Title: Does bariatric surgery improve adipose tissue function?

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Abbreviations:

CRP	C Reactive Protein
FFA	Free Fatty Acids
FGF19	Fibroblast Growth Factor 19
FGF21	Fibroblast Growth Factor 21
FXR	Farnesoid X Receptor
iNKT	invariant Natural Killer T cells
MAIT	Mucosal Associated Invariant T cells
RYGB	Roux-en-Y gastric bypass
SAT	Subcutaneous Adipose Tissue
TG	Triglycerides
VAT	Visceral Adipose Tissue
VSG	Vertical Sleeve Gastrectomy

Abstract

Bariatric surgery is currently the most effective treatment for obesity. Not only do these types of surgeries produce significant weight loss but also they improve insulin sensitivity and whole body metabolic function. The aim of this review is to explore how altered physiology of adipose tissue may contribute to the potent metabolic effects of some of these procedures. This includes specific effects on various fat depots, the function of individual adipocytes, and the interaction between adipose tissue and other key metabolic tissues. Besides a dramatic loss of fat mass, bariatric surgery shifts the distribution of fat from visceral to the subcutaneous compartment favoring metabolic improvement. The sensitivity towards lipolysis controlled by insulin and catecholamines is improved, adipokine secretion is altered, and local adipose inflammation as well as systemic inflammatory markers decrease. Some of these changes have been shown to be

weight loss independent and novel hypothesis for these effects includes include changes in bile acid metabolism, gut microbiota, and central regulation of metabolism. In conclusion bariatric surgery is capable of improving aspects of adipose tissue function and do so in some cases in ways that are not entirely explained by the potent effect of surgery.

Introduction

Bariatric surgery is widely acknowledged as the most effective treatment for obesity, and intensive efforts over the past few years have not only added to our understanding of the mechanisms by which surgery improves metabolism and resolves type 2 diabetes in some patients but have also shifted our understanding of how metabolism is regulated. Mechanical explanations for the success of surgery such as restriction of stomach volume and intestinal malabsorption have given way to physiological explanations that emphasize alterations in gut signals to other organs[1, 2]. A key question is the degree to which these signals have direct or indirect impacts on adipose tissue metabolic function. A growing body of evidence links adipose tissue dysfunction to key aspects of the metabolic dysregulation that accompanies excess body weight. For this reason, our aim with the current review is to provide an overview of how adipose tissue responds to bariatric surgery and whether there are weight loss independent mechanisms involved in these responses.

Bariatric surgery procedures

The two dominant bariatric operations used in the clinic are Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy[3] (Figure 1). The Roux-en-Y gastric bypass leaves the patient with a small stomach pouch under the esophagus and the gut anatomy is re-arranged such that nutrients are diverted from the upper to the middle part of the small intestine. RYGB not only induces significant weight loss but improves insulin resistance with remission of type 2 diabetes in many cases. Vertical sleeve gastrectomy (VSG) is an anatomically simpler operation, involving removing approximately 80% of the stomach along the greater curvature, leaving small intestinal anatomy unaltered. These procedures were formerly believed to be effective solely due to malabsorptive and restrictive properties, however, this paradigm has changed over the past decade as growing evidence supports that alterations in gut anatomy has profound effects on physiology including alterations in gut hormone secretion important for regulating feeding and metabolism. From the restrictive/malabsorptive point of view VSG would be expected to be inferior to RYGB since it involves a larger gastric reservoir and no intestinal bypass. Remarkably and counterintuitively however, the efficacy of VSG is not far from RYGB[4].

Adipose depot type and adipocyte size

The most obvious effect of bariatric surgery is loss of up to half of total adipose tissue mass within the first year after surgery along with improvements in systemic metabolism[5]. These metabolic improvements associated with bariatric surgery do not correlate directly with reduction of adipose mass *per se*, but also relate to the extent different adipose tissue anatomic depots are affected. White adipose tissue may be divided into two broad categories: visceral adipose tissue (VAT) located in the peritoneal cavity, and subcutaneous adipose tissue (SAT), located under the skin. These two depots may be functionally subdivided even further: VAT includes omental (attached to the stomach), retroperitoneal (surrounding the kidneys), and mesenteric (attached to the intestines) subdepots, while SAT can be subdivided into deep and superficial as well as truncal and extremity compartments, each of which displays different functional characteristics[6].

Excess VAT is an independent risk factor for type 2 diabetes and cardiovascular disease and is more strongly correlated to these disease states than SAT[7-9]. Adipose tissue depots manifest different physiologic profiles, with VAT demonstrating increased lipoytic capacity, inflammation, vascularization, and secretion of specific adipokines. In addition, VAT drains its venous effluent directly to the liver via the portal venous system, thus exerting a disproportionate effect on hepatic and systemic metabolism[10]. Despite the epidemiologic association of VAT with metabolic disease, studies of omental fat removal in humans, generally performed in combination with a bariatric procedure, have yielded conflicting results. Most of these studies demonstrate no change in metabolic disease relative to non-omentectomy controls, although one study reported greater weight loss[11], [11-16]and another found that omentectomy amplified the reduction in expression of inflammatory markers in skeletal muscle associated with RYGB[14]. As omental fat only constitutes a minority of VAT, with mesenteric and retroperitoneal subdepots comprising a substantial proportion of total VAT mass, such findings emphasize the ability of distinct depots to not only store fat but also to impact metabolism.

Most studies of depot-specific fat mass find pronounced reductions in both VAT and SAT within the first few months after surgery [5, 17-19]. That said, magnetic resonance imaging of patients before and up to two years after bariatric surgery demonstrated that the vast majority of total fat mass is lost from SAT[20]. However, studies with longer post-operative follow-up demonstrate further declines in VAT but not SAT, suggesting that late weight loss may disproportionately involve VAT [5, 20-22]. The particular significance of VAT was underscored in a study by Faria et al.[19] where metabolic parameters between subjects with persisting metabolic syndrome 1 year post RYGB were compared with patients that underwent type 2 diabetes remission and found that VAT mass was significantly decreased even though BMI and SAT area were similar. Finally, Toro-Ramos et al.[20] found that intramuscular adipose was highly reduced after surgery

as well, suggesting that loss of mass from non-canonical adipose tissue depots may also contribute to the metabolic effects of bariatric surgery[23]. These data highlight the fact that surgically induced weight loss involves different anatomic adipose tissue depots to different degrees, and suggests that the beneficial effects of bariatric surgery result not only from overall loss of fat mass but also a metabolically beneficial redistribution among different anatomic depots.

