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REVIEW

Revisiting the Ghrelin Changes Following Bariatric and Metabolic Surgery

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Abstract

Since the description of ghrelin in 1999, several studies have dug into the effects of this hormone and its relationship with bariatric surgery. While some aspects are still unresolved, a clear connection between ghrelin and the changes after metabolic surgery have been established. Besides weight loss, a significant amelioration in obesity-related comorbidities following surgery has also been reported. These changes in patients occur in the early postoperative period, before the weight loss appears, so that amelioration may be mainly due to hormonal changes. The purpose of this review is to go through the current body of knowledge of ghrelin's physiology, as well as to update and clarify the changes that take place in ghrelin concentrations following bariatric/metabolic surgery together with their potential consolidation to outcomes.

Keywords Ghrelin · Diet-induced obesity · Bariatric/metabolic surgery · Comorbidity resolution

Introduction

The description of ghrelin in 1999 opened up the field of gastrointestinal hormones participating in appetite control [1]. Subsequently, ghrelin has been also identified as one of the gut-derived hormones involved in changes after bariatric surgery [2]. However, the body of evidence generated so far has not been able to clearly establish the exact role of the changes in ghrelin following bariatric surgery and their relationship with the observed outcomes and their chronology after the surgical interventions. Therefore, the aim of the present review is to provide an accurate and balanced view of the physiological regulation of ghrelin first, in order to better analyse the changes in ghrelin after bariatric and metabolic surgery as well as to better understand the outcomes observed. This approach provides novel insights together with an improved understanding of the specific pathophysiological conditions changed by the interventions and the surgery-induced effects of ghrelin.

Methods

Briefly, we searched from 1999 the Pubmed/MEDLINE database using the following Medical Subject Headings (MeSH)

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"ghrelin" combined with "bariatric surgery", "mini gastric bypass", "adjustable gastric banding", "sleeve gastrectomy", "gastric bypass", "biliopancreatic diversion" and "duodenal switch". The language of full texts was limited to English. We excluded not relevant articles, studies with animals, letter or reply and reviews. Randomised controlled trials and prospective studies were included. The PRISMA flow (Fig. 1) was applied for the selection of articles.

Ghrelin Physiology

Ghrelin Structure

Ghrelin is a 28-amino acid peptide hormone whose name derives from the Protoindoeuropean word "ghre-" meaning growth and "-relin" meaning secretion [1]. The human gene that codifies this peptide is localised on the short arm of chromosome 3, at locus 3p25-26. Ghrelin is a pleiotropic hormone that exerts a wide variety of functions *(*Fig. 2*)* [2–4]. It is mainly secreted by the neuroendocrine cells of the oxyntic glands located in the mucosa layer of the gastric fundus. In lower quantities, ghrelin is also expressed in the hypothalamic arcuate nucleus neurons, pituitary, pancreas, adrenal gland, lung, skeletal muscle, ovary, testis and small bowel, with its expression decreasing from duodenum to colon [2]. Tschöp et al. described in 2000 that ghrelin acts in the brain regulating food intake, body weight, adiposity and glucose homeostasis [5]. Ghrelin has largely been described as a "hunger hormone" but increasingly studies have shown the complex role this hormone exerts in the organism through either central or peripheral pathways.

Proghrelin is acylated in the endoplasmic reticulum by ghrelin-*O*-acyltransferase and then matures in the Golgi apparatus where it is released in two forms: acylated and desacylated ghrelin (DAG). Acylated ghrelin (AG) accounts for approximately 5% of total ghrelin concentrations and is the endogenous ligand for the growth hormone secretagogue receptor (GHS-R1a), capable of stimulating growth hormone (GH) release due to a *n*-octanoyl group on serine 3 (Ser3) [2]. DAG (95% of total ghrelin) was originally described as a biologically inactive metabolite of AG. Later, it was suggested that DAG was able to exert metabolic and endocrine responses per se, and even more, antagonize AG effects on insulin secretion and glucose metabolism [4]. Table 1 summarises the main effects of each ghrelin isoform that will be developed in detail along the text.

Ghrelin Receptors

Two ghrelin receptors have been described: the GH secretagogue receptors GHS-R1a and GHS-R1b. At physiological concentrations, only AG binds to GHS-R1a, while some studies describe that at supraphysiological conditions, DAG is also capable of binding this receptor [2, 6]. On the contrary, neither AG nor DAG bind GHSR-1b, so that at the beginning it was considered an inactive receptor [7].

Ghrelin Secretion

Ghrelin release is mediated through multiple physiological processes. However, evidence to date is scarce, and it is still a matter of debate. Ghrelin increases pre-prandially and decreases within the first hour after meal initiation in response to caloric intake and macronutrients showing a higher decrease after a carbohydrate meal compared to fat intake [8]. The release of ghrelin is regulated by the autonomous nervous system, with both adrenergic and cholinergic pathways being involved. Zhao et al. showed in mice that ghrelin-producing

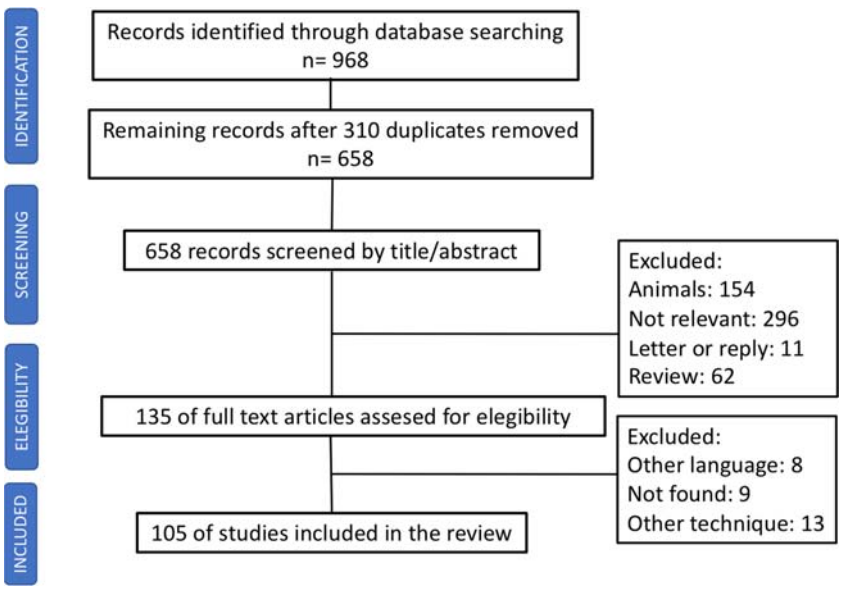

Fig. 1 PRISMA flow diagram for the selection of the original articles for the review

