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REVIEW ARTICLE

Adipose Tissue Composition in Obesity and After Bariatric Surgery

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Abstract

The adipose tissue is a complex organ that regulates food intake and energy expenditure as well as induces low-grade inflammation. This review deals with changes in the composition and activity of the adipose organ after bariatric surgery, focusing on epicardial and ectopic fat and on relationships between white and brown adipose tissues. Postoperative improvements of ectopic fat and epicardial fat size and composition account for the metabolic recovery and the decreased cardiovascular risk. Following Roux-en-Y gastric bypass or biliopancreatic diversion, a proportional increase in the size and activity of the metabolically active brown adipose tissue was observed, most likely related to the postoperative rearrangement of the entero-hormonal pattern with an increase of GLP-1 production: this aspect would promote the postoperative weight loss and maintenance of post-surgery benefits.

Keywords Obesity · Epicardial fat · Ectopic fat · Brown adipose tissue · Bariatric surgery

Introduction

According to the original rationale, bariatric surgery induces a decrease of the subject's energy intake by obstructing the alimentary consumption or by limiting nutrient absorption: so energy balance becomes negative and body weight starts to reduce [1]. When the subject's energy expenditure being decreased for the weight loss meets the energy intake being reduced due to surgical procedures, energy balance is restored, body weight stabilizes at a lower level than at the baseline, and obesity status disappears or improves. In recent decades, encouraging results were obtained in severely obese patients undergoing bariatric surgery [2, 3]. Meanwhile, morbid obesity increasingly emerged as detrimental to longevity and quality of life [4]. Even the unbalance in cytokine network occurring in obesity has been associated with cancer growth and dissemination [5]. In this context, as surgically induced weight loss may actually normalize longevity [6, 7], a large body of experimental and clinical studies was carried out to clarify genetic, biochemical, clinical, and surgical patterns. More recently, novel and unexpected insights were drawn about the physiology of the gastrointestinal tract, the gut-brain relationships [8–10], and the morphology and functions of the adipose system [11, 12]. Therefore, adipose tissue is no longer considered a substantially homogeneous compartment energy storing; indeed, the "adipose organ" [10] can play an active role in both the control of food intake [13] and metabolic control [14]. In line with the above evidence, bariatric surgery is no longer a simple weight loss procedure but can favor morphological, functional, and biochemical changes on a different adipose depot and related tissue. This brief narrative review will focus on bariatric surgery-induced modifications occurring in the various components of the adipose organ.

The Adipose Organ and the Adipose Tissues

Obesity is generally caused by the imbalance between energy intake and expenditure. Adipocytes are known to store energy excess in the form of white adipose tissue (WAT) beneath the skin as subcutaneous adipose tissue (SAT) or surrounding the internal organs as visceral adipose tissue (VAT). WAT accumulates an excess of energy as single triglyceride droplets within adipocytes, which express high levels of leptin and exhibit few mitochondria. WAT generally represents as much as 20% of body weight in normal adults, primarily serving as the storage site for fat. WAT also acts as thermic insulator

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contributing to the maintenance of body temperature homeostasis [10]. Whereas changes in WAT size reflect the state of energy balance, adipocyte number is quite static in adult humans and largely independent of body weight variations. Adipocyte number is set during childhood and adolescence, and only approximately 10% of fat cells are annually renewed in humans [15]. However, WAT expansion is a common finding in obesity and strongly influences metabolic complications. Hypertrophic obesity has been associated with dyslipidemia and insulin resistance, whereas subcutaneous hyperplasia might even exert a protective role against metabolic derangement [16]. Alongside adipocytes, WAT contains pre-adipocytes, macrophages, eosinophils, and regulatory T cells: these elements are involved in the tissue expansion and cell turnover, ensure tissue integrity, and orchestrate recruitment and activation of immune cells involved in adipocyte control metabolism [11, 15]. Especially macrophages may alternatively polarize into pro-inflammatory or anti-inflammatory phenotypes in response to environmental cues [17]. The resulting pattern of cytokines, chemokines, and microRNAs has been demonstrated to regulate adipogenesis, angiogenesis, and insulin sensitivity. Macrophage inflammatory gene expression in WAT is upregulated in both genetically and diet-induced mice obesity prior to and associated with insulin resistance. Notably, a normalization in the M1 cytokine profile was shown following a switch back to normal chow diet even before changes in macrophage density [18]. Furthermore, an improvement of glycemic profile has been reported after MHC class II silencing in both macrophages and adipocytes, thus underlying the role of antigen presentation in metabolic derangement [19]. More specifically, the CD40 and DPP4 signalings have been shown to promote antigen presentation in macrophages, leading to CD4+ T cell recruitment in mice [2–5].