Reduction in adipocyte hypertrophy is a dominant feature of fat mass loss. Adipocyte size dramatically influences intracellular metabolic function. Larger adipocytes are associated with type 2 diabetes and metabolic disease in multiple studies[24-26]. A proposed putative mechanism for the link between adipocyte hypertrophy and metabolic dysfunction involves induction of cellular hypoxia as adipocyte hypertrophy beyond the diffusion distance of oxygen, leading to inflammation and insulin resistance[27]. Hypertrophy is also associated with a reduced capacity of adipose tissue to store energy in the form of triglycerides (TGs) in the fed state and to release free fatty acids (FFA) during fasting[10].

While the correlation between adipocyte hypertrophy and metabolic disease in the obese population is strong, this relationship is complex and context-dependent, which needs to be taken into account when interpreting adipocyte size changes after weight loss. Lean humans with smaller adipocytes have greater metabolic deterioration in response to overfeeding, suggesting that in the lean state, larger adipocytes are beneficial and a measure of nutrient buffering capacity[28]. In obese patients, however, a hypertrophic threshold may be reached beyond which adipocyte buffering capacity is exceeded[29], leading to ectopic lipid deposition in peripheral tissues. Consistent with this concept extreme adipocyte hypertrophy in the obese state correlates positively with the degree of obesity and metabolic disease in humans and mice.

Studies investigating adipocyte size after bariatric surgery find that adipocytes become smaller [30, 31] ultimately approaching diameters similar to lean controls[30], yet, total adipocyte number remains unchanged [32]. These data are primarily restricted to SAT, since access to VAT samples in humans is limited after surgery. In line with these observations, Anderson et al.[32] reported that improvements in whole body insulin sensitivity 2 years after RYGB correlated strongly with a larger reduction in adipocyte size. Cotillard et al.[29] found significantly smaller adipocytes in subjects where type 2 diabetes risk was reverted 6 months post RYGB as compared to those patients where diabetes risk did not improve.

There are very few studies looking into adipocyte size in animal models. It has been shown that the mesenteric WAT[33] and the eWAT[34] contain smaller adipocytes after RYGB and VSG. One

report observed that the weight loss induced by ileal interposition (a procedure where a portion of the ileum is moved to the jejunum) in diabetic rats was the result of decreases in mean adipocyte size in SAT as well as VAT[35]. However, in another type of operation, the biliopancreatic diversion, SAT adipocytes shrink more than the cells found in the VAT[36]. More clinical and pre-clinical research is needed to fully understand the intracellular changes in adipocytes after surgery. However, it is clear that overall bariatric surgery reduces both the size of the individual depots and adipocytes, and decreases the ratio of VAT to SAT. These changes are well known for their beneficial impact upon metabolic health and support a contributory role for improved adipose metabolic function after bariatric surgery.

Regulation of lipolysis

The physiologically most important function of adipose tissue is to act as an energy buffer. During positive energy balance, adipose tissue stores excess energy in a safe and accessible manner that allows for appropriate energy release primarily via lipolysis in times of negative energy balance. This balance between storage and release of lipids is regulated by a complex interplay of neuro-humoral regulation for which insulin and plasma catecholamines play an integral role. A multitude of other factors regulate these processes as well, yet we will focus on 1) basal lipolysis, 2) insulin inhibition of lipolysis, and 3) catecholamine stimulation of lipolysis.

Basal lipolysis. Basal unstimulated lipolysis in isolated adipocytes has been shown to increase with obesity and seems to relate to the adipocytes being hypertrophic and thus dysfunctional[37-39]. The information of *ex vivo* basal lipolysis with weight loss induced by reduced caloric intake is sparse with a few reports of no changes[37, 40-42] and a single study showing a 50% reduction[43]. To the best of our knowledge there are no studies reporting basal lipolysis rates in isolated adipocytes after bariatric surgery. A more clinically relevant measure of basal lipolysis is the outflow of FFA into the circulation during fasting. Yet, in the interpretation of data it has to be considered that systemic FFA levels not only are affected by lipolysis but also by clearance by muscle and liver. In general it is found that FFA levels increase systemically in the first few months after surgery after which they decrease[44-46]. In studies where the follow ups are performed at 6 months after surgery, the most common finding is decreased levels of FFA when compared to pre-surgery levels[12, 21, 47, 48] but not as compared to the levels found in lean control subjects[46]. A handful of studies report no significant changes after surgery[49-51].

Regulation by insulin. Even though insulin receptor stimulation of adipocytes promotes lipogenesis and uptake of fatty acids in addition to inhibiting lipolysis, this latter metabolic effect is by far the most important. The absence of insulin during fasting can relieve lipolytic inhibition

to such an extent that it may cause intermittent fasting induced hepatic steatosis[52-54] and insulin resistance in this system manifests itself as a lack of ability to properly control the flow of FFAs in the transfer between fed and fasted states. The ability of the adipose tissue to respond to insulin can be measured by including plasma FFA in the hyperinsulinemic euglycemic clamp procedure, which has the distinct advantage of tightly controlling insulin levels. When compared to basal fasting levels of FFA as described above, the clamp studies report that insulin's ability to suppress FFA outflow is impaired with obesity[45, 55]. Shortly after surgery FFA levels are increased compared to obese pre-surgery levels both in the absence and presence of insulin clamping[45, 56], whereas insulin inhibition of lipolysis is fully comparable to lean control levels a few years after surgery[55]. Interestingly this effect described by Curry et al.[55] seemed to depend on a higher dose of insulin.