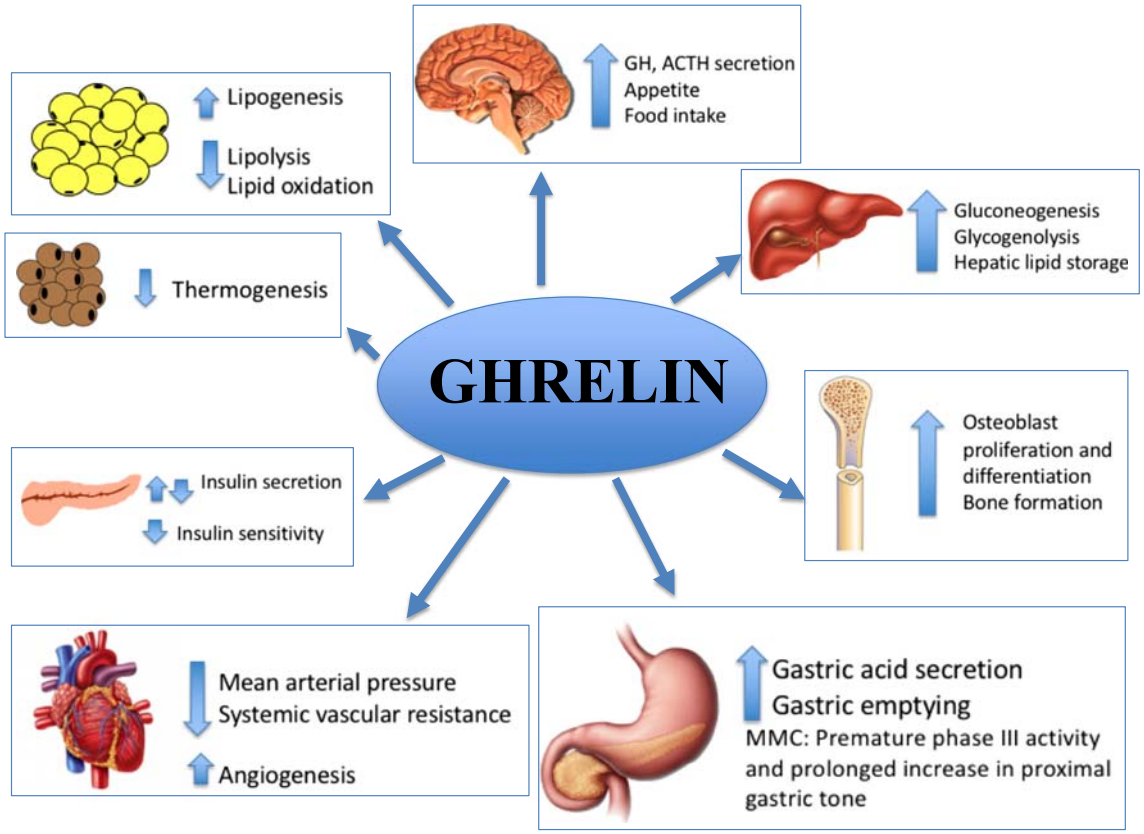

Fig. 2 Central and peripheral ghrelin actions. MMC migrating motor complex

cells have beta1-adrenergic receptors and that in the fasting state ghrelin secretion is mediated through the sympathetic nervous system [9]. Epinephrine and norepinephrine increase ghrelin release, unlike atenolol (a beta1-adrenergic antagonist) that decreases its levels. Additionally, the relationship between the cholinergic system and ghrelin release has been confirmed. Vagotomyzed rats exhibit a decrease in plasma ghrelin concentrations. Furthermore, cholinergic agonists such as pyridostigmine also stimulate ghrelin release while cholinergic antagonists (pirenzepine) decrease ghrelin concentrations in humans [10].

Regarding the postprandial ghrelin decrease, neither gastric distension nor detection of macronutrients in the stomach was enough to decrease the levels. Contrarily, after the direct infusion of nutrients in the duodenum or jejunum of mice, a rise in ghrelin concentrations was demonstrated [11]. These findings may be explained by the type of cells; while in the stomach closed-type cells, without direct contact with the lumen are

Table 1 Main effects of acyl and desacyl ghrelin

Acyl ghrelin Main effect	Evidenced in	Desacyl ghrelin Main effect	Evidenced in
Decreases insulin sensitivity	Humans	Improves insulin sensitivity	Humans
Increases plasma glucose levels	Humans	Decreases plasma glucose levels	Humans
Stimulates food intake	Humans	Decreases food intake	Rodents
Increases gastric motility	Humans	Decreases gastric emptying	Rodents
Release of GH	Humans		
Release of ACTH/cortisol	Humans		
Release of prolactin	Humans		
↑ lipogenesis/↓ lipolysis	Humans	↑ lipogenesis/↓ lipolysis	Humans
Protective effect on muscle atrophy	Rodents	Protective effect on muscle atrophy	Rodents
Cardioprotective effect	Humans	Cardioprotective effect	Humans

found those along the gastrointestinal tract are opened-type cells, with direct contact [2]. Furthermore, ghrelin release is blunted by gastrointestinal hormones (such as somatostatin, GIP, GLP-1, PYY and CCK) and certain metabolites (including triglycerides and total parenteral nutrition). Thus, ghrelin stimulation is mediated through neuroendocrine signals, whereas its suppression is modulated by macronutrients and paracrine factors [12].

GOAT/GO-CoA-Tat

Ghrelin-*O*-acyltransferase (GOAT), described in 2008, is a membrane-bound enzyme, that octanoylates the Ser3 of the ghrelin peptide enabling AG to bind GHS-R1a [13]. GOAT appears to be predominantly expressed in stomach, brain and pancreas with its expression increasing in positive energy balance situations, such as obesity, while decreasing in anorexic patients when compared with lean controls. There is a direct correlation between GOAT expression and body mass index (BMI) together with an inverse relationship with ghrelin [2, 14, 15]. GO-CoA-Tat is an enzyme described in 2010 by Barnett et al. with a potent inhibitory effect of GOAT. It catalyses the binding of the *n*-octanoic acid with ghrelin rising DAG levels [16]. Furthermore, human treatment with GO-CoA-Tat decreases appetite and increases glucose-induced insulin secretion and sensitivity [17, 18] by diminishing AG levels.

Obestatin

Obestatin is a 23-amino acid peptide encoded by the ghrelin gene with controversial effects on food intake. Like ghrelin, it is mainly produced by the stomach, as well as by a wide range of other tissues [19] and its levels decrease in the postprandial period in both normal weight and borderline individuals with obesity [19, 20]. Obestatin was initially shown to antagonise ghrelin effects, suppressing food intake, and decreasing body weight gain in rats [21], but subsequently several studies failed to reproduce the anorexigenic effect of this hormone [22]. However, in certain circumstances, obestatin can inhibit ghrelin effects on food intake and on GH secretion in humans and promotes survival and proliferation of pancreatic beta cells preventing its apoptosis [23]. Fasting obestatin plasma levels of individuals with obesity have shown to be significantly lower as compared to lean controls [24, 25].