In turn, positive energy stimulates the increase of adipocyte size within SAT, while fat accumulation in VAT is substantially accounted for specific cell proliferation: pre-adipocytes and stromal cells are recruited for new adipose tissue building, whereas the vasculature and extracellular matrix are reshaped by growth angiogenic factors and proteolytic enzymes [11]. Furthermore, adipocytes act as endocrine cells by secreting a variety of hormones. In this context, leptin triggers the brain feedback that reduces food intake and activates the nervous system for counterbalancing the energy excess, while adiponectin and apelin promote insulin secretion to enhance glucose homeostasis [11, 15]. When the energy overload is sustained, such otherwise physiological responses become pathogenic. Endoplasmic reticulum stress in the leptin-sensible neurons generates central leptin resistance and the loss of the leptin beneficial effects on alimentary consumption [20]. Furthermore, oversized adipose tissue is characterized by reduced adiponectin and apelin secretion with decreased overall energy expenditure and increased insulin resistance. Such adipokine unbalance leads to a shift toward pro-inflammatory factor environment [21]: the infiltration of T and B lymphocytes, macrophages, eosinophils, NK cells, and other immune cells in the WAT further sustains such pro-inflammatory conditions and contributes to impaired glucose oxidation, increased insulin resistance, and free fatty acid uptake, as well as the enhancement of oxidative stress and activation of renin-angiotensin-aldosterone system. Conversely, regulatory T (Treg) cells are also resident within adipose tissues. Their number is regulated by age, gender, and environmental factors, but they also express different phenotypes specialized in the regulation of immune function [6]. A potential role of regulatory T cells in reversing obesity-related metabolic disease has been suggested [7]. However, the results observed after Treg depletion are controversial [8, 9]. It is then conceivable that metabolic derangements characterizing obesity are driven by a primitive disorder within adipose tissue [22]. Within WAT, VAT is more metabolically active than SAT, being characterized by a more significant infiltration of inflammatory cells. As a consequence, VAT becomes dysfunctional earlier than SAT, and adipocytes are more likely to undergo apoptosis and autophagy, being gradually substituted by infiltration of undifferentiated, interstitial, and immune cells [21, 22]. Ultimately, VAT expansion is strongly associated with chronic low-grade inflammation and the prevalence of cardiovascular diseases, type 2 diabetes, and hypertension [23–26].

Brown Adipose Tissue

Non-shivering thermogenesis is essential for the postnatal cold adaptation in most mammals for the arousal from hibernation in some species and for sufficient defensive capacity against cold during whole life in small animals. In this context, brown adipose tissue (BAT) plays a substantial role in maintaining constant core body temperature by producing heat in response to beta-adrenergic stimulation [12, 27]. In mammals, BAT is WAT embedded in the neck and the supraclavicular and cervical region. According to the type and strength of the cold stimulus, BAT may substitute WAT in many other sites throughout the entire body [12, 22, 27]. In humans, BAT develops mainly in the first years, while in the adult life, the core body temperature is maintained at a nearly constant level by shivering thermogenesis, muscular voluntary activity, and accurate thermic insulation warranted by WAT. In adult humans, BAT seems to be only a residual tissue, the size being estimated at 30–300 g, contributing only 10–15% to the individual energy expenditure [28]. In physiological conditions, BAT does not store energy, and its morphological and functional properties are markedly different from those of WAT: adipocytes in BAT are smaller and contain tiny multilocular lipid droplets and a large amount of mitochondria expressing uncoupling protein. Furthermore, BAT is characterized by