In addition to evaluating the systemic effect of insulin upon adipose tissue by measuring FFA in the blood, insulin resistance within distinct adipose depots can also be investigated by quantification of downstream insulin receptor signaling. These types of studies are generally more widespread in animal models of bariatric surgery than in the clinic. Yet, studies that have investigated this in SAT biopsies after RYGB in humans and have found increased activation of the insulin receptor signaling pathway upon insulin stimulation[49, 57]. In the study by Carvalho et al[49] this effect was shown to compare to lean control levels 6 months after surgery despite decreased insulin sensitivity prior to RYGB. Thus, at least in SAT, the obesity-induced insulin resistance is reduced after surgery. However, in rat models of RYGB few changes were observed in insulin receptor stimulation as validated by its phosphorylation or in expression of its downstream signaling molecules in adipose tissue [58, 59] while one study found increased activation of downstream insulin receptor signaling via phosphorylation of Akt in the mesenteric depot[60]. These apparently conflicting results most likely reflect that samples were obtained under conditions that were not optimal to reflect acute stimulation with a comparable level of insulin. The groups of animals differed in insulin levels and not all studies fasted the animals to down-regulate endogenous insulin prior to harvesting the samples.

Catecholamines. In contrast to insulin, plasma catecholamines play an important role in stimulation of lipolysis. Previous research has suggested that obesity causes "catecholamine resistance" preventing adipose tissue from being appropriately catabolized when energy demand is high (e.g. fasting and/or exercise). Nonetheless this area of research has received relatively little attention over the past several decades. However, there is reason to revisit this phenomenon[61]. Substantial evidence exists that adipose tissue in obese individuals indeed is resistant to catecholamine-induced lipolysis[62, 63] which also explains why lipids accumulate in adipose depots despite obesity being linked to increased sympathetic activation[64].

Catecholaminergic stimulation of lipolysis in adipocytes takes place via stimulation of adrenergic receptors of which the adipocyte contains several types. The best described receptor subtype is the beta-3 adrenergic receptor, which elicits a strong lipolytic response upon activation. In contrast, the alpha 2 receptor inhibits lipolysis. It has been hypothesized that the balance between these receptor sub-types changes with obesity and result in changes in the lipolytic response. Yet information about catecholaminergic responsiveness in adipose tissue after RYGB or VSG is sparse. Kaartinen et al.[65] isolated adipocyte membranes from obese subjects and patients, who had achieved substantial weight loss with bariatric surgery and found that lipolytic effects of pharmacological stimulation of beta adrenergic receptors were reduced with obesity as compared to lean subjects whereas the response after surgery was higher than in the lean controls despite no difference in receptor density between the groups. A mouse study examining beta-3 adrenergic receptor gene expression after RYGB found the levels to be increased in VAT[66]. These findings match the increases in adrenergic response seen after weight loss in obese individuals[43, 67].

In the setting of beta-adrenergic regulation of adipocytes it is worth mentioning the brown adipose tissue, which is highly metabolically active upon adrenergic stimulation and has a catabolic effect by converting fatty acids released by lipolysis to heat. Brown adipose tissue has only recently been proven active in human adults and there is a great interest in exploring the therapeutic potential of its activation as it has been suggested as an explanation for the increased energy expenditure reported with RYGB[68-70]. However, discrepancies have been reported between species with studies in rodents collectively failing to show such an effect[36, 70-72] whereas data from the clinic suggests activation[68, 69, 73]. As the function of this tissue in relation to metabolism, obesity, and bariatric surgery is still not fully established, more information needs to be generated to understand its significance in these settings.

In general, the bulk of the evidence points towards surgery improving adipose tissue metabolic adaptability in terms of postprandial storage and fasting-induced release of fatty acids when appropriate. These changes do not occur immediately after surgery but rather take significant time to become evident. The profound hypocaloric state and attendant weight loss that follows surgery should be considered a significant confounder when interpreting changes in lipolytic capacity of adipose in the first weeks and months after surgery. More studies are needed to elucidate the molecular mechanisms behind depot specific long-term responsiveness towards insulin and catecholamines and also to clarify to which extent changes are bariatric surgery specific.

Adipokine secretion

Besides functioning as a storage depot, adipose tissue is also considered an endocrine organ secreting hundreds of different signaling proteins (adipokines) into the circulation[74]. The actions of adipokines span autocrine signaling involved in lipid homeostasis and adipogenesis, crosstalk with the immune system, and conveying information on energy status to the central nervous system (CNS) and other metabolic organs such as muscle and liver. The most well-known adipokine is the hormone leptin, which is the major contributor to the communication between adipose tissue and the CNS serving to suppress appetite when lipid storage is high. Similar to insulin, leptin responsiveness seems to be adversely affected by obesity such that despite increases in circulating leptin with adipose expansion, leptin is not able to successfully convey this surplus energy status to the brain[75]. In addition to this leptin has been shown to stimulate proinflammatory immune responses[76]. Adiponectin is another well characterized adipokine, which acts on the peripheral metabolic tissues (liver and muscle). However, unlike leptin, plasma levels of adiponectin decrease, rather than increase with overall fat mass expansion, and as adiponectin is highly correlated to metabolic derangements of obesity and type 2 diabetes[77] the secretion of this adipokine is considered to be a hallmark of healthy adipocyte function. This is consistent with the observation that large dysfunctional adipocytes tend to decrease secretion of this adipokine to the circulation[78]. Adiponectin exerts its effects via receptors expressed in muscle and liver and to some extent by autocrine actions causing improved insulin sensitivity as well as stimulating glucose utilization and fatty acid oxidation[79]. Other less investigated adipokines that have been linked to metabolic function and obesity are visfatin and chemerin. Visfatin is produced primarily in VAT and has been linked to glucose usage, albeit the mechanism for this is still highly debated. Yet, several studies have shown a strong positive correlation between visfatin and impaired metabolic health[80]. Chemerin has received interest for its autocrine actions in adipocyte. Especially since it is a necessary factor for adipogenesis and also it regulates adipocyte cellular metabolism[81]. In addition to these there are a multitude inflammatory cytokines produced in adipose tissue but these will be described in more detail in the inflammation section below.