The relationship between obestatin and bariatric surgery outcomes remains controversial. Some studies show an increase in obestatin levels after Roux-en-Y gastric bypass (RYGBP) [24, 26] while others do not describe differences in obestatin concentrations when compared to controls [27]. Moreover, a decrease in the ghrelin/obestatin ratio has been described in patients who underwent bariatric surgery [27], while no changes are described by others [26].

Ghrelin and Obesity

Food Intake

AG exerts its hypothalamic action in three different ways: via the systemic circulation crossing the blood-brain barrier, via vagal afferent nerves and via local synthesis in the hypothalamus where it exerts a paracrine effect [28]. Ghrelin acts via neuropeptide Y (NPY) and agouti-related peptide (AgRP) on the hypothalamic nucleus arcuatus increasing appetite, food intake and, therefore, body weight. Ghrelin secretion in lean patients follows a circadian rhythm rising before meals [29] and decreasing after food intake. Furthermore, postprandial suppression is related to the caloric intake and meal composition [30]. Under circumstances of negative energy balance, such as anorexia nervosa, total ghrelin concentrations remain high and do not change after food intake suggesting insensitivity to this endocrine signal [31].

Diet-Induced Obesity

Obesity results from an imbalance between energy intake and expenditure. The increased adiposity produced by diet-induced obesity (DIO) blunts the neuronal responses to metabolic challenges in hypothalamic centres which control feeding behaviour and energy balance. Furthermore, DIO desensitises ghrelin-secreting cells to physiological signals of caloric restriction and food intake [12]. Ghrelin secretion and plasma ghrelin levels are reduced in subjects with obesity compared to normal body weight controls, as a physiological adaptation to a positive energy balance [32]. Indeed, ghrelin does not decrease in response to meals in individuals with obesity as it does in lean subjects [33] contributing to reduce satiety and overeating [34]. Moreover, weight cyclers have increased ghrelin levels leading to a more appetite-stimulating profile and promoting weight regain [35]. A difference in both isoform concentrations has also been described, with lower DAG concentrations compared to lean controls and, therefore, an increase in the AG/DAG ratio being observed [36, 37]. BMI and waist circumference were positively correlated with AG levels [36].

The ghrelin resistance caused by DIO arises from reduced NPY/AgRP responsiveness to plasma ghrelin and the neuroendocrine ghrelin axis signalling, which operates at a diminished capacity. Thus, DIO may be induced by hyperphagia [15]. Other studies argue that peripheral ghrelin resistance is associated with inflammation in the nodose ganglia of high-fat diet-fed mice, resulting in an impairment of the vagal afferent system [38]. DIO also impairs the release of GH and alters the blood-brain barrier permeability [39].

Weight loss after DIO resensitises the brain to ghrelin by increasing total plasma ghrelin and AG, thereby indicating a reversal of the ghrelin resistance triggered by DIO following

diet-induced weight loss [12]. However, it may take more than 12 months for ghrelin to return to normal levels after weight loss [40]. Energy homeostasis is affected by negative energy balance signals rather than by body weight per se. Long-term DIO changes the body weight set-point with ghrelin counteracting this effect [12, 40].

Ghrelin regulates short-term effects on weight loss mediating appetite and meal initiation. Furthermore, ghrelin concentrations are directly related to body energy stores and change according to energy balance. Besides, ghrelin influences neuronal activity in the brain regulating body weight and its exogenous administration alters food intake. All these roles are possibly related to long-term weight loss; however, the literature is inconsistent in this regard [41]. Some studies describe a persistent increase in ghrelin concentrations after 1 year of diet-induced weight loss suggesting that weight regain is partly due to physiological reasons [40, 42]. Others, instead, observe a return to normal values, indicating ghrelin is only related to short-term outcomes [43].

Regarding bariatric surgery, sleeve gastrectomy patients experience a long-term ghrelin decrease [44]. Nevertheless, a meta-analysis performed with 16 studies regarding ghrelin levels after RYGBP concludes that fasting ghrelin concentrations change according to the time course of the surgery. Ghrelin decreases in the short term (< 3 months) and then, in the long term (> 3 months) rises significantly. Ghrelin levels increase as weight loss continues to decrease concluding that ghrelin is not directly involved in the long-term weight loss effect of RYGBP [45]. Nevertheless, it has to be stated that physiological functions such as appetite and body weight control are regulated by multifactorial influences in order to allow survival of the species. Thus, ghrelin together with the neuroendocrine factors modulates the response to weight change and homeostasis. In addition, in humans, a large interindividual variability in ghrelin and other hormones in response to interventions take place, which we are currently investigating in our research group. Other mechanisms, such as nutritional education, exercise and fear of becoming obese again, may also influence the long-term weight loss effects.

Ghrelin and Glucose Metabolism

Ghrelin regulates glucose metabolism through pancreatic GHS-R1a. AG decreases insulin secretion and increases glucose plasma levels and glucagon release. Instead, DAG shows beneficial effects on insulin sensitivity and secretion, through GHSR-independent mechanisms [46, 47]. After AG administration in healthy volunteers, there is an impairment in glucose tolerance, a suppression of glucose-stimulated insulin release and a rise in GH, glucagon and cortisol secretion [48, 49]. In accordance with these findings, plasma glucose levels are decreased in mice lacking ghrelin in comparison to controls [50]. In humans, the increase in blood glucose in response to ghrelin administration was blunted after RYGBP compared with a normal response before surgery [51]. Furthermore, ghrelin deletion improves glucose sensitivity and enhances glucose-stimulated insulin secretion [50].

After a 7-day calorie restriction diet in mice, blood glucose was maintained as long as ghrelin was produced. During starvation, ghrelin levels rose higher each day keeping plasma GH levels high and assuring enough glucose blood concentrations to prevent death. In accordance with that, the GOAT mechanism plays a key role avoiding hypoglycemia after a calorie restriction diet [52]. Furthermore, some authors conclude that ghrelin is not essential for hunger during starvation because studies did not show robust changes in food intake in ghrelin-deficient mice compared to controls, supporting that ghrelin's main function is controlling blood glucose levels [52]. However, other groups do not consider that the GOAT/ghrelin system is essential for preventing hypoglycemia because there are other counter-regulatory mechanisms that take part in order to avoid it [49]. Pharmacological inhibition of ghrelin, administrating GHSR1a antagonists, inverse agonists or inhibiting GOAT, may improve glycemic control by increasing glucose-stimulated insulin release and ameliorating glucose sensitivity [49].