hick vascularization and non-adrenergic innervation [29]. In light of this, the BAT is a tissue designed for maintaining body temperature through non-shivering thermogenesis, which occurs by energy dissipation and oxidation of glucose and fatty acid oxidation and mitochondrial uncoupling protein [29, 30]. BAT adipocyte is then a high energy-consuming and insulin-sensitive cell very efficient in substrate consuming. Studies in recent years further confirm the cardioprotective role of BAT due to its effects on lipoprotein cholesterol and glucose metabolism [31]. Moreover, BAT influences vascular tone and cardiac metabolism by releasing specific adipokines (BATkines as IL-6, adiponectin) with glucose-sensitive properties [29, 30, 32, 33]. BAT activity is substantially stimulated by the exposure to cold temperature but also by some anti-diabetic or anti-obesity drugs, gastrointestinal incretins, and statins [12, 22, 27–29]. Furthermore, browning of white fat depots has been observed in chronically elevated sympathetic activation, exercise, severe burn injury, and cancer cachexia but only in mice [31]. Under particular conditions (e.g., cold exposure, β-3 adrenoceptors antagonist, incretin stimulation by GLP-1 agonists, or DPP-4 inhibitors), WAT may shift toward BAT phenotype (and vice versa) through a form called beige adipose tissue (bBAT): as compared with the BAT ones, bBAT adipocytes are intermediate cells in terms of size and number of mitochondria. They are likely originated by multipotent pre-adipocytes located in various WAT depots or from trans-differentiation of a white adipocyte into a beige (and later brown) adipocyte according to the so-called WAT browning [32]. Like the BAT ones, the bBAT adipocytes modulate the thermogenesis producing heat in response to adrenergic stimulation of mitochondria, which contain UCP1 and are largely represented both in the brown and beige cells [29, 30, 34]. Furthermore, secretin was demonstrated to increase facultative thermogenesis by stimulating BAT metabolism. The secretin receptor is highly expressed in BAT, and co-incubation with secretin increases its expression and oxygen consumption by a mechanism independent of sympathetic stimulation [35]. In other words, WAT and BAT are interchangeable tissues to meet environment needs: whitening to allow energy storing during surplus and browning when thermogenesis is chronically required, bBAT being an intermediate morphological and functional structure [36]. Recent studies by positron emission tomography have demonstrated some BAT activity in the majority of the adult human individuals so that a substantial role of BAT in the body weight regulation has been hypothesized [31]. With aging, the BAT size and activity decreased for defective hormonal signals, BAT stem cell alteration, mitochondrial dysfunction, and decreased brain activity. As a rule, the BAT structure and activity are barely detected at over 60 years of age [37]. In obese subjects, BAT mass and cold-exposure activity are markedly reduced, alongside total energy expenditure [33]. The low-grade chronic inflammation characterizing obese subjects may potentially explain the shift of BAT toward bBAT and then dysfunctional VAT [12, 27, 32, 33]. In diabetic patients, the BAT mass and functions (e.g., glucose uptake) are suppressed, further contributing to insulin resistance [38, 39].

Epicardial Adipose Tissue

Epicardial adipose tissue (EAT) has to be considered both embryologically and morphologically as WAT. EAT accounts for about 15–20% of the whole cardiac mass and is placed between myocardium and visceral pericardium, enveloping nearly 80% of the heart surface [30]. The lack of a definite cleavage suggests a very close functional interaction between EAT and the underlying myocardium through a shared microcirculation [40–42].

In the epicardium, adipocytes are small and show typical BAT features, including fatty acid oxidation, by which adjacent tissues are fed. Furthermore, a large amount of stromal cells characterizes EAT: lymphocytes, macrophages, and mast cells may also act as pre-adipocytes and pro- or anti-inflammatory effectors, according to the metabolic and environmental requests [41]. Under physiological conditions, EAT exerts important protective functions. On the one hand, EAT sustains and shields cardiac structures from the mechanical consequences of artery pulse and cardiac contraction [40, 42]. On the other, EAT acts as a true paracrine organ, releasing several mediators involved in lipid and glucose homeostasis directly within the myocardial tissue [40, 42–44]. By modulating fatty acid uptake and release, EAT supplies energy requirements under metabolic stress or in pathological circumstances or alternatively remove the excess of fatty acids, thus preventing the potential fat harmful consequences on the coronaries and myocardial tissue [43, 45] Furthermore, EAT-released adiponectin protects cardiomyocytes from hypertrophic stimuli and suppresses both pro-inflammatory and fibrotic processes. With regard to the coronary circulation, EAT directly promotes the effect of insulin and stimulates the vasodilatation through topic secretion of angioactive peptides such as adrenomedullin, omentin, and adiponectin itself [46, 47].

As for other VAT, in obesity, EAT size significantly increases, with changes in its morphological and functional characteristics [48, 49]. BAT adipocyte features shift toward a "WAT-like" phenotype: large lipid droplets accumulate within adipocyte, mitochondrial mass, and activity decrease along with vascularization and energy expenditure. Failure of triglyceride storing increased lipolysis and pro-inflammatory cell infiltration further characterizes dysfunctional EAT [11, 12]: dendritic cells, T and B lymphocytes, macrophages, and eosinophils massively infiltrate the dysfunctional EAT, whereas pre-adipocyte elements differentiate into mesenchymal cells. Because of the intimacy of the epicardium-myocardium interface, the metabolic derangement of

dysfunctional EAT is directly transmitted to the underlying cardiac muscle, thus determining vascular and myocardial distress [14, 36, 42, 49]. In line with the above evidence, EAT volume and dysfunction have been associated with the development of heart failure with preserved ejection fraction, which represents the most common myocardium disorder in obese patients [41–43, 48].