As would be predicted based on fat mass changes, leptin decreases[82-87] whereas adiponectin increases[82, 85, 86, 88-90] after bariatric surgery (see table 1 for more references). These findings point strongly towards adipose tissue regaining its endocrine capacity after surgery. It has also been reported that SAT expression of leptin goes down after RYGB[91] whereas adiponectin gene expression in primarily SAT was reported to increase in only one out of five studies[84, 91-94]. In the context of these findings it is worth mentioning the novel hypothesis that adiponectin is produced in significant amounts by adipocytes in the bone marrow[95]. In support of this hypothesis

Coughlin et al.[96] found adiponectin expression to be highly upregulated in femoral adipose tissue after surgery. Both visfatin and chemerin have generally been found to decrease after surgery[11, 90, 97-102] and some studies report a correlation between reductions in the levels of these adipokines and improvements of other metabolic parameters such as insulin resistance, fatty liver and/or inflammation [90, 98-100, 102] Whether the secretion of adipokines plays significant role in the improved metabolic state after surgery or is rather just a reflection of changes in adipose tissue mass is not fully elucidated and there are still mechanisms of action with many of the newly discovered adipokines, that are not well understood yet, but it has been described that adiponectin production in SAT after surgery is doubled after only 2 weeks[103] – before significant weight loss has occurred – suggesting weight loss independent adipokine responses.

Adipose inflammation

Low grade chronic inflammation within adipose tissue is associated with obesity. The fact that adipose mass in the obese may constitute as much as 50% of bodyweight and contain more than 1 million immune cells/g accentuates the significance of this tissue as an immunological organ with capacity to influence systemic immune function [104]. Adipose inflammation has been hypothesized to be an important contributor to systemic insulin resistance and multiple other metabolic derangements[105]. Despite its potential importance, the precipitating events for this inflammatory process are still being debated. Hypertrophic adipocytes increase production of pro-inflammatory adipokines[106] and also saturated fatty acids in the extracellular space have the capability to initiate a direct inflammatory response in macrophages through activation of pattern recognition receptors such as Toll-like receptors[107].

Chronic low-grade inflammation in adipose tissue contributes to levels of inflammatory markers in the circulation and for this reason bariatric surgery follow-up studies frequently apply measurements of common biomarkers such as CRP (C-Reactive Protein), TNF-alpha, and/or IL-6. IL-6 is mostly consistently reported to decrease after surgery[15, 31, 49, 85, 108] albeit there are reports of no change as well[82]. There is less consensus with TNF-alpha levels as they have been reported to decrease[108, 109], stay unaltered[110], or even increase [111] in patients after surgery as compared with levels before surgery and between groups of obese versus operated patients. In addition the presence of the inflammatory adipokine Monocyte Chemotactic Protein-1 (MCP-1) in the blood has likewise been reported to decrease [11]. Inflammation has also been evaluated within the adipose depots by protein or gene expression of these pro-inflammatory cytokines and the results resemble the findings from blood with decreased expression of IL-6, TNF-alpha, and MCP-1[46,31, 93, 112-114].

CRP originates primarily from the liver. Still it is considered a marker of adipose inflammation as the liver is highly affected by obesity and CRP has consistently been shown to be upregulated with obesity. After bariatric surgery CRP levels show rapid[11] and large[115] declines that persist for up to 10 years[109] post-surgery.

Another aspect of inflammation is the abundance and inflammatory phenotype of immune cells residing within the adipose tissues. SAT, relative to VAT contains not only fewer immune cells/mm^3 in general[116] but also the macrophage population[31], their assembly into crown like structures[117] and the balance of pro-inflammatory over anti-inflammatory macrophages[118] decrease after surgery[118]. These findings are supported by a recent comprehensive RNAseq analysis of gene expression in SAT showing that 3 months after surgery clusters of genes related to specific immune populations all decreased[119].

With inflammation comes fibrotic remodeling and potential excessive synthesis of extracellular matrix components[120] and accordingly studies within animals models have shown that adipose fibrosis is reduced when macrophages are depleted[121]. One of the major consequences of fibrosis is that the adipose tissue loses the plasticity to expand or contract with metabolic demands such that fibrosis in the obese state negatively affects the ability to lose weight after surgery[82, 122]. Yet whether surgery improves the ability of the fibrotic adipose to heal better than with weight loss induced by calorie restriction has not been examined.

To the best of our knowledge, very few studies have successfully measured local inflammation within adipose tissues after surgery in animal studies. However, these limited findings do indicate that inflammation decreases within the distinct adipose depots as assessed by TNF-alpha and IL-6 mRNA expression as well as number of macrophages and T-cells residing within the mesenteric depot in particular[33, 60, 82, 123]. These observations support the contention that bariatric surgery reduces inflammation associated with obesity.

Future directions

Bariatric surgery is by far the most effective treatment for obesity, yet the resources required to treat the obesity epidemic with surgery outstrip our ability to deliver these surgical interventions to a large percentage of those impacted. An understanding of the mechanisms that underlie the potent effects of bariatric surgery on systemic metabolism will lead to novel targets for the development of therapeutics for obesity and metabolic disease. Towards this goal it is crucial to distinguish between physiologic changes resulting from weight loss secondary to reduced caloric

intake and those that are a direct and independent effect of surgery *per se* as many responses will overlap In animal studies, weight loss-independent effects are confirmed with weight-matched or pair-fed control groups. As seen in table 1, few clinical studies include a weight loss control group due to the challenging if not impossible task of inducing weight loss of the same magnitude by diet restrictions in humans. Also this discrepancy in bodyweight outcome makes it difficult to compare studies with surgery alone to those studies where other interventions are investigated. Alternative approaches include comparing different types of surgery in the same study or avoiding pooling results from several different surgeries (a significant number of studies were excluded from table 1 for this reason) to better define the distinct effects of different operations. In addition physiological changes that occur before significant weight loss might be detected by studying subjects in the early post-operative period. So far the studies that have used these approaches have shown that bariatric surgery independently reduces the mass of VAT, improves the circulating adipokines[123] as well as reduces lipid accumulation in the liver and blood[123-127]. We propose that the following mechanisms could be responsible but require more investigation to be fully elucidated (see figure 3):