Adiposity

Another pivotal action of ghrelin is the stimulation of adiposity, independently of food intake or GH secretion, suggesting the existence of different neuronal pathways controlling feeding and adiposity [5, 53]. An increase in adiposity and body weight is observed in rodents after ghrelin administration either centrally or peripherally [54]. Furthermore, ghrelin administration to mouse white adipocytes, stimulated triglyceride uptake, increased lipogenesis and inhibited lipid oxidation [53, 54]. In addition, via a non-type 1a GH secretagogue receptor both ghrelin isoforms antagonise the catecholamine-stimulated lipolysis in humans [55]. In fact, AG and DAG reportedly stimulate lipid accumulation within the cytoplasm at the same time as exhibiting an anti-lipolytic effect. Noteworthy, ghrelin reportedly promotes the proliferation of human primary preadipocytes via an IGF-1 expression increase [56]. Concerning ghrelin isoforms at the central level, both AG and DAG increase adiposity in individuals independently of the hyperphagic effect [36]. Moreover, in rats, DAG in the brain mimics the effect of AG on adiposity and hyperinsulinemia but without significant effects on other parameters that are regulated by central AG such as food intake [57]. Not surprisingly, ghrelin might be involved in the relationship between cardiometabolic risk and adipose tissue inflammation [58].

The effects on adiposity can further be observed at the liver level with increasing hepatic lipid storage leading to the development of obesity-associated NAFLD. Ghrelin represents

a protective factor that counteracts hepatocyte cell death. In fact, the elevated AG/DAG ratio in patients with obesity and NAFLD might be contemplated as a compensatory mechanism to overcome hepatocyte apoptosis, autophagy, and pyroptosis induced by TNF-α [59]. Interestingly, AG and DAG inhibit steatosis and inflammation of hepatocytes, whereby the increased relative AG concentrations following bariatric surgery potentially contribute to mitigate obesity-associated hepatic inflammation, mitochondrial dysfunction and endoplasmic reticulum stress [58, 59].

Cardiovascular Functions

Ghrelin is present in human cardiomyocytes and exerts different actions on the cardiovascular (CV) system exhibiting cardioprotective effects. Although the mechanisms underlying ghrelin actions on the CV system remain unclear, there are indications that its beneficial effects are mediated through both direct physiological actions, including increased GH levels and improved energy balance, and regulation of the autonomic nervous system activity [60].

Ghrelin is able to block the renin-angiotensin system improving hypertension and cardiovascular disorders. Indeed, chronic treatment with ghrelin decreases mean arterial pressure and systemic vascular resistance in chronic heart failure without increasing heart rate, because its administration decreased norepinephrine plasma levels meanwhile epinephrine levels were increased [61–63]. Moreover, ghrelin treatment reduces cardiac sympathetic nerve activity, inflammation and oxidative stress in the heart, and induces angiogenesis [4]. Furthermore, ghrelin administration protects against ischemia and reperfusion injury, attenuates post-infarction ventricular dysfunction and remodelling improving the prognosis of myocardial infarction and heart failure [60, 62, 63].

Bariatric and Metabolic Surgery

Adjustable Gastric Banding

Ghrelin levels following adjustable gastric banding (AGB) are summarised in Table 2. Leonetti et al. [64] described lower ghrelin concentrations in patients who underwent AGB in comparison with normal weight controls and individuals with obesity. Others, however, do not describe significant changes in the postoperative ghrelin levels during a follow-up of at least 12 months [65]. Shak et al. [66] observe that fasting levels of acylated and total ghrelin do not change after the AGB-induced weight loss. They conclude that this surgical technique has a direct effect suppressing the increase in ghrelin that should take place after losing weight. Noteworthy, most studies describe an increase in ghrelin concentrations during a follow-up from 6 months to 4 years [67–70]. Some of them describe lower ghrelin levels than the ones expected due to AGB-induced weight loss, so they conclude that AGB affects somehow the release of ghrelin [71–73]. Kruljac et al. [74] highlight the fact that people with obesity who undergo AGB have increased satiety in spite of the increasing ghrelin, an orexigenic peptide. They hypothesise that changes in ghrelin levels after AGB may be a consequence of gastric fundus manipulation. Schindler et al. [78] explain that the weight loss after AGB is independent of ghrelin levels and relies on changes in eating behaviour. Other studies instead defend that the increase observed in ghrelin levels depend on the weight loss that takes place after this type of surgery, discarding any direct effect of AGB on ghrelin levels [75–77]. These findings are in accordance with other studies that show a rise in circulating ghrelin levels in patients with diet-induced weight loss [78, 79] concluding that ghrelin increases after procedures involving restriction or dietary intervention, providing thereby an explanation for the lack of success of these approaches regarding long-term weight loss.

Vertical Sleeve Gastrectomy

Although classified as a restrictive procedure, the vertical sleeve gastrectomy (VSG) has proven to go beyond mere restriction, triggering significant changes in ghrelin (briefly described in Table 3) and other gut hormones, and showing comparable outcomes with RYGBP in short-term weight loss and metabolic resolutions [80, 81]. In the VSG, the main ghrelin source, the gastric fundus, is removed, thereby substantiating the need for functional integrity of the fundus for adequate ghrelin release [82, 83]. Several studies have described a decrease in fasting and postprandial plasma ghrelin levels in comparison to non-surgical controls in the short and long term [44, 84–88]. Moreover, in the VSG, the removal of the greater curvature of the stomach leads to impaired gastrointestinal motility. This translates into an acceleration of gastric emptying and an early chyme delivery, enhancing distal small intestine stimulation [89, 90], where several gut hormones such as GLP-1 and PYY increase achieving satiety, weight loss and glucose metabolism improvement [44, 80, 86, 87]. However, a recent MRI study analysed gastric motility before and after VSG, without showing changes in antral motility before and after the surgery, not showing peristalsis in the sleeve stomach [91].