Perivascular Adipose Tissue

Perivascular adipose tissue (PVAT) surrounds main arteries (aorta, carotid, subclavian, femoral) and veins (cava vein) in the body. In comparison to VAT, PVAT shows a lower adipocyte differentiation, a more irregular shape and less defined boundary [44]. Functionally, PVAT substantially acts as EAT. In physiological conditions, PVAT exerts a beneficial effect on vascular structures, promoting remodeling through the paracrine release of vascular relaxant factors, such as adiponectin [50]. In pathological conditions, the PVAT enlarges and becomes dysfunctional, with infiltration of both stromal and immune cells. Due to the lack of anatomical barrier with the vascular wall, PVAT is harmful to the great artery and vein health, promoting or sustaining disorders along all vascular tree [51, 52].

Ectopic Fat

Alongside VAT modification, the current paradigm of adipose tissue dysfunction (referred to as "adiposopathy") also includes the deposition of ectopic fat. The so-called ectopic fat theory hypothesizes that hypertrophic SAT adipocytes, as well as small adipocytes unable to adequately expand, may trigger lipids storing in non-physiological organs, such as the liver, pancreas, heart, and skeletal muscle. Therefore, the recognition of the amount and distribution of ectopic fat depots provides useful information about different obesity phenotypes. More specifically, excessive food intake leads to dysplastic adipose tissue storage, with massive infiltration of cells as pre-adipocytes, macrophages, eosinophils, and regulatory T cells that induces chronic low-grade inflammation and insulin resistance [11, 15]. Inflammation also drives insulin resistance by impairing endothelial function [53]. Indeed, microvasculature is an important insulin action site and critically regulates insulin delivery to the underlying tissues. In the case of perivascular adipose dysplasia, due to the intimate contact with an arterial bed in several organs, it promotes ectopic fat deposition in the vascular wall, determining both cardiovascular and parenchymal harmful effects. Furthermore, ectopic fat deposition affects insulin resistance, spreading the inflammatory status and causing further ectopic fat deposition.

Lipid accumulation within the liver may be due to the insulin-induced de novo lipogenesis or the increased NEFA supply from abdominal adipose tissue [21, 49, 54, 55]. In the skeletal muscle, a reduced capacity to glucose oxygenation may be accompanied by mitochondrial dysfunction [56]. Hence, a vicious circle exists between the progressive increase of insulin resistance and ectopic fat accumulation. In insulin-sensitive tissues (liver and muscle), glucose uptake and oxidation, glycogen synthesis and breakdown, lipid storage and lipolysis may be further deranged [54, 55, 57, 58]. In turn, nonalcoholic fat liver disease (NAFLD) is characterized by an increased hepatic glucose production, de novo lipogenesis, and VLDL-triglyceride secretion rate, which ultimately leads to glucose output suppression and increase the fasting blood glucose [59, 60]. NAFLD is frequently associated with insulin resistance and is characterized by increased risk of mortality from type 2 diabetes and cardiovascular diseases. Furthermore, fatty liver infiltration may progress to nonalcoholic steatohepatitis and fibrosis and rarely to more severe liver disorders [61]. Likewise, insulin resistance suppresses lipid oxidation in the skeletal muscle as well as the switch from carbohydrates to fat oxidation [57, 62, 63]. Reduction of mitochondrial function may lead to overproduction of reactive oxygen species and to an imbalance between lipid supply and lipid oxidation and conversion in triglycerides. Decreased mitochondrial function may cause overproduction of reactive oxygen species and free radical, further contributing to oxidative stress and chronic inflammatory status [64, 65]. Furthermore, as the insulin resistance increases, in the skeletal muscle, the fat content increases for the accretion of intramyocellular triglycerides. The augmented muscle lipid content interferes with regard to intracellular tyrosine phosphorylation and insulin signaling and then reduces insulin-stimulated glucose transport activity: this leads to further accumulation of intracellular fat and, as a harmful metabolic sequence, to a further increase of muscle insulin resistance [57, 63, 66]. Subjects with severe insulin resistance show a compensatory low hepatic clearance of insulin associated with a sharply increased secretion from overactive pancreatic beta cells that, however, tend to exhaust in the long term and decrease the insulin production [67]. The increased lipogenesis, the high level of circulating fat-free acids and fat lipids, and the deranged glucose synthesis promote fat deposition within beta cells. Recent magnetic resonance studies in obese and diabetic subjects have demonstrated a mature adipocyte infiltration in the pancreatic tissue and a triglyceride accumulation into islet and acinar cells. Pancreatic fat deposition impairs beta cell function and reduces the insulin synthesis and secretion, further worsening diabetic status. The contribution of the glucotoxicity that supervenes when true diabetes develops and the effect of pro-inflammatory cytokines released by the dysfunctional adipose tissue finally close the vicious circle [68–72].