A) One of the current candidates for weight loss independent mechanisms is changes in bile acid levels. Plasma bile acids have been shown to increase after surgery in humans[128] and animals[126] - an effect that is weight independent and has been hypothesized to underlie the dramatic effects of bariatric surgery on metabolism[129]. Bile acids act as endogenous ligands for several receptors of which FXR (Farnesoid-X Receptor) and TGR5 (G protein-coupled bile acid receptor 1) have received particular attention. FXR is a nuclear receptor that regulates lipid metabolism and trafficking as it is expressed in the intestine, liver, and adipose tissue[130]. FXR and its target genes have been shown to modulate adipocyte phenotype and function [131]. Interestingly, in our search to identify molecular mechanisms behind the metabolic effects of sleeve gastrectomy, we found that deletion of FXR abolished the effect of VSG in high fat fed mice[132]. TGR5 is a cell-surface receptor which is expressed in BAT but not WAT and deletion of this receptor does accordingly not affect weight loss after VSG in mice, yet it reduces the glucoregulatory improvements that occur after surgery [133]. One of the potential mechanisms by which bile acid receptor activation is hypothesized to exert beneficial effects is by reducing endoplasmic reticulum (ER) stress – a stress response proven to be increased in adipose tissue with obesity in animal models as well as in clinical studies [134, 135] having impact on insulin sensitivity and inflammation. Recent work from Cummings et al. has confirmed this as a possible mechanism of action[60]. In addition to neural and hormonal input,

adipose tissues also receive metabolic regulatory input by other mechanisms. FGF21 (Fibroblast Growth Factor 21) and FGF19 (Fibroblast Growth Factor 19) are two endocrine FGFs that have both been shown to be upregulated by bariatric surgery in humans[136 137]. FGF21 controls the adipose metabolic phenotype and has been shown to hold great therapeutic potential for treating type 2 diabetes and obesity[138, 139]. Interestingly, Lips et al.[136] compared RYGB directly to gastric banding and weight loss by calorie restriction, and found that FGF21 levels were robustly upregulated with RYGB only. An additional aspect of interest with FGF21 is that it is differentially expressed in type 2 diabetes and furthermore gene expression in the liver after RYGB differs between patients with diabetes remission and those without[140]. However, a caveat with FGF21 is that it appears to differ between rodents and humans, such that translational extrapolations may be hard to establish.

B) Also it is worth considering the impact of bariatric surgery on the function of adipose tissue as an immunological organ capable of modulating not only immune populations in other tissues but also metabolic outcomes. This aspect of immune function has not been discovered until very recently but adds to our understanding of how immune cells directly influence the regulation of metabolism[141]. Recently discovered key players of interest in this setting are distinct sub population of T-cells, namely iNKT (invariant Natural Killer T) cells and MAIT (Mucosal Associated Invariant T) cells. Magalhaes et al.[142] studied these two T-cell populations in obese and diabetic patients and found that both these types of T cells decreased in the circulation with obesity and type 2 diabetes. The MAIT cells were found to recruit to the adipose tissues in obesity and type 2 diabetes where they shifted to a distinct IL-17 cytokine profile. With bariatric surgery the abundance of these cells in the circulation increased (albeit not to the level of the lean controls) and they produced less IL-17. What makes these cell populations of specific interest in the setting of bariatric surgery are that 1) in contrast to the inflammatory component of the immune system these cells maintain a healthy homeostasis[143, 144], 2) iNKT seems to be able to interact directly with adipose metabolism by the adipocytes presenting lipid antigens to these T-cells, which in return regulate insulin sensitivity in the adipocytes[145] 3) MAIT are known to be associated to the gut mucosa and thus provides a potential missing link to the potent effects of surgery to alter the microbiota can directly impact the adipose tissue function. Such findings emphasize that the immune system could be involved in the metabolic benefits observed after surgery.

C) Alterations in the gut-brain axis may contribute to weight loss-independent effects of bariatric surgery such as gut signaling to the CNS regarding postprandial status via humoral and neural signals. The CNS, in turn, can regulate metabolic function via

efferent neuronal activity of target metabolic organs, including adipose tissue which has been shown to become hypertrophic when denervated due to lack of sympathetic nervous system stimulation of lipolysis [146-148]. In addition, sympathetic stimulation not only affects the release of fatty acids through lipolysis but also induces "beige" or "brite" adipocyte differentiation[149] with a concomitant increase in thermogenesis and fatty acid catabolism. Accordingly, it has been demonstrated that animals with more beige adipocytes are protected from obesity and diabetes[150] even though it is not yet fully understood if this effect relates to increased thermogenesis alone or whether there are secretory factors at play as well[151]. The presence of beige adipocytes within SAT upon stimulation after bariatric surgery have not yet been fully investigated, but we hypothesize that induction of beige adipocytes might be one of the mechanisms by which bariatric surgery improves metabolism as catecholaminergic responsiveness seem to be increased after surgery. Evidence for this comes from Neinast et al. who reported upregulation of genes involved in beigeing after RYGB in mice[66]. The CNS has also been shown to be a regulator of beige fat and so could be a mediator of any such surgical effects to increase the number of beige adipocytes after surgical intervention.

Conclusion

To advance our understanding of obesity and why bariatric surgery is superior to other treatment options we will have to strive for a deeper understanding of how different physiological processes and organs interact in the setting of metabolism. Current literature holds tantalizing hints that bariatric surgery affects adipose tissue far beyond mere reduction in lipid content. We believe this is important given the crucial role of adipose tissue in organism survival and energy usage. Adipose tissue communicates directly with multiple metabolic target organs regarding acute and chronic energy status and is likely a key component to the success of surgery.

