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REVIEW ARTICLE

Adipokine Pattern After Bariatric Surgery: Beyond the Weight Loss

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Abstract Besides the role in energy storing and body health isolating, adipose tissue produces proteins, the so-called adipokines, with pro-inflammatory or anti-inflammatory actions that contribute to metabolic control and to appetite and energy expenditure regulation. The marked adipose tissue loss following bariatric surgery corresponds to a rearrangement of serum adipokine pattern, with increase of anti-inflammatory and decrease of pro-inflammatory agents. This might play a relevant role in the postoperative improvement of metabolic conditions. However, after surgically induced weight loss, other investigations failed to evidence significant modifications of serum concentration of some adipokines. This review speculates that the composition of adipose tissue lost could influence postoperative changes in some adipokine concentration and that an adequate adipokine pattern plays a pivotal role for the long-term metabolic outcome.

Keywords Obesity · Adipokines · Bariatric surgery

Obesity is a complex disease accounted for by an increase of body fat mass size as percent and absolute value, and each obese patient presents metabolic alterations of a different clinical relevance. Obese patients have an increase of peripheral insulin resistance that may result in a frank type 2 diabetes and tend to display defects of lipid metabolism, getting them prone to cardiovascular disorders [1–3]. In addition, obesity is the typical chronic disease, evolving after years in a heavily complicated clinical picture: As a result, life expectancy is shorter in subjects with obesity than in their lean counterpart [4–7].

Bariatric surgery is the more efficient therapy for obesity. Bariatric procedures cause sustained weight loss: Body weight steadily falls within normal values, weight regain or obesity relapse occurring in only a minority of the patients [8–10]. Moreover, the surgically obtained weight loss is usually associated with a recovery of the metabolic consequences of obesity: Insulin resistance decreases, and in most subjects, a long-lasting diabetes remission is observed [11–14], as well hypertension and atherogenic dyslipidemia [15, 16]: These changes explain a lower mortality from cardiovascular disease and an overall higher life expectancy in former obese patients after bariatric surgery in comparison with their counterparts not surgically treated [17, 18].

Weight loss is accounted for by the forced reduction of food intake in gastric restriction procedures and by the limitation of intestinal absorption of calorie-rich substrates in biliopancreatic diversion (BPD) and in BPD with duodenal switch; when energy expenditure of the decreased body mass matches the restricted energy intake from food or the reduced energy absorption from intestinal tract, the weight loss brings to end and body weight stabilizes unless any further changes occur [19–21]. The mechanisms for the postbariatric surgery metabolic recovery are still partly unknown. In most cases, marked metabolic changes are observed from the first phases following the operation, when body weight is still in the obese range: Therefore, a specific effect of the operation independent of the weight loss was suggested. Functional studies have indicated that the new anatomo-functional conditions of the gastrointestinal tract created by the Roux-en-Y gastric bypass (RYGBP) and by BPD entail an intestinal transit of indigested food and consequent deep changes in entero-hormonal

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pattern. At short term following RYGBP and BPD, a marked increase of gastrointestinal insulinotropic polypeptide (GIP) and of glucagon-like peptide 1 (GLP-1) production is observed, with a powerful stimulation of insulin production, a slowing gastric motility, and a peripheral and central inhibition of appetite; these new pathophysiological events partly explain the beneficial effects of bariatric procedures, accounting for both the improvement of glucose control and the overall reduction of food intake [22–26]. Moreover, the transit in the distal small gut of not digested ailments enhances the intestinal secretion of PYY, an entero-hormone that sharply stimulates satiety [27, 28]. Furthermore, the rerouting of entero-hepatic circulation and the changes in gut micobioma ecology could have a role in modulating postsurgical reduction of body mass and in improving the glucose tolerance [29–31]. For long limb RYGBP and BPD, the fat intestinal malabsorption due to the operation causes a significant lipid and caloric deprivation from the first postoperative days and then a marked decrease of the intracellular lipid storage, that sharply increases muscle insulin sensitivity [32]. Moreover, the functional exclusion of the ghrelin system deeply influences the appetite/satiety balance after RYGBP and sleeve gastrectomy (SG), thus promoting weight loss all the more [33–35].

