Impact of Bariatric Surgery on Adipose Tissue Biology

Subjects: Endocrinology & Metabolism | Surgery

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Bariatric surgery (BS) procedures are actually the most effective intervention to help subjects with severe obesity achieve significant and sustained weight loss. White adipose tissue (WAT) is increasingly recognized as the largest endocrine organ. Unhealthy WAT expansion through adipocyte hypertrophy has pleiotropic effects on adipocyte function and promotes obesity-associated metabolic complications. WAT dysfunction in obesity encompasses an altered adipokine secretome, unresolved inflammation, dysregulated autophagy, inappropriate extracellular matrix remodeling and insufficient angiogenic potential.

bariatric surgery | adipose tissue | obesity | subcutaneous adipose tissue | visceral adipose tissue | cytokines | adipokines | adipocyte

1. Introduction

White adipose tissue (WAT) has evolved to become the largest endocrine organ. Its plasticity in response to excess or deficit of nutrients is crucial to maintain metabolic health. The remodeling and expansion capacity of adipose tissue implies the orchestrated response of adipocytes, immune cells, endothelial cells, fibroblasts, the extracellular matrix, and its secretome (cytokines, hormones, microRNAs) as mediators of crosstalk between the main organs involved in metabolic health. Dysfunctional expansion of adipose tissue emerges as a key determinant of obesity-related complications. WAT expansion beyond the subcutaneous adipose tissue (SAT) capacity leads to visceral adipose tissue (VAT) expansion and ectopic fat deposition in other tissues, which are major contributors to cardiovascular disease and metabolic risk above body mass index (BMI) [1]. The precise mechanism leading to impaired adipose tissue expandability are not fully understood. Bariatric surgery (BS) currently results in weight loss and better control of comorbid obesity conditions than medical therapy. BS is also associated with a reduced risk of mortality and of some types of cancer [2]. Currently, Roux-en-Y gastric bypass (RYGBP), sleeve gastrectomy (SG), and biliopancreatic diversion (BPD) are the main surgical techniques used worldwide [3].

2. Bariatric Surgery—Related Changes in White Adipose Tissue Biology

Since there is no standardization and the definition of short-, mid- and long-term terminologies can vary among published reports [4], from here on, the current knowledge on this topic is summarized across five follow-up time

points commonly used to report BS outcomes: ≤3 months (3 m), 6 m, 1 year (1 y)—all often considered to be short-term; ≥2 y <5 y—referred to as medium-term; and >5 y—frequently regarded as long-term post-surgery. All bariatric interventions considered in **Table 1** consisted of SG, RYGB, or BPD.

Table 1. Short-, medium- and long-term outcomes of bariatric surgery on fat depot parameters, circulating and adipose tissue expression levels of cytokines, adipokines, and microRNAs.

	Short-Term						Medium-Term		Long-Term	
Parameter	**≤3 m**		**≈6 m**		**1 y**		**≥2 y**		**≥5 y**	
Depot size										
Subcutaneous	↓	[5]	↓	[5][6][7][8]	↓	[5][6][9]	↓	[5][10][11]	↓	[12]
Visceral	↓	[5][13]	↓	[5][6][7][8]	↓	[5][6][9][14]	↓	[5][10][11]	↓	[12]
Fat cell area										
Subcutaneous	-		↓	[15][16]	↓	[16][17]	↓	[11]	↓	[12]
Visceral	-		-		↓	[17]	-		-	
Proinflammatory cytokines										
TNF-α	↑	[18][19]	↓	[20]	↓	[21][22][23]	↑	[24]	-	
	=	[25][26]	=	[27][28][29]	=	[25][27][29][30][31]	=	2 y [32], 3 y [33]	-	
					↑	SAT [34]				
IL-1β	=	[26]	-		↓	[21]	-		-	
IL-6	=	[26][29][35]	=	[20][28][29][36]	↓	[18][21][22][23][29][31][35][37][38][39]	↓	[40]	-	
	↓	[19][35][41]	↓	[18][39][42], SAT [27]	-		-		-	
IL-8	=	[26]	=	[36]	=	[31]	-		-	
	↑	[35]			↓	[43]				
	↓	[41][44]								
IL-18	-		-		↓	[20]	-		-	

	Short-Term						Medium-Term		Long-Term	
Parameter	**≤3 m**		**≈6 m**		**1 y**		**≥2 y**		**≥5 y**	
MCP-1	↓	SAT [45]	↓	[44][46]	↓	[29][44][47]	-		-	
TGF-β	=	[35]	-		↓	[35]	-		-	
Anti-inflammatory cytokines										
IL-4	=	[19]	↑	[48]	-		-			
			↓	MNC [49]						
IL-10	=	[26]	↑	[20][48]	↑	[50]	=	2 y [24], 4 y [51]	-	
			=	[42]	↓	[44]	-			
			↓	[44]						
IL-13	-		↑	[48]	↓	[23]	-		-	
Proinflammatory adipokines										
Leptin	↓	[19][28][42][52]	↓	[20][27][28][29] [42][52]	↓	[23][27][29][35] [37][43][50]	↓	2 y [24] [32], 3 y [33], 4 y [51]	-	
Resistin	=	[29]	↓	[20]	↓	[21][37][50]	↓	[24]	-	
			↑	[29]	=	[29][53]				
Visfatin	=	[29]	=	[29]	=	[29]	-		-	
Anti-inflammatory adipokines										
Adiponectin	↑	[26][28][35]	↑	[18][20]	↑	[18][20][21][29] [35][37][50]	↑	2 y [24] [32], 3 y [33]	↑	[12]
	=	[25][29][35]	=	[29][42]			=	4 y [51]		
Omentin	↑	[54]	↑	[54]	↑	[54][55]	-		-	
Other adipokines										
Apelin	-		↓	[56]	-		-		-	
Vaspin	-		-		↓	[57]	-		-	