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Figure 1. Bariatric surgery procedures

In the Roux-en-Y Gastric Bypass procedure a small stomach pouch is created under the esophagus. The jejunum is then attached to this pouch causing nutrient flow to bypass the proximal part of the duodenum. In the vertical sleeve gastrectomy procedure about 80% of the stomach is removed along the greater curvature. The intestines are left unaltered.

Figure 2. Changes in adipocytes after surgery

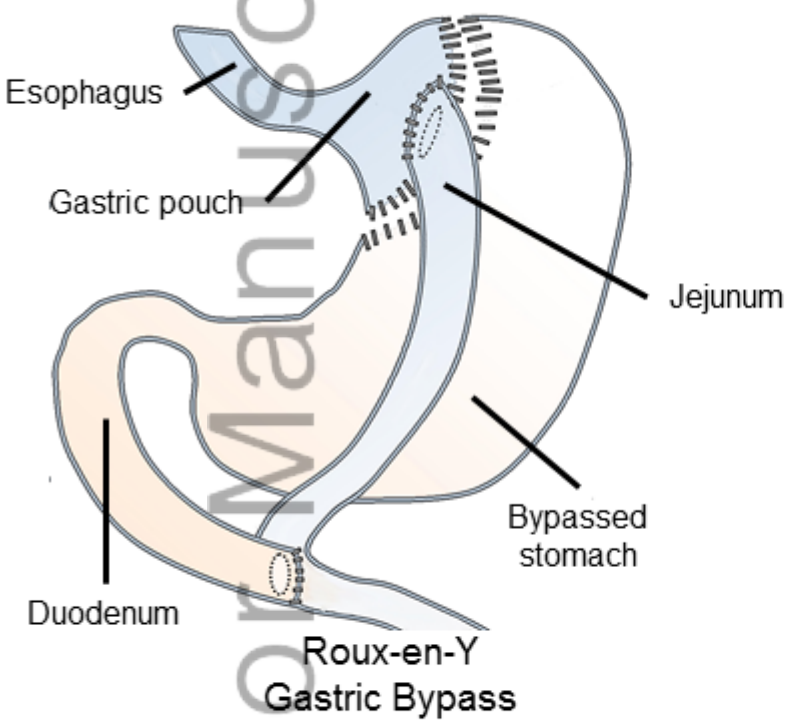
After surgery the number of adipocytes stays the same but adiposity is decreased by a reduction in the lipid content/size of the individual cells. The amount of inflammatory immune cells residing within the adipose tissue also decreases.
Individual adipocytes respond differently to lipolytic stimuli before and after surgery. In the obese state insulin is not able to suppress lipolysis causing leakage of FFA in the fed state and catecholamine stimulated lipolysis is hampered. Leptin secretion is high causing hyperleptinemia whereas adiponectin production is low. Also the adipocyte secretes pro-inflammatory adipokines such as MCP-1 and Il-6. After surgery the response towards lipolytic signals improve with insulin inhibiting FFA release and responsiveness towards catecholamines being restored. Leptin secretion decreases whereas adiponectin is upregulated. Proinflammatory adipokines are downregulated.

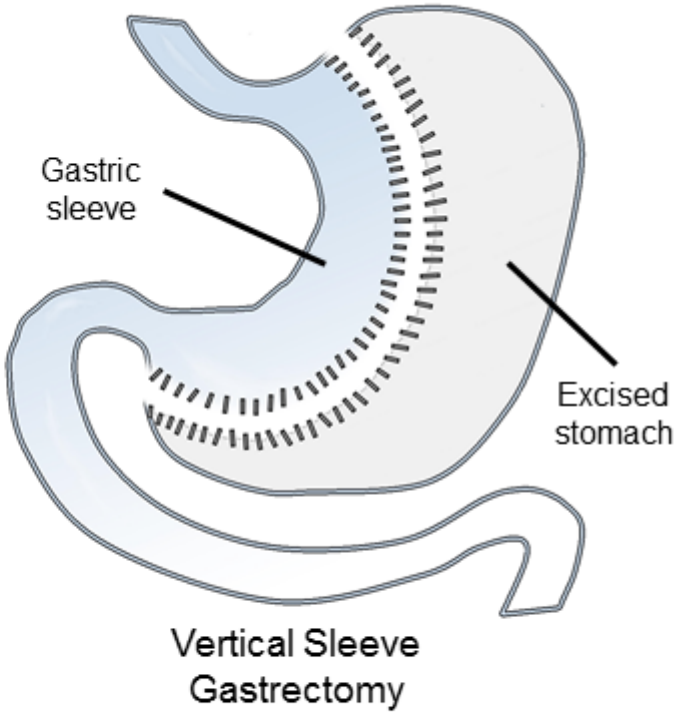
Figure 3. Proposed novel mechanisms for adipose improvement after surgery

A) It is persistently reported that plasma bile acid levels go up after bariatric surgery. Bile acids can act upon the FXR receptor causing effects in metabolic tissues and genetic deletion of the FXR receptor eliminates the effect of sleeve gastrectomy in mice. We propose that changes in bile acid signaling induced by bariatric surgery has the capacity to improve the function of the adipocyte
B) With surgery the composition of the bacteria in the gut changes. There is a tight interaction between the microbiota and the immune system. With the recent discoveries that immune cells have ability to regulate metabolic outcomes and that immune cell populations known to respond to microbiota changes are found in the adipose tissues, there is the possibility that cells of the immune system can significantly impact adipose function and that these changes can be initiated by bariatric surgery
C) Adipose tissue receives innervation from the CNS and this has physiological impact as denervation of specific depots causes hypertrophy. As bariatric surgery causes metabolic changes related to central regulation of metabolism this draws attention to the possibility that neural output to the adipose tissues are altered with surgery causing physiological changes