Roux-en-Y Gastric Bypass

RYGBP is one of the most effective approved treatments for obesity [92], reducing body weight due to, among others, its restrictive and malabsorptive mechanisms. Furthermore, behavioural changes after RYGBP have also been described, including loss of appetite, decrease in meal frequency and reduced consumption of high-calorie foods despite profound negative energy balance, suggesting the activation of other

Table 2 Ghrelin changes after adjustable gastric banding and other bariatric surgery procedures

Author	Year	Type of study	*N*	Bariatric procedures	Follow-up	Changes	Ghrelin measured	State
Leonetti	2003	Case control	47	AGB (10) RYGBP (11)	12 months	Fasting: lower ghrelin after AGB and RYGBP than after controls* PP: NSC	TG	F and PP
Frühbeck	2004	Case control	24	AGB (8) RYGBP (8)	6 months	Diet: high AGB: high RYGBP: low*	AG	Fasting
Dixon	2004	Case control	34	AGB (17)	26 months	NSC	TG	F and PP
Hanusch-Enserer	2004	Prospective no randomised	18	AGB (18)	12 months	High*	TG	Fasting
Mariani	2005	Prospective no randomised	30	AGB (30)	36 months	Similar	TG	Fasting
Nijhuis	2004	Prospective no randomised	17	AGB (10) VBG (7)	24 months	AGB: high* VBG: high*	TG	Fasting
Schindler	2004	Case control	23	AGB (23)	6 months	High*	TG	Fasting
Stoeckli	2004	Prospective no randomised	20	AGB (8) RYGBP (5)	24 months	AGB: high* RYGBP: NSC	AG	Fasting
Langer	2005	Prospective no randomised	20	AGB (10) SG (10)	6 months	AGB: high* SG: low*	TG	–
Ram	2005	Prospective no randomised	23	AGB (23)	14 months	High (NS)	TG	Fasting
Rodieux	2008	Case control	22	AGB (6) RYGBP (8)	–	Fasting: NSC PP: enhanced suppression after RYGBP*	TG	F and PP
Shak	2008	Prospective no randomised	24	AGB (24)	12 months	Similar (AG and TG)	AG and TG	Fasting
Korner	2009	Prospective no randomised	43	AGB (15) RYGBP (28)	12 months	AGB: NSC Fasting—RYGBP: low PP—RYGBP: NSC	TG	F and PP
Bose	2010	Prospective no randomised	20	AGB (9) RYGBP (11)	12 months	Fasting—AGB: high (NS) Fasting—RYGBP: high (NS) PP—AGB: high (NS) PP—RYGBP: high (NS) AUC—RYGBP: high*	TG	F and PP
Plum	2011	Prospective no randomised	31	AGB (8) RYGBP (16)	–	NSC	TG	F and PP
Gelisgen	2012	Case control	37	AGB (21)	6 months	High*	AG	Fasting
Hady	2012	Prospective no randomised	100	AGB (100)	6 months	High*	TG	Fasting
Krieger	2012	Prospective no randomised	30	AGB (30)	12 months	Similar	TG	Fasting
Lips	2014	Case control	66	AGB (11) RYGBP (31)	3 weeks	F and PP—AGB: NSC Fasting RYGBP: low* AUC RYGBP—NG: high* AUC—RYGBP DM: low*	TG	F and PP
Kruljac	2016	Prospective no randomised	51	AGB (21) SG (15) RYGBP (15)	12 months	AGB: high* SG: similar RYGBP: similar	TG	Fasting
Wroblewski	2016	Case control	67	Endoscopic (25) AGB (10) SG (32)	12 months	Low*	TG	–

AGB adjustable gastric banding, *VBG* vertical banded gastroplasty, *SG* sleeve gastrectomy, *RYGBP* Roux-en-Y gastric bypass, *TG* total ghrelin, *AG* acyl ghrelin, *F* fasting, *PP* postprandial, *NSC* nonsignificant changes; *statistically significant

Table 3 Ghrelin changes after sleeve gastrectomy and other bariatric surgery procedures

Author	Year	Type of study	*N*	Bariatric procedures	Follow-up	Changes	Ghrelin measured	State
Karamanakos	2008	RCT	32	SG (16) RYGBP (16)	12 months	Fasting—SG: low* PP—SG: low* Fasting—RYGBP: NSC PP—RYGBP: NSC	TG	F and PP
Peterli	2009	RCT	27	SG (14) RYGBP (13)	3 months	Fasting SG: low* Fasting—RYGBP: low* PP SG & RYGBP: Low*	TG	F and PP
Bohdjalian	2010	PNR	26	SG (26)	5 years	Low*	TG	–
Ramon	2011	RCT	15	SG (8) RYGBP (8)	12 months	Fasting—SG: low* Fasting—RYGBP: NSC PP SG and RYGBP: NSC	TG	F and PP
Goitein	2012	PNR	20	SG (20)	3 months	Low*	TG	Fasting
Hady	2012	PNR	100	SG (100)	6 months	Low*	TG	Fasting
Peterli	2012	RCT	23	SG (11) RYGBP (12)	12 months	SG: low* RYGBP: NSC	TG	F and PP
Dimitriadis	2013	Case control	30	SG (15)	12 months	Fasting: low* PP: low*	AG	F and PP
Haluzikova	2013	Case control	32	SG (17)	24 months	Low*	AG	Fasting
Nannipieri	2013	PNR	35	SG (12) RYGBP (23)	12 months	Fasting SG: low* Fasting RYGBP: low* PP SG: low* PP RYGBP: low*	DAG	F and PP
Palikhe	2013	PNR	31	SG (14)	6 months	Low*	TG	Fasting
Terra	2013	Case control	90	SG (17) RYGBP (13)	12 months	SG: high (NS) RYGBP: high (NS)	TG	Fasting
Yousseif	2013	PNR	18	SG (8) RYGBP (10)	3 months	Fasting—SG: low* PP—SG: NSC Fasting—RYGBP: NSC PP—RYGBP: NSC	AG	F and PP
Buzga	2014	PNR	37	SG (37)	12 months	Low*	TG	Fasting
Carrasco	2014	PNR	43	SG (20) RYGBP (23)	12 months	SG: low* RYGBP: NSC	TG	Fasting
Malin	2014	RCT	53	SG (19) RYGBP (18)	24 months	Fasting—SG: low* Fasting—RYGBP: NSC PP SG and RYGBP: low*	AG	F and PP
Braghetto	2015	PNR	16	SG (16)	12 months	Low (NS)	AG	–
Major	2015	PNR	35	SG (16) RYGBP (19)	12 months	SG: low* RYGBP: low*	TG	Fasting
Mans	2015	Case control	40	SG (8)	6 months	Fasting: low* PP: low*	TG	F and PP
Alamuddin	2016	Case control	64	SG (18) RYGBP (23)	18 months	Fasting—SG: low* Fasting—RYGBP: high* PP: NSC	TG	F and PP
Dogan	2016	PNR	30	SG (30)	6 months	High*	TG	–
Farey	2016	Case control	33	SG (11)	3 months	Low*	TG	Fasting
Kalinowski	2016	PNR	72	SG (36) RYGBP (36)	12 months	SG: low* RYGBP: high*	TG	Fasting
Nosso	2016	PNR	33	SG (19) RYGBP (14)	12 months	Fasting—SG: low* PP—SG: low* Fasting—RYGBP: NSC PP—RYGBP: NSC	TG	F and PP
Ozmen	2016	PNR	80	SG (40) OAGB (40)	3 months	SG: low* OAGB: similar	–	–
Vigneshwaran	2016	PNR	20	SG (20)	6 months	Fasting: low* Decreased AUC*	TG	F and PP
Buzga	2017	PNR	127	SG (84) GCP (43)	18 months	SG: low* GCP: high*	TG	Fasting
Arhire	2018	PNR	75	SG (75)	12 months	Low (NS)	AG	Fasting
Holsen	2018	PNR	18	SG (18)	12 months	Low*	AG	Fasting

