252-4-8
6. de Castro-Catala M, Mora-Solano A, **Peña E**, Cristóbal-Narváez P, Barrantes-Vidal N, Rosa A.2018. *Use of Polygenic Risk Scores in non-clinical phenotypes.*100-114. En: Actas del XX Congreso de la Sociedad Española de Antropología Física. "La Antropología Física en la Era de la Genómica". ISBN: 978-84-948252-4-8

14. de Castro-Catala M, Mora-Solano A, **Peña E**, Cristóbal-Narváez P, Barrantes-Vidal N, Rosa A. 2018. *The utility of Genome-Wide Association Studies for the comprehension of complex phenotypes in healthy populations.* 88-99. En: Actas del XX Congreso de la Sociedad Española de Antropología Física. "La Antropología Física en la Era de la Genómica". ISBN: 978-84-948252-4-8.

COURSES AND SEMINARS

1. IV Curso Intensivo de Introducción a la Investigación Básica en Neurociencias: el Cerebro en la Depresión (16 November 2012). Organized by Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB), Barcelona.
2. Advances in the Research of Intellectual Disabilities and Autism (23 November 2012). Organized by Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER). Aula Novartis, Barcelona.
3. Jornada sobre la Prevención de Riesgos en los laboratorios de Investigación (12 December 2012). Organized by Oficina de Seguridad, Salud y Medio Ambiente. Facultat de Física y Química (UB), Barcelona.
4. VII Curso Intensivo de Introducción a la Investigación Básica en Neurociencias: Actualización en investigación en trastornos del espectro autista (3 July 2013). Organized by Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB), Barcelona.
5. On-line curse "Drugs and the Brain" (10 February 2013). Organized by California Institute of Technology (CALTECH).

6. VIII Curso Intensivo de Introducción a la Investigación Básica en Neurociencias: Interacción Gen-Ambiente en la causalidad de la enfermedad mental (22 November 2013). Organized by Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB), Barcelona.
7. IV Jornada de cromatina y epigenetica. Organitzat pel la Secció de Biologia Molecular de la Societat Catalana de Biologia, Sala Prat de la Riba de l'Institut d'Estudis Catalans, 18 March 2014, 10 hours.
8. X Curso Intensivo de Introducción a la Investigación Básica en Neurociencias: Familia, genes y enfermedad mental: Mecanismos etiopatogénicos y avances metodológicos en su investigación (6 February 2015). Organized by Centro de Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB), Barcelona.
9. Jornada Institucional de Recerca de FIDMAG Germanes Hospitalàries. Organized by FIDMAG Germanes Hospitalaries, Fundació per a la Investigació i la Doncència Maria Angustias Gimenez (13 March 2015), Auditori Hospital Sant Rafael, Barcelona.
10. III Laboratorio de ideas para jóvenes investigadores: "Encontrando las sinergias en la investigación biomédica", (28-29 May 2015). Organized by Centro de Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB), Barcelona.
11. XI Curso Intensivo de Introducción a la Investigación en Neurociencias: Psicopatologia y neurobiología del estrés psicosocial (26 June 2015). Organized by Centro de Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB), Barcelona.
12. Curs d'estadística aplicat a ciències biològiques. Organized by the representative of PhD students of the Department of Animal Biology and held in the Facultat de Biologia (Universitat de Barcelona) on 25-27 January 2016.
13. VIII Jornada d'Actualització sobre el Transtorn Psicòtic Incipient: Estrès i Psicosi (15 April 2016). Organized by Comissió Pedagògica del Pla Director de Salut Mental i Addiccions. Hospital del Mar, Barcelona.
14. XII Curso Intensivo de Introducción a la Investigación bàsica en Neurociéncias: Nuevos paradigmes en la investigación de la enfermedad mental grave (22 April 2016). Organized by Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB), Barcelona.
15. XIII Curso Intensivo de introducción a la Investigación básica en Neurociéncias: The early origin of adult mental health (2 June 2016). Organized by Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB), Barcelona.
16. XIV Curso Intensivo de introducción a la Investigación básica en Neurociéncias: Cannabis y Enfermedad Mental (27 January 2017). Organized by Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB), Barcelona.
17. XV Curso Intensivo de introducción a la Investigación básica en Neurociéncias. The early origin of mental health (28 June 2017). Organized by Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB), Barcelona.
18. XVI Curso Intensivo de introducción a la Investigación básica en Neurociéncias. Estrés oxidativo e inflamación en enfermedad mental ¿Causa o consecuencia? (27 April 2018) Organized by Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB), Barcelona.

19. XVII Curso Intensivo de Introducción a la Investigación en Neurociencias. Neuroendocrinología del trastorno mental infanto-juvenil (10 May 2019). Organized by Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB), Barcelona

AWARDS RECEIVED

Name:	**IX Edition of the Gemma Rossell i Romero Awards / IV Research Week.**
Title:	Association between the candidate gene for schizophrenia p250GAP and schizotypy: Study in healthy population (Finalist)
Organization:	Premi Gemma Rossell i Romero
Place and date:	Facultat de Medicina de la Universitat de Barcelona, 7- 9 de May 2013.

Name:	**Awards of the Societat Catalana de Biologia 2014 (51st call). Call of Sant Jordi 2014 awards**
Title:	Vulnerabilitat per psicosi mesurada en població sana catalana: el gen p250GAP (Psychosis vulnerability in a Catalan healthy sample: the p250GAP gene.
Organisation:	Societat Catalana de Biologia (Institut d'Estudis Catalans).
Place and date:	Barcelona 22 April 2014. Institut d'Estudis Catalans, Barcelona

GRANTS

Name:	**Beca de suport als Màsters Oficials de Biologia.**
Organization:	Universitat de Barcelona
Place:	Facultat de Biologia, Universitat de Barcelona
Period:	1st of march of 2016 – 31st of July 2018.
Activity:	Support: i) maintenance of master website ii) coordination of GRAD programme iii) orders preparation iv) surveys analysis and v) support in pre-enrolment and enrolment process.

Name:	**Eurolife Winter school 2018 grant.**
Organization:	Comité Eurolife
Place:	Obergurgl (Austria)
Period:	15th of December – 21st of December 2018.
Activity:	Structure and function of genomes in homeostasis and disease.

Name:	**Grant for a predoctoral stay**
Organization:	Fundació Montcelimar. Universitat de Barcelona
Place:	Social, Genetic and Developmental psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London
Period:	2nd of July – 22nd of September 2019.

Name:	**Beca de col·laboració en projectes de recerca.**
Organization:	Fundació Bosch i Gimpera. Universitat de Barcelona
Place:	Secció de Zoologia i Antropologia Biològica. Dept. Biologia Evolutiva, Ecologia i Ciències Ambientals. Facultat de Biologia. Universitat de Barcelona, Spain.
Period:	11th of November of 2019 – 15th of March of 2020.
Activity:	Collaboration in the project 600065 "Genes, ambiente y Desarrollo: Una visión longitudinal en la comprensión del origen de la enfermedad mental y la diversidad del comportamiento humano" directed by Dra. Lourdes Fañanás.