	End point	Gastric bypass	VSG	Weight loss control group included	No effect with RYGB	No effect with VSG
	Clinical studies					
Depot size	Decreased SAT size	21, 17, 152, 48, 153, 19, 154, 20, 155	5, 156			
	Decreased VAT size	88, 157, 21, 17, 152, 48, 153, 19, 154, 20, 155	5, 156			
Adipocyte size	Adipocyte size decreased	32, 30, 31, 32, 85, 29, 116, 158		158	93	
Lipolysis	Improved insulin suppression	55, 47, 158		158		
	Catecholaminergic stimulation improved	65				
Adipokine secretion	Increased adiponectin in blood	88, 82, 98, 11, 159, 160, 49, 31, 86, 93, 12, 85, 44, 161, 111, 84, 96, 162, 163, 164, 165, 57, 166	152, 167, 168, 169, 159, 89	88	103	170
	Decreased leptin in blood	82, 11, 159, 160, 49, 31, 86, 93, 12, 85, 44, 161, 87, 55, 111, 84, 163, 171, 172, 164, 166	152, 167, 168, 169, 159, 89, 170			
Inflammation	Decrease in inflammatory markers in blood/adipose tissue	88, 173, 174, 152, 82, 48, 115, 175, 108, 11, 159, 49, 31, 86, 93, 12, 112, 85, 19, 116, 154, 163, 171, 172, 164, 176, 166, 177, 178, 179	169, 115, 180, 108, 15, 159, 89, 156	88	82, 111, 110, 165, 103	
	Decreased amounts of inflammatory cells	30, 31, 33, 118, 117				
	In vivo studies					
Depot size	Decreased SAT size		34, 181	34, 182, 181		34, 182
	Decreased VAT size	33	124, 34, 182, 181	124, 34, 182, 181		
Adipocyte size	Adipocyte size decreased	33	34	34		
Lipolysis	Improved insulin suppression					
	Catecholaminergic stimulation improved					
Adipokine secretion	Increased adiponectin in blood	59, 183	184, 185	185	186	
	Decreased leptin in blood		187, 188, 185, 189, 34	185, 182	183	182, 181

Inflammation	Decrease in inflammatory markers in blood/adipose tissue		[190]			[190]
	Decreased amounts of inflammatory cells		[191]	[191]		





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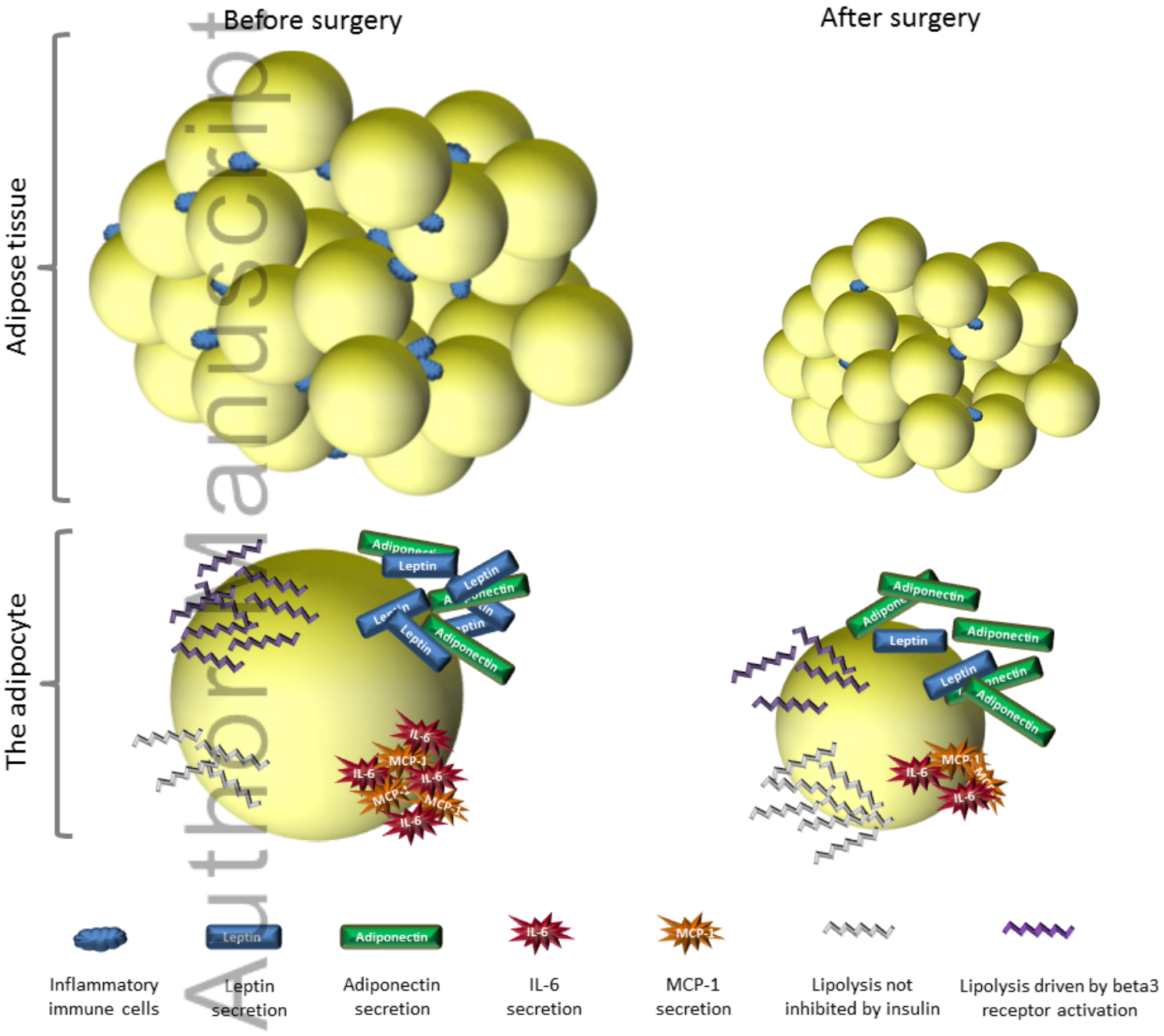