Table 3 (continued)

Author	Year	Type of study	*N*	Bariatric procedures	Follow-up	Changes	Ghrelin measured	State
Sethi	2018	PNR	70	SG (70)	6 months	Low*	TG	Fasting
Sharma	2018	PNR	90	SG (90)	6 months	Low*	TG	Fasting
Sista	2018	PNR	91	SG (91)	36 months	F and PP: low*	TG	F and PP
Yang	2018	PNR	20	SG (10) RYGBP (10)	12 months	LSG: low* RYGBP: NSC	TG	Fasting
Yin	2018	PNR	60	SG (60)	12 months	Low*	TG	–
Zhang	2018	Case control	56	SG (30)	1 month	Low*	TG	Fasting
Li	2019	Case control	41	SG (22)	1 month	Low*	TG	Fasting
Svane	2019	Case control	36	SG (12) RYGBP (12)	–	Lower levels fasting and PP after LSG than RYGBP and controls*	TG and AG	F and PP

RCT randomised controlled trial, *PNR* prospective nonrandomised, *TG* total ghrelin, *AG* acyl ghrelin, *DAG* desacyl ghrelin, *F* fasting, *PP* postprandial, *GCP* greater curvature plication, *SG* sleeve gastrectomy, *RYGBP* Roux-en-y gastric bypass, *OAGB* one anastomosis gastric bypass, *NSC* nonsignificant changes; *statistically significant

pathways, especially by hormonal changes among which ghrelin secretion stands out [93] (Table 4). The effect of RYGBP on ghrelin concentrations has been widely studied showing controversial results [94]. On the one hand, some groups report a significant decrease in ghrelin levels (fasting and postprandial) after RYGBP when compared to obese and lean controls [68, 76, 82, 83, 95–100]. This reduction starts already within 24 h after gastric bypass and extends even 5 years after the surgical procedure. These low levels of ghrelin after RYGBP could determine the increased satiety and reduced food intake, helping to explain the long-term effects this surgery exerts in patients with severe obesity. However, other studies have not observed changes in ghrelin after RYGBP, suggesting its unlikely contribution to the suppression of food intake in the postoperative stage [74, 86, 101]. Others, instead, have reported higher ghrelin concentrations after RYGBP than before surgery [77, 85, 102] and even more, Barazzoni et al. [103] suggest that RYGBP not only fails to normalise but also enhances excess AG levels, impairing glucose homeostasis and increasing body weight.

One plausible explanation for the diverse results regarding RYGBP and ghrelin may be the differences in the surgical technique like the length of the alimentary limb or the size of the new gastric pouch. In this context, our group was the first to report that the reduction in circulating ghrelin concentrations after bariatric procedures depends on the degree of fundus exclusion and the isolation of ghrelin-producing cells from direct contact with ingested nutrients [76, 82, 83]. Noteworthy, we further showed a dramatic decrease in ghrelin concentrations already 24 h after RYGBP supporting a direct effect irrespective of body weight loss [82]. Another group performed a prospective study comparing patients who underwent two types of RYGBP, one preserving food contact with the gastric fundus and another avoiding it [104]. They did not find significant differences in ghrelin concentrations between both procedures, suggesting food contact with ghrelin-producing cells is not the only explanation for stimulating ghrelin secretion.

An alternative hypothesis to the discordant results in ghrelin concentrations after RYGBP may be due to the absence of consensus regarding vagal denervation between surgeons. It has been reported that the blockage of the vagal impulses by atropine reduced ghrelin levels and, moreover, in vagotomised subjects, the exogenous administration of ghrelin did not increase food intake [105, 106]. Sundbom et al. [107] measured ghrelin and pancreatic polypeptide (PP), an indicator of vagal functionality, in subjects after RYGBP, observing a correlation between both hormones, although the decrease in ghrelin concentrations was transitory with a return to preoperative levels, suggesting vagal denervation may influence ghrelin secretion but does not explain the whole effect of RYGBP on weight loss.

A further explanation for ghrelin variations may be due to the amount of weight loss and the presence of an active negative energy balance at the time of the analysis. Faraj et al. [108] reported that circulating ghrelin levels depend on the dynamic status of weight loss, remaining low in weight-stable subjects and increased in subjects experiencing active weight loss, thereby suggesting that energy balance may be a more important determinant of postsurgical ghrelin levels than body weight per se. Noteworthy, a long-term adaptation of other ghrelin-producing cells along the remaining gastrointestinal system cannot be discarded as regarding the differences observed between different groups, thus highlighting the need for specific studies.

Biliopancreatic Diversion With/Without Duodenal Switch

The biliopancreatic diversion whether the classical Scopinaro (BPD) or with duodenal switch (BPD-DS) are two bariatric procedures with excellent results regarding weight loss and improvement of obesity-related comorbidities but with high