	Short-Term						Medium-Term		Long-Term	
Parameter	**≤3 m**		**≈6 m**		**1 y**		**≥2 y**		**≥5 y**	
RBP-4	↓ = SAT [58] [58]		↓	[59][60]	↑	[30]	↓	[61]	-	
Fibrosis										
Subcutaneous	-		=	[62]	-		-		-	
Lipolysis										
Basal	=	[63]	=	Isolated SAT adipocytes [63]	-		= ↓ Male [64] Female [12][64]		= ↑ [12] SAT release [12]	
Stimulated	=	Isolated SAT adipocytes [63]	↓	Isolated SAT adipocytes vs. 1 m [63]			= ↓ Male [64] Female [64]		-	
Insulin-supressed	-		↑	[16][65]			↑	[66]	-	
FFA	↑ = [27][63] [70]		=	[27][67][68]	↑ = [69] [27]		=	[66]	-	
Angiogenesis										
VEGF-A	-		-		↓	[71][72]	-		-	
ANGPT-2, follistatin, HGF, PECAM-1	-		-		↓	[72]	-		-	
Autophagy										
Subcutaneous	-		↑	3–12 m post-BS [73]	-		-		-	
microRNAs										
	↑ ↓ 7 Circulating miRNAs [74]		-		= Circulating miR-99b [75]		↑ ↓ 15 SAT miRNAs [76]		-	

[5][6][7][8][9] [5][6][7][8][9][13]

[14] depots progressively reduce their size, and this is accompanied by a reduction in the area of subcutaneous [15] [16][17] and visceral [17] adipocytes, respectively. A large adipocyte size was independently associated with a lower incidence of insulin resistance 6 months after RYGBP [15].

	Short-Term			Medium-Term	Long-Term
Parameter	**≤3 m**	**≈6 m**	**1 y**	**≥2 y**	**≥5 y**
[80]	↓ 1 VAT and 13 SAT miRNAs [45] [77] *		↑ Circulating miR-221, miR-222 [75]	↓ SAT miR-221-3p [78] ↓ 12 SAT miRNAs [79]	

(HAM56+ in CD40+ nths after Ms again ile others

generate conflicting results between studies or do not seem to be modulated in the short term after BS. Thus, among the proinflammatory cytokines, MCP-1 was found to be concomitantly decreased during this period [45][29][46][47], while TGF-β or IL-1β seem to decrease only at 1 year after BS [21][26][35]. Reports on IL-6 production give conflicting results at 3 and 6 months but agree on a consistent decrease 1 year after surgery [18][21][22][23][25][29][31][35][37][38][39][50]. Similarly, reduced circulating levels of IL-18 were found 1 y post-BS [20] and after massive BS-induced weight loss, irrespective of the time elapsed since surgery [81][82].

In contrast, there is less consensus about TNF-α and IL-8, which have been found in different studies to both be increased [19][34][35][83], decreased [20][21][22][23][43][44], or unchanged [25][26][27][28][29][30][31][36] during this period. Similarly, BS-related outcomes on anti-inflammatory cytokine production have yielded highly contradictory results between studies during the short-term follow-up period, as is the case with IL-4 [49][19][48], IL-10 [20][26][42][44][48][50], and IL-13 [23][48]. Interestingly, circulating omentin levels decrease as early as 24 h post-BS, before any fat mass loss, and maintained for 1 y [54].

Inasmuch as surgical weight loss predominantly reduces the body fat content, it is understandable that leptin levels were found to be consistently reduced following BS [19][20][23][27][28][29][35][37][42][43][50][52]. The leptin levels were also reduced after the novel endovascular bariatric procedure [84]. Nevertheless, systemic leptin levels are not directly related to the amount of body weight or fat loss, since early reductions of adiposity more dramatically reduce leptin levels than later periods of weight loss [42][52]. Again, there is a lack of consensus regarding the short-term effect of BS on resistin levels, given several studies have found it to be decreased [20][21][24][37][50] or unchanged [29][53]. In the case of visfatin, Lima et al. showed unaltered levels throughout the first year after BS [29].