The consistent weight loss and the rearrangement of the gastrointestinal physiology due to the operations promote a permanent modification of the metabolic attitudes of the obese patients, and in the majority of the cases, the positive postoperative effects are steadily maintained in the long run [8–10, 36–40]. However, in some patients, the weight loss tends to be regained throughout the time toward a frank obese condition, and the postoperative metabolic benefits are lost, with type 2 diabetes or dyslipidemia relapse at long term. The mechanisms that produce the stabilization of the weight and metabolic outcome have to be investigated.

Adipokines

The main function of adipose tissue is traditionally the triglyceride storage as fat under conditions of excess energy intake and their release during period of famine: Moreover, adipose tissue offers mechanical protection to internal organs and plays a fundamental role as thermal isolator. Recently, adipose tissue has also been recognized as a complex endocrine organ contributing to the release of bioactive peptides, the so-called adipokines [41]. Although the full set of human adipokines is not still entirely identified, adipose tissue produces more than 600 forms of hormone-like proteins that contribute to regulating appetite and satiety, insulin secretion and sensitivity, fat distribution, energy expenditure, and endothelial function; moreover adipokines control the inflammation mechanisms, the blood pressure, and the hemostasis system [42]. Alterations in adipokine secretion may be of clinical relevance for the link between obesity and its inflammatory and metabolic and cardiovascular comorbidities [41–44]. The discovery of leptin in 1994 could be considered the initial milestone for adipokine research [45]. Leptin is a protein substantially produced by the adipose with a blood concentration directly proportional to body fat size. Leptin controls appetite and food intake acting as satiety signal, influences energy expenditure, and may act as insulin sensitizer by regulating both beta cell mass and apoptosis [45–47]. Adiponectin is secreted by adipocytes and has strong insulin sensitizer, anti-inflammatory, and anti-apoptotic properties [48–50]. Adiponectin increases energy expenditure acting on the brain, thus promoting weight loss, and stimulates insulin production and exocytosis: In clinical studies, circulating adiponectin is negatively related to the different facets of the metabolic syndrome, including insulin resistance, abdominal fat accumulation, increased blood pressure, and dislipidemia [48–51]. FGF21 is produced by the liver, adipose tissue, and skeletal muscle, stimulates glucose uptake into adipocytes, increases thermogenesis and energy expenditure, and promotes fat utilization, these different actions resulting in a substantial improvement of glucose and lipid metabolism [52, 53]. BMP-4 and BMP-7 are proteins produced in different tissues (adipose tissue, placenta, thyroid gland, skin, gastrointestinal systems) that during organogenesis regulate brown and white adipogenesis and energy expenditure [54, 55]. In adult life, BMP-4 and BMP-7 are expressed by large adipocytes, increase peroxisome proliferator activated receptor γ (PPAR γ), and drive preadipocytes toward brown phenotype. In hypertrophic obesity, the adipocyte resistance to BMP-4 may contribute to the limitation of expansibility of adipose tissue and then may prevent obesity-related diseases [56, 57]. Vaspin is highly expressed in visceral adipose tissue, and elevated serum vaspin concentration is associated with central obesity, impaired insulin sensitivity, decrease metabolic fitness, and increased leptin level [58, 59]. Apelin is expressed in adipose tissue, central nervous system, heart skeletal muscle, and stomach [48, 60]. Apelin contributes to the regulation of glucose metabolism and to the control of blood pressure; furthermore, apelin modulates food intake, lipolysis, cardiovascular and fluid homeostasis, cell proliferation, and angiogenesis [60, 61]. In obesity and diabetes, increased circulating apelin would be a symptom of apelin resistance as adaptation to elevated endogenous apelin levels [42]. Visfatin is produced and secreted in visceral adipose tissue, as well as in a variety of cells including lymphocytes, monocytes, and hepatocytes [62]. Visfatin and insulin bind different sites of the same receptor, and data on the effects of visfatin on insulin action and on body fat size after weight loss are inconclusive [63]. Resistin is produced by adipocytes and by immunocompetent cells [64]. By other effects, resistin decreases the peripheral insulin sensitivity acting on the specific membrane receptors, and it has been considered as a link