Table 4 Ghrelin changes after Roux-en-Y gastric bypass and mini-gastric bypass

Author	Year	Type of study	*N*	Bariatric procedures	Follow-up	Changes	Ghrelin measured	Estate
Cummings	2002	Case control	33	RYGBP (5)	6 months	Normal meal-related fluctuations and diurnal rhythm absent after RYGBP	TG	24 h
Faraj	2003	PNR	50	RYGBP (50)	15 ± 6 months	Weight-stable: NS Active weight loss: high*	TG	Fasting
Geloneze	2003	Case control	28	Ringed-RYGBP (28)	12 months	Low*	TG	Fasting
Holdstock	2003	PNR	66	RYGBP (66)	12 months	High*	TG	Fasting
Tritos	2003	Case control	23	RYGBP (6)	24 months	F and PP: low*	TG	F and PP
Korner	2004	Case control	32	RYGBP (12)	12 months	Fasting TG: NSC Fasting AG: low* PP TG: NSC PP AG: NSC	TG and AG	F and PP
Lin	2004	Case control	48	Anti-reflux (4) VBG (4) RYGBP (34)	–	Low*	TG	Fasting
Morinigo	2004	Case control	14	RYGBP (8)	6 weeks	Fasting: low* PP: NSC	TG	F and PP
Vendrell	2004	Case control	174	RYGBP (34)	6 months	High*	TG	Fasting
Christou	2005	Case control	44	RYGBP (36)	3 years	Fasting: low* PP: NSC	TG	F and PP
Mancini	2005	PNR	10	RYGBP (10)	6 months	NSC	TG	F and PP
Borg	2006	PNR	6	RYGBP (6)	6 months	Fasting and PP: NSC	TG	F and PP
Couce	2006	Case control	68	RYGBP (49)	6 months	NSC	TG	Fasting
Korner	2006	Case control	37	RYGBP (9)	6 months	NSC	TG and AG	F and PP
Engström	2007	Case control	40	RYGBP (10)	42 ± 11 months	Fasting: NSC PP: increased suppression*	TG	F and PP
Foschi	2007	PNR	22	VBG (12) RYGBP (10)	–	Fasting VBG: high* Fasting RYGBP: low* PP VBG: low* PP RYGBP: NSC	AG	F and PP
Sundbom	2007	PNR	15	RYGBP (15)	12 months	High	TG	Fasting
Whitson	2007	PNR	10	RYGBP (10)	6 months	NSC	DAG and AG	F and PP
Roth	2008	PNR	18	RYGBP (18)	24 months	Low*	TG	Fasting
Ybarra	2008	PNR	115	RYGBP (49)	12 months	High*	TG	Fasting
Olivan	2009	PNR	30	RYGBP (11)	–	Fasting: NSC PP: NSC	TG	F and PP
Perez Romero	2010	Case control	96	RYGBP (46) Ringed-RYGBP (50)	24 months	High*	TG	Fasting
Carrasco	2011	PNR	50	RYGBP (24) RYGBP + FR (26)	12 months	RYGBP: NSC RYGBP ± FR: low*	TG	Fasting
Martins	2011	Case control	26	RYGBP (9)	36 months	Fasting: high* PP: NSC	TG	F and PP
Chronaiou	2012	RCT	24	RYGBP (12) RYGBP + FR (12)	12 months	Fasting RYGBP: high* Fasting RYGBP ± FR: low* PP after both: low*	TG	F and PP
Werling	2012	RCT	82	VBG (36) RYGBP (30)	6 years	F and PP: NSC	TG	F and PP
Barazzoni	2013	PNR	28	RYGBP (28)	12 months	TG: high* AG: high*	TG and AG	Fasting
Bryant	2013	PNR	12	RYGBP (12)	12 months	Fasting: high* AUC ghrelin: NSC	TG	F and PP
Samat	2013	PNR	9	RYGBP (9)	12 months	Fasting: high* PP: NSC	TG	F and PP
Pellitero	2015	PNR	76	RYGBP (33) Ringed-RYGBP (43)	24 months	High*	TG	Fasting
Santo	2015	PNR	24	RYGBP (24)	26 months	NSC	TG	F and PP
Halliday	2019	PNR	23	RYGBP (6)	–	Fasting: low* AUC: low*	TG	F and PP
Liou	2008	PNR	68	MGBP (68)	12 months	NSC	TG	Fasting
Dardzinska	2018	PNR	45	SG MGBP RYGBP	12 months	Fasting DAG: low* Fasting AG: NSC PP DAG and AG: NSC	AG and DAG	F and PP

NSC nonsignificant changes, *RCT* randomised controlled trial, *PNR* prospective no randomised, *TG* total ghrelin, *AG* acyl ghrelin, *DAG* desacyl ghrelin, *F* fasting, *PP* postprandial, *VBG* vertical banded gastroplasty, *SG* sleeve gastrectomy, *RYGBP* Roux-en-y gastric bypass, *RYGBP + FR* Roux-en-y gastric bypass with fundus resection, *MGBP* mini-gastric bypass; *statistically significant

morbidity, such as malnutrition and severe metabolic disturbances, that sometimes even need revisional or reversal surgery [109, 110]. The Scopinaro BPD involves a distal gastrectomy leaving the gastric fundus intact, so that there are no changes in the interaction between nutrients and ghrelin-producing cells (Table 5). The majority of studies regarding BPD do not describe any significant differences in ghrelin levels before and after surgery [111–114]. There are other papers describing an increase in fasting ghrelin levels after BDP [83, 115, 116]. Most of these previous studies highlight that the changes in ghrelin concentrations rely on preserving the contact between nutrients and gastric fundus. Accordingly, different outcomes regarding ghrelin levels following BPD-DS can be found. This technique includes SG with the removal of the gastric fundus. Kotidi et al. [117] describe a decrease in ghrelin levels after this technique leading to the long-lasting weight-reducing effect.

Other Techniques

Other bariatric procedures such as the single duodenoileal anastomosis (SADI) have not yet been studied enough and no ghrelin results have been published so far. Regarding the mini-gastric bypass surgery (MGBP), few groups have studied its effect on ghrelin (Table 4). Liou et al. and Dardzinska et al. do not observe significant changes in ghrelin concentrations during a follow-up of 12 months. They both agree that the weight loss changes and metabolic improvement that take place after this technique are not correlated with ghrelin concentrations [37, 118].

Other techniques such as the left gastric artery embolization (LGAE) have also been examined. There is still scarce literature about this procedure. A meta-analysis of 2019 included 6 nonrandomised prospective trials in humans with a mean significant weight loss of 8.7 kg ± 1.2 kg after a mean of 12 months of follow-up [119]. A decrease in ghrelin levels in the first months was shown, while later, at 6 months, a

Table 5 Ghrelin changes after biliopancreatic diversion and biliopancreatic diversion with duodenal switch

Author	Year	Type of study	*N*	Bariatric procedures	Follow-up	Changes	Ghrelin measured	State
Adami	2003	Case control	21	BPD (15)	2 months	Similar*	TG	Fasting
Adami	2004	Prospective no randomised	24	BPD (24)	12 months	High*	TG	Fasting
Frühbeck	2004	Prospective no randomised	16	AGB (7) RYGBP (6) BPD (3)	4–7 months	AGB: high* RYGBP: low* BPD: high*	AG	Fasting
García-Unzueta	2005	Prospective no randomised	30	BPD (30)	12 months	High*	TG	Fasting
Mingrone	2006	Case control	12	BPD (6)	14 months	Fasting: high* AUC: high*	AG	F and PP
Valera Mora	2007	Prospective no randomised	11	BPD (11)	18 months	Fasting: NSC AUC: high*	AG	F and PP
García - Fuentes	2008	Case control	80	RYGBP (13) BPD (38)	7 months	RYGBP: high* BPD: NSC	TG	Fasting
García de la Torre	2008	Prospective no randomised	45	VBG (17) RYGBP (17) BPD (11)	12 months	VBG: NSC RYGBP: low* BPD: low*	TG	Fasting
Tsoli	2013	Prospective no randomised	24	SG (12) BPD (12)	12 months	Fasting—SG: low* Fasting—BPD: NSC PP: NSC AUC RYGBP 12 m: similar* AUC SG 12 m: low*	TG	F and PP
Santiago-Fernández	2017	Case control	124	SG (26) RYGBP (30) BPD (47)	6 months	RYGBP: high* SG: low* BPD: similar	TG	Fasting
Kotidis	2006	Prospective no randomised	40	VBG (13) BPD-DS (13)	18 months	Diet: high* VBG: high* BPD-DS: low*	TG	Fasting
Plourdé	2014	Case control	26	BPD-DS (18)	5 days	Fasting: lower only in normoglycemic* PP: NSC	AG	F and PP