The Adipose Organ After Surgically Induced Weight Loss

The effects of bariatric surgery on adipose organ are summarized in Table 1. After surgically obtained weight loss, in most studies, a significant decrease in EAT size was observed [63–66]. However, controversial results were published [79–81]. Although wide heterogeneity crosses the studies, a recent meta-analysis clearly demonstrated a significant postoperative decrease in EAT [82]. This may partially explain the marked reduction in cardiovascular mortality observed after bariatric surgery in all controlled studies [6, 7]. Regardless of the type of surgical procedure, the amount of EAT size reduction is dependent on the amount of the total weight loss, which in turn is tightly correlated to the initial degree of adiposity. Conversely, whether small non-surgical intentional weight loss would have a role in reducing EAT dimensions and in improving myocardial function is not clear [83], most likely for an insufficient decrease of EAT size. Therefore, it may be hypothesized that EAT does not change early after bariatric surgery [81] at the beginning of weight reduction when only a small decrease in WAT size has occurred and the patient is still in the obese range. On the contrary, the EAT changes become evident at long term after a consistent weight loss and a noticeable reduction of WAT size [76]. In addition, it should be considered that the heterogeneity of reduction of ectopic fat depots might be related to different time-course for their mobilization after surgical weight loss [84]. As EAT directly acts as a paracrine agent on the neighboring myocardium, the changes of EAT size morphology after bariatric surgery may produce a marked improvement of cardiac function. Indeed, post-surgical weight loss has been widely associated with reduced prevalence of heart failure with preserved ejection fraction, a pathological condition strongly associated with EAT and increasingly observed in the young obese population [43, 48, 49].

The NAFLD is increasingly reported as the hepatic manifestation of the metabolic syndrome [85, 86]. As said above, the accumulation of excess lipids within hepatocytes overwhelms the usual pathways of lipid metabolism, causing increased oxidative stress, insulin resistance, inflammation, hepatocellular apoptosis, and necrosis. Persistent hepatic inflammation secondary to steatosis and lipotoxicity (steatohepatitis) can trigger fibrotic changes within the liver, ultimately leading to cirrhosis [77, 78]. Due to the massive weight loss, the increased secretion of gastrointestinal hormones and to the rearrangement of the cytokine and adipokine pattern, bariatric surgery improves lipid metabolism, restores insulin sensitivity, and reduces chronic inflammation [82, 83]. As a result, after bariatric surgery, in the majority of the cases, the steatosis is no more evident, which indicates a total disappearance of the ectopic fat accumulation in the liver [76]. Regression of steatosis then corresponds to an overall marked improvement in liver function with a reversion of the hepatic insulin resistance. Conversely, when hepatic steatosis persists in spite of reduced body weight and normalized insulin resistance and adipokine pattern, a liver injury independent of obesity/metabolic syndrome should be considered. Massive fat infiltration of the muscle is frequently observed and histologically documented in obese patients [74, 75]. Magnetic resonance studies confirmed those findings and prove a tight association with insulin resistance [87]. Notably, the intramyocellular fat accumulation disappears early after bariatric surgery, and fat is substantially detectable only within the extracellular spaces: this could account for the early normalization of insulin sensitivity observed at 1/2 months following biliopancreatic diversion but not following Roux-en-Y gastric bypass [69, 88–90]. In the obese patients, the fat accumulation within the pancreatic islets plays a substantial role in the development of type 2 diabetes, whose prevalence is fourfold more frequent in comparison with that observed in non-obese individuals [71, 72, 76]. Pancreatic fat steadily disappears after surgery-induced weight loss with a satisfactory recovery of both insulin secretion and sensitivity. The reduction of adipocyte infiltration within the pancreatic exocrine tissue and the endocrine isles is due to the decreased fat availability for the postoperative changes in alimentary intake or intestinal absorption. Moreover, the specific effects of the operation might have a direct effect on the restoration of fat metabolism [91]. Few clinical studies have so far investigated the changes in BAT morphology and function after bariatric surgery. Increased BAT size, both in absolute and relative terms, has been observed after Roux-en-Y gastric bypass [92, 93]. The marked increase in oxidizing fatty acids'