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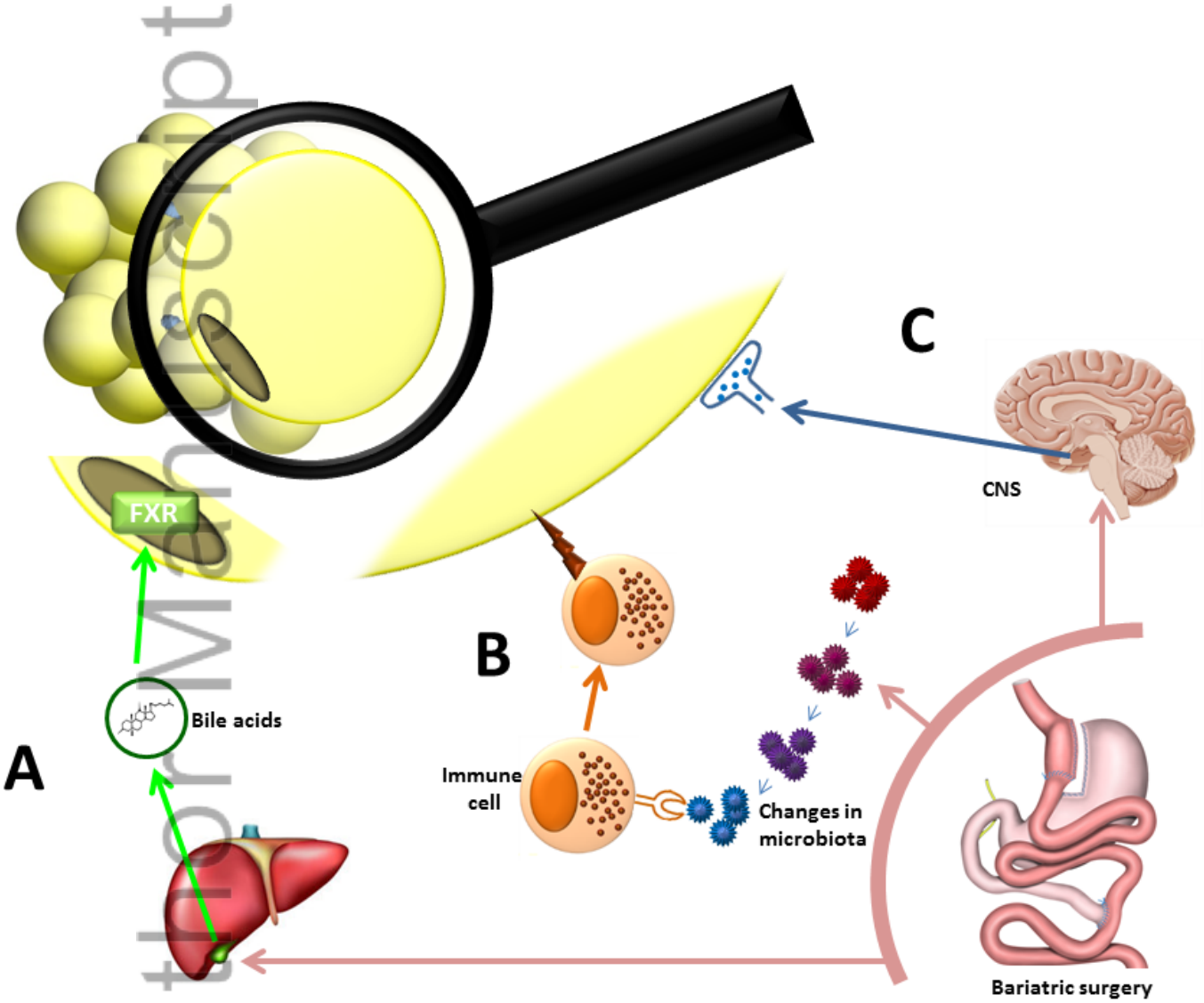

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	End point	Gastric bypass	VSG	Weight loss control group included	No effect with RYGB	No effect with VSG
	Clinical studies					
Depot size	Decreased SAT size	21, 17, 152, 48, 153, 19, 154, 20, 155	5, 156			
	Decreased VAT size	88, 157, 21, 17, 152, 48, 153, 19, 154, 20, 155	5, 156			
Adipocyte size	Adipocyte size decreased	32, 30, 31, 32, 85, 29, 116, 158		158	93	
Lipolysis	Improved insulin suppression	55, 47, 158		158		
	Catecholaminergic stimulation improved	65				
Adipokine secretion	Increased adiponectin in blood	88, 82, 98, 11, 159, 160, 49, 31, 86, 93, 12, 85, 44, 161, 111, 84, 96, 162, 163, 164, 165, 57, 166	152, 167, 168, 169, 159, 89	88	103	170
	Decreased leptin in blood	82, 11, 159, 160, 49, 31, 86, 93, 12, 85, 44, 161, 87, 55, 111, 84, 163, 171, 172, 164, 166	152, 167, 168, 169, 159, 89, 170			
Inflammation	Decrease in inflammatory markers in blood/adipose tissue	88, 173, 174, 152, 82, 48, 115, 175, 108, 11, 159, 49, 31, 86, 93, 12, 112, 85, 19, 116, 154, 163, 171, 172, 164, 176, 166, 177, 178, 179	169, 115, 180, 108, 15, 159, 89, 156	88	82, 111, 110, 165, 103	
	Decreased amounts of inflammatory cells	30, 31, 33, 118, 117				
	In vivo studies					
Depot size	Decreased SAT size		34, 181	34, 182, 181		34, 182
	Decreased VAT size	33	124, 34, 182, 181	124, 34, 182, 181		
Adipocyte size	Adipocyte size decreased	33	34	34		
Lipolysis	Improved insulin suppression					
	Catecholaminergic stimulation improved					
Adipokine secretion	Increased adiponectin in blood	59, 183	184, 185	185	186	
	Decreased leptin in blood		187, 188, 185, 189, 34	185, 182	183	182, 181
Inflammation	Decrease in inflammatory markers in blood/adipose tissue		190			190
	Decreased amounts of inflammatory cells		191	191		