between obesity, insulin resistance, and diabetes [65, 66]. Retinol banding protein 4 (RBP4) is produced in the liver and in the mature adipocytes and is the unique transport protein for retinol. The plasma RBP4 level is higher in postmenopausal women and in patients with visceral obesity and type 2 diabetes, and blood RBP4 concentration is positively associated to the severity of insulin resistance and the development of visceral obesity in children and adolescents [67–69]. Adipose tissue is an additional source of dipeptidyl peptidase-4 (DPP-4) [70] a strong antagonist of GIP and GLP-1. The rapid GIP and GLP-1 rapid degradation results in impaired insulin action leading to chronic hyperglycemia [71]. In human adipose tissue, DPP-4 is more highly expressed in dysfunctional adipose tissue, and recent data suggest that low-grade chronic inflammation can upregulate DPP-4 expression, leading to the appearance or to the worsening of obesity-related type 2 diabetes [72, 73]. TNFα is a pro-inflammatory adipokine that is expressed by monocytes and by macrophages [42]: TNF is produced in dysfuncional adipose tissue, correlates with the degree of obesity, and strongly impairs insulin signaling and insulin secretion [74, 75]. IL-1β is a pro-inflammatory cytokine that is produced by the immune cells and by the dysfunctional adipose tissue and may have a role in beta cell destruction and apoptosis, contributing to the development and to the progress of diabetes [76]. In humans with obesity and diabetes, IL-1β release increases with glycemic deterioration; moreover, IL-1β was identified as key players in paracrine inflammatory pathways in adipose tissue [77].

Adipokines, Obesity, Low-Grade Inflammation, and Insulin Resistance

In overweight and in obese individuals, genetic and environmental factors result in a chronic positive energy balance that leads to the weight gain and to changes in adipose tissue size, distribution, function, and cellular composition. The expansion of adipose tissue deeply influences adipocyte biology and adipokine production and secretion. In physiological conditions, harmonic adipokine modifications follow the increase of the adipose tissue size: In humans, approximately 20 % of the obese population remains fully insulin-sensitive and metabolically normal, the metabolically health obese subject [78, 79]. On the other hand, most individuals develop abnormal adipose tissue accumulation, with hypertrophy, ectopic fat deposition, hypoxia, chronic stress, and fat macrophage and neutrophil infiltration. When the accumulated adipose tissue produces excess of pro-inflammatory factors, a low degree inflammation develops, which predisposes to atherosclerosis, cancer, and cardiovascular diseases [63, 80–84]. Moreover, the pro-inflammatory adipokines regulate with inhibitory molecules the muscle and adipocyte glucose uptake, the muscle and liver glycogen, and protein synthesis and the hepatic neoglycogenesis, thus determining a reduction of peripheral insulin action and increasing insulin resistance [41, 80]. In addition, environmental factors such as hypoxia and chronic stress may cause adipose tissue dysfunction, with macrophage, lymphocytes, fibroblasts, and endothelial cell deposition [85], and ectopic fat deposition is followed by production of factors (RBP4, resistin, and apelin) leading to insulin resistance and insulin secretion inhibition [45, 86]. When fat accumulates, the adipose tissue cell infiltration might increase, producing a surplus of pro-inflammatory factors determining the usual metabolic complications of the obese status [87, 88].

In the overweight and obese patients, the metabolic health is relatively independent of the adipose tissue size, the occurrence of metabolic derangements being mainly accounted for by the body fat distribution, composition, morphology, and physiology and by consequence by the adipokine secretion pattern. In the so-called benign obesity, some patients may show a true obese status without significant increase of insulin resistance and with a good cardiovascular health, while in other individuals, the type 2 diabetes and the cardiovascular diseases can develop in condition of overweight or only mild obesity.