Table 1 Changes in adipose organ sectors size after bariatric surgery. *BAT* brown adipose tissue, *RYGBP* Roux-en-Y gastric bypass, *SG* sleeve gastrectomy

		Size after bariatric surgery	Reference
BAT	RYGPB	Increased	[19, 23, 28, 73–75]
	SG	Unchanged	
Epicardial fat	Small weight loss	Unchanged	[67–69]
	Massive weight loss	Decreased	[6, 64–66]
Ectopic fat	Liver	Disappeared	[76]
	Muscle	From intra to extracellular	[59, 77]
	Pancreas	Disappeared	[60, 78]

capacity also suggests a shift of the white fat tissue to bBAT [94]. In spite of the increase of BAT size and activity, the overall adipose tissue size results markedly decreased. Conversely, no significant changes in BAT size and function were observed in patients that underwent sleeve gastrectomy or gastric great curvature plication without any gastrointestinal bypass [91]. Recent experimental findings in mice have revealed that GLP-1 and GLP-1 analogs improve thermogenesis and increase the size and functionality of BAT, stimulating vagal afferent neurons [30, 95–97]. A similar effect has also been reported as a direct consequence of the new structural and functional conditions generated by Roux-en-Y gastric bypass and biliopancreatic diversion in the upper gastrointestinal tract. Therefore, it can be suggested that the increase of BAT size and function after Roux-en-Y gastric bypass is specifically due to the increase of GIP ad GLP1 secretion. This hypothesis is also supported by an experimental investigation: in obese mice, a parallel increase of BAT volume and of the IGF-1 levels after Roux-en-Y gastric bypass has occurred, while after a merely restrictive bariatric procedure no changes in composition and in metabolic activity of the adipose tissue were observed [98]. Therefore, in addition to improving insulin action and inhibiting hunger sensation, GIP and GLP-1 would stimulate BAT size and function and lead to an increase of adipose tissue metabolic activity. Recent data indicates that the BAT size significantly contributes to the overall individual energy expenditure (12). The relative increase of energy expenditure observed after RYGBP and biliopancreatic diversion in spite of the marked reduction of body mass loss [99, 100] strongly suggests a postoperative increase of BAT size and function. Beside adequate changes in the current eating behavior, an overall increase in resting energy expenditure seems to play a substantial role in the mechanisms for the weight loss and maintenance of a long-term satisfactory body weight after surgery, at least, in mice [98]. This explains the better weight loss results currently obtained following RYGBP bypass than after sleeve gastrectomy [2].

Conclusion

This narrative review highlights the substantial role that the postoperative modifications of the adipose tissues can play in determining both weight and metabolic outcome. The normalization of adipokine/cytokine production and secretion is mandatory for the withdrawal of the conditions of chronic inflammation and insulin resistance that characterize the obese status and are prejudicial for the cardiovascular system. The disappearance of ectopic fat and the exchange of dystopic with normal adipose tissue warrant a positive metabolic outcome after bariatric surgery, with an increase of the overall life expectancy and a highly satisfactory reduction of the cardiovascular events.

In this regard, it should be acknowledged that some limitations exist. At first, the quantification of insulin resistance within the adipose tissue, based on the determination of lipolysis fluxes by tracer-dilution techniques, is quite expensive and difficult to perform routinely in clinical practice. Other indices remain to be validated [101]. Furthermore, ectopic fat quantification has not standardized yet. Ultrasound evaluation is the most feasible and safe approach, but it is still biased by low reproducibility. Conversely, computerized tomography (CT) and magnetic resonance are currently considered as the gold standard for ectopic fat quantification. Nevertheless, the high costs, high time expenditure, and exposure to radiation (for CT) still limit the use of those techniques in patients. Finally, in spite of the considerable body fat reduction, after Roux-en-Y gastric bypass, a progressive browning of the white adipose tissue does occur, with a resulting increase in energy expenditure, and this greatly contributes to the long-term successful weight outcome.

Compliance with Ethical Standards This article does not contain any studies with human participants or animals performed by any of the authors. Informed consent statement does not apply.

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

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