TG total ghrelin, *AG* acyl ghrelin, *F* fasting, *PP* postprandial, *VBG* vertical banded gastroplasty, *AGB* adjustable gastric banding, *SG* sleeve gastrectomy, *RYGBP* Roux-en-y gastric bypass, *BPD* biliopancreatic diversion, *BPD-DS* biliopancreatic diversion with duodenal switch, *NSC* no significant changes; *statistically significant

rebound was observed probably due to the establishment of collateral circulation to the gastric fundus or due to the compensatory ghrelin production at other sites of the body [120, 121].

Ghrelin and Eating Behaviour After Bariatric Surgery

A shift in preference away from high-fat and high-sugar foods after bariatric surgery enabling a change in the patients' eating behaviour has been reported [122, 123]. Further studies have looked at this finding, reporting decreased liking of highly palatable foods, with new food aversions and changes in taste and smell, without describing changes in the weight-stable and caloric restriction patients [124–126] and without differences between RYGBP and VSG [127, 128]. These results are in accordance with the changes in ghrelin levels described before (decreasing after VSG and RYGBP and increasing after diet-induced-weight loss and AGB), with ghrelin changes plausibly mediating these responses.

Furthermore, after bariatric surgery, food becomes less rewarding and the underlying mechanism is controlled by neural pathways showing differences between non-obese individuals and those with obesity [129, 130]. In this context, ghrelin receptors are present in the main area involved in food reward: the ventral tegmental area (VTA). Moreover, the central administration of this hormone enhances the search for rewarding substances such as alcohol and high-caloric food [131]. After bariatric surgery, mainly after RYGBP, an increase in alcohol consumption and alcohol use disorders has been described [132–134]. Several studies have reported an increased risk 2 years after RYGBP surgery, which is not consistent with the "addiction transfer" theory based on switching food consumption with alcohol in the short term. The anatomical changes that take place after these surgeries alter the metabolism and pharmacokinetics of alcohol. Weight loss after surgery, reduced gastric volume and accelerated gastric emptying increase alcohol sensitivity leading to higher concentrations and lower tolerance [132, 135]. Besides these metabolic changes, brain reward processing mediated through ghrelin may also play an important role [136]. Ghrelin interacts with mesolimbic dopaminergic pathways modulating the rewarding process of food and drugs of abuse. The administration of this hormone increases alcohol intake and the blockage of its receptor, GHS-R1a, reduces it [137]. Moreover, the majority of studies have been carried out with RYGBP. Recent studies with VSG in rats, describe less risk for alcohol use disorders following this technique, which may be explained by the decrease in ghrelin concentrations after fundus removal [138]. Further studies are needed, because patients with increased susceptibility to alcohol may benefit from VSG instead ofRYGBP.

Regarding suicide and self-harm, prevalence is also higher between patients who undergo bariatric surgery [135, 139]. Risk factors related to suicide go beyond weight loss and weight regain because some authors have found that people who commit suicide had similar or greater weight loss than people who did not [139]. Factors such as low self-esteem, recurrence of obesity-related comorbidities, drug abuse, pre-existing psychiatric disorders, changes in pharmacokinetics of antidepressant drugs, nutrient deficits due to malabsorption and unaccomplished expectations, among others also play a role on these findings [135]. Taken together all these factors may have an influence on the increased suicide rate observed in bariatric patients. Besides, hormone changes such as ghrelin, GLP-1 and PYY that exert effect on anxiety and depression may also be involved [140].

Several studies have found that ghrelin secretion is stimulated in stress situations and exert antidepressant and anxiolytic effects [141]. Ghrelin interacts with the dopaminergic mesolimbic pathways and inhibits the release of inflammatory cytokines. However, ghrelin inhibits serotonin release and stimulates the hypothalamic-pituitary-adrenal axis, both related to depression development [142]. Other studies instead only observe anxiolytic effects after ghrelin administration [143]. Results are still controverted, and literature is scant regarding bariatric surgery, so further investigation is needed. However, multidisciplinary teams to give long-term support and a careful patient selection are vital to prevent the development of alcohol abuse and depression.

Conclusions and Future Perspectives

In conclusion, bariatric-metabolic surgery exerts multifactorial effects producing changes on a pleiad of hormones, including ghrelin. It is really important to understand the biological behaviour and changes that take place after bariatric surgery in order to develop a tailored approach to each patient and be able to diagnose adverse factors that may lead to a failure of bariatric surgery [92, 144]. Ghrelin reduction may play a key role in weight loss and comorbidity resolution in bariatric surgery patients.

In this context, different possibilities to alter ghrelin signalling have been studied such as ghrelin blocking agents, anti-ghrelin vaccination, GOAT inhibition, ghrelin receptor antagonists and inverse agonists with promising results in animals and in vitro [145]. However, blocking ghrelin may lead to several side-effects that are not yet fully understood. Studies in rats show that peripheral injection of a ghrelin antagonist increases arterial pressure and heart rate [146]. Furthermore, ghrelin signalling has influence on cognitive performance so, after ghrelin receptor antagonist administration an impairment in memory consolidation in rats has been observed [147]. Regarding oncological effects, there is no clear evidence yet because some studies have found ghrelin as an antiproliferative factor and others as a growth stimulator of cancer cells so

further studies are needed. About bone formation, studies in rats observe a negative influence on bone formation and growth after a ghrelin antagonist administration [148].

Studies in humans are scarce and did not show promising results. The first randomised clinical trial in humans with anti-ghrelin vaccination was safe and well-tolerated but despite the strong antibody response against ghrelin, no effect on weight loss was observed [149]. PF-05190457, a selected inverse agonist of GHSR, was also tested in humans but no data on body weight was reported. Nevertheless, its administration reduced the gastric emptying rate and half-emptying time by 20–30%. Besides, PF-05190457 increased heart rate and induced somnolence [150].

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Compliance with Ethical Standards

Conflict of Interest The authors declare that there is no conflict of interest.

Ethical Approval Statement This article does not contain any studies with human participants or animals performed by any authors.

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