Adipokine and Bariatric Surgery

Following bariatric surgery, the near totality of the bariatric patients leads a completely normal life in the long run, thus demonstrating a completely normal nutritional status. Therefore, it can be presumed that after the operation, the protein pool has remained within physiological limits and that the weight loss is substantially represented by a reduction of adipose tissue size. Until recently, the adipose tissue was considered a homogeneous and nearly metabolically inert body sector, without significant functional changes after a surgically obtained size reduction. Recently, the intense and broadly differentiated adipose tissue endocrine and paracrine activity prompted to hypothesize that the quality of the adipose tissue lost would be of great relevance in determining the weight and the metabolic postoperative outcome.

In the past decade, some studies were carried out investigating the effects of the surgical obtained weight loss on the adipokine serum concentration. Leptin substantially reflects the subject's adiposity: After bariatric surgery, the serum leptin concentration reduces during the period of weight loss, remains unchanged when body weight is maintained, and may progressively increase paralleling the weight regain [63, 89–93]. The marked fall of serum leptin concentration at very short term following BPD or RYGBP is likely due to the postoperative temporary break of food intake [23, 94], and the early recovery of leptin resistance can partly account for the marked improvement of the insulin sensitivity observed in the first phases after RYGBP and BPD. However, data of

recent studies suggest that in the diabetic patients undergoing BPD, changes in leptin production play only a minor role in the recovery of insulin function [89]. The surgically induced weight loss is accompanied by a marked and progressive rise in serum adiponectin level [63, 89, 95–99]. Adiponectin has powerful insulin-sensitizing and anti-inflammatory properties, and the increased serum adiponectin level partly accounts for the metabolic benefits obtained by bariatric procedures in most operated patients [42, 48]. In addition, since adiponectin increases energy expenditure, the rise of serum adopinectin level may contribute in promoting the postoperative weight loss and maintenance [51]. Moreover, a higher adiponectin serum concentration is associated to a reduced cardiovascular risk, and this could reflect the decrease of cardiovascular mortality after weight loss surgery [100]. In the diabetic patients, unlike leptin, the postbariatric surgery adiponectin increase appears to be related more to the restoration of insulin secretion than simply to weight loss [89, 101, 102]. In other words, the balance between the adipose tissue pro-inflammatory product and its anti-inflammatory counterpart would play a pivotal role in determining the metabolic outcome of the operation [103].

The studies carried out on the postbariatric surgery production and serum concentration of the other adipokines give only inconclusive and contradictory results [63]. The classical pro-inflammatory cytokines, such as TNF-α and IL-1β, are largely produced not in the adipose tissues and have predominant paracrine action, the circulating levels being only negligible [42, 48]: For these reasons, the postoperative changes in TNF-α and IL-1β serum concentration might be unapparent or not clinically relevant [97, 99, 104–106]. Plasma visfatin levels increase after bariatric surgery, and values are positively related to the percentage of waist circumference reduction [107, 108]: Furthermore, the visfatin has well documented insulin-mimetic actions [109], and it might indicate a role for visfatin in improved insulin sensitivity. The effect of bariatric surgery on plasma resistin levels is inconclusive: Some studies reported a postoperative decrease of resistin after RYGBP [110–112] and a positive relationship between resistin level and glucose intolerance [111–113], while in other investigations, no change in resistin concentration was observed in spite of positive metabolic outcome after the operation [64, 113, 114]. A marked decrease of serum apelin concentration was demonstrated after bariatric surgery in severely obese patients with impaired glucose tolerance, and the adipose tissue expression of apelin is positively related with the improved insulin sensitivity [115, 116]. Likewise, the blood vaspin levels decrease after surgically induced weight loss [117–119], values reflecting however more the insulin action than the obesity degree. Retinol banding protein levels are decreased following surgically obtained weight loss, reflecting a postoperative improvement in insulin resistance and a reversal of the glucose intolerance [69, 120, 121].

When an abnormally great fat storage is chronically present for decades, it is not surprising that adipose tissue dysfunction may develop [88, 122, 123]. Adipose tissue dysfunction entails changes in adipose tissue composition and increased number of immune cells within the adipose tissue promoting apoptosis, fibrosis, and adipocyte autophagy. In addition, the so-called epicardial fat accumulates, a visceral thoracic fat depot in the mediastinum and along the heart cavities, and fat may be stored in nonadipose tissues, infiltrating multiple organs including the liver, pancreas, and skeletal muscle [124–126]. Adipose tissue dysfunction and accumulation of ectopic fat could lead to changes in adipokine secretion, thus causing modification of the cytokine pattern with development of the low-grade inflammation and the insulin resistance that characterize obesity. During the surgically obtained weight loss, the demolition of dysfunctional adipose tissue may result in deranged blood adipokine or cystokine pattern with predominance of cytokines with pro-inflammatory action: This would prevent both an optimal weight loss and a stable metabolic recovery. A postoperative increase of the absolute or relative delivery of TNF-α, IL-β, visfatin, or apelin could explain the persistence of type 2 diabetes or the diabetes relapse in the follow-up, and the lack of recovery of leptin resistance would influence food consumption and lead to postoperative weight regain.

Type 2 diabetes is considered as a progressive disease for a gradual deterioration of insulin secretion due to the increased beta cell apoptosis [127, 128]: Therefore, after bariatric surgery, a progressive worsening throughout the years of the metabolic conditions has to be expected: In contrast, the majority of the diabetic individuals having undergone RYGBP and BPD achieve indefinitely in maintaining a completely normal glucose metabolism. Since the early gastrointestinal effects are substantially similar in all patients, it can be speculated that the steadily positive metabolic results could be accounted for by the long-term maintenance of an optimal balance between pro-inflammatory and anti-inflammatory proteins. This hypothesis is supported by the positive association between the blood adiponectin concentration and the beta cell insulin secretion at long term after BPD observed in patients with stable type 2 diabetes postoperative resolution [89]. Furthermore, among the postobese subjects after RYGBP or BPD, the prevalence of new onset type 2 diabetes is markedly lower than in the general population, suggesting factors that specifically prevent the physiological decline of insulin secretion throughout the time [129, 130].

Conclusion and Future Directions

The body of literature of the past decade has explained the weight-independent metabolic benefits obtained after bariatric surgery by means of gastrointestinal theories: Since the good

weight and metabolic outcome are maintained at long and at very long term by most operated patients, these effects are regarded as permanent. Though following RYGBP and BPD the entero-hormonal pattern does not change throughout the postoperative years, diabetes relapse after the operation occurs in more than a quarter of the operated patients who were diabetic prior to the operation independently of weight regain [11–14]. Therefore, the presence of other factors influencing postbariatric surgery clinical results has to be assumed.

In the vast majority of the obese patients, a deranged blood adipokine pattern is present, most likely reflecting an adipose tissue dysfunction of moderate or severe degree. After massive weight loss obtained by bariatric procedures, profound modifications of adipokine production may develop, that could be related to the amount and to the composition of the adipose tissue lost: The predominance of anti-inflammatory products such as adiponectin corresponds to a recovery from metabolic complications, while the presence of a relative or absolute excess of pro-inflammatory protein, such as leptin, visfatin, resistin, apelin, or RBP, could be associated with negative metabolic outcome and/or weight regain and obesity relapse.

Therefore, after the initial weight loss and the benefic effects of the entero-hormones, an adequate adipokine and cytokine environment could play a substantial role in determining the long-term and very long-term results of any bariatric procedure.

To the present, adipose tissue morphology in obesity of extreme degree is only poorly known, and very few data are available on the adipose tissue dysfunction on the related serum adipokine pattern: Furthermore, the cellular composition of the adipose tissue loss after massive surgically or not surgically induced weight reduction is still unknown.

Moreover, only small information is available on the adipokine pattern at long term following bariatric surgery, with the related clinical correlation in terms of both weight and metabolic outcome. Each body sector consuming energy communicates with the system that absorbs (gastrointestinal tract) and with the system that stores (adipose tissue) energy. A good nutritional health throughout the time implies an accurate balance between energy intake and expenditure, then an adequate enterokine and adipokine function. Therefore, for a true recovery from obesity, the stable reduction of body weight must also correspond to the normalization of the adipokine pattern.

Compliance with Ethical Standards

Conflict of Interest G.F. Adami, N. Scopinaro, and R. Cordera declare no conflict of interest.

This article does not contain studies with human participants or animals performed by any of the authors.

Informed consent does not apply to the data of this article.

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