Despite some conflicting reports in the very short term [25][26][28][29][35], circulating adiponectin levels appear to be consistently increased 1 year after BS [18][20][21][29][31][35][37][50]. For its part, omentin was found to be increased as early as 24 h after BPD [54], and such a change is maintained for up to 1 year [54][55]. Apelin, a multifaceted biomarker [56], and vaspin, an insulin-sensitizing adipokine [57], are less investigated adipokines that showed a short-term reduction after BS. Regarding RBP-4, most studies reported a decrease in the circulating [59][60] or SAT mRNA [58] levels early after BS.

One study performed by Chabot and collaborators showed no resolution of SAT fibrosis 6 months after BS and suggested a transient association between SAT fibrosis and insulin resistance in humans with obesity [62]. Similarly, Katsogiannos et al. did not find significant differences in either the basal or stimulated lipolysis rate in SAT adipocytes at 1 and 6 months after BS but reported a decrease in isoproterenol-stimulated lipolysis at 6 versus 1

month after BS [63]. Conversely, insulin-suppressed free fatty acid (FFA) release has been found to be enhanced at 4 months [16], 7 months [65], and 1 year after RYGBP [69]. While some authors found increased FFA levels in the early months after BS [69][27][63], others reported no differences in this period [27][67][68][70].

García de la Torre et al. found higher VEGF-A levels in obese women undergoing BS compared to lean controls, and such levels significantly decreased 1 y after surgery, irrespective of the surgical procedure performed [71]. At this same follow-up period, another recent study showed, in addition to VEGF-A, lower levels of several angiogenesis biomarkers such as angiopoietin 2 (ANGPT-2), follistatin, hepatocyte growth factor (HGF), and the platelet endothelial cell adhesion molecule (PECAM-1) in patients who underwent SG or laparoscopic adjustable gastric banding (LAGB) [72].

Finally, Soussi et al. found attenuated WAT autophagy in obesity, and pre- versus post-BS comparisons indicated ameliorated adipocyte autophagic clearance in all patients within 3 to 12 months after the intervention, although at different degrees because of the large time-frame in post-surgery sample collection [73].

2.2. Medium Term

Two years after surgery, both visceral and subcutaneous depots maintain reduced sizes [5][10][11] as does the abdominal subcutaneous fat cell volume [11]. There is much less data available on circulating parameters beyond 1 y after BS. While IL-6 levels are consistently found reduced 2 y [24][32], 3 y [33], and 4 y after BS [51], reports on TNF-a continue to report conflicting data [24][33]. Although reports on IL-10 also seem quite inconsistent, some authors find that, after a temporary rise in the short term, its levels return to baseline values at 2 y [24], or even continue falling at 4 y [51].

BS outcomes on leptin and adiponectin levels seem much more solid. Circulating leptin has been repeatedly found to be reduced at 2 [24][32], 3 [33], and 4 y [51], and such reductions seem to be mainly attributed to early changes in WAT. Conversely, adiponectin levels continue to progressively rise in the medium term [24][32][33]. Only one report seems to oppose this view, a contradiction that could arise from the limited number of subjects and the variety of surgical techniques included in the study [51].

Beyond the short-term inconsistencies mentioned above, a single study showed that circulating resistin, after an early decline, recovered baseline levels 2 y after gastric bypass [24]. Finally, the RBP-4 levels were found still lowered 24 months after BS. Such changes were more pronounced in the subgroup without metabolic syndrome and correlated with reductions in the waist and visceral fat diameter [61].

Despite negative results reported by Katsogiannos et al. in the short term in a mixed-sex cohort [63], Löfgren and collaborators found reduced basal and stimulated lipolysis rates at 2 y after BS exclusively in females [64], where differences in the basal rates remained only significant when lipolysis was expressed per cell surface area. In another study, the glycerol release in women who underwent RYGBP was found to be decreased postsurgically at 2 y and then increased dramatically to similar levels observed before surgery at 5 y [12]. Similarly, Manco et al.

found reduced FFA levels in normoglucose-tolerant obese women 3 years after BPD [33]. Finally, insulin-mediated suppression of FFA outflow has been found to be enhanced 3 years after RYGBP [66].

2.3. Long Term

Studies on long-term outcomes after BS are restricted almost exclusively to weight-loss parameters. Thus, a recent meta-analysis at 10 or more years after all bariatric procedures reported weighted means of 56.7% excess weight loss (EWL) after GB, 45.9%EWL after LAGB, 74.1%EWL after BPD and 58.3%EWL after SG [85]. The same study reported a 48.9%EWL and 22.2%TWL 20 y after LAGB. Very similar results were previously reported by the same group at 15 y after LAGB [86]. A lower incidence [87] and greater remission [88] of T2DM have also been reported in the long term; reductions in all-cause, cardiovascular, and T2DM mortality have also been found [89]. Nevertheless, the potential impact of body fat loss on these metabolic outcomes deserves further investigation since some variables appear to be more weight-dependent, while others seem to be more adiposity-dependent from the medium-term [90].

Regarding the outcomes in WAT exclusively, we only have evidence from a single study carried out in women by Hoffstedt and collaborators at the long-term follow-up [12]. The authors reported decreased amounts of estimated SAT and VAT at 2 and 5 y and diminished SAT cell volume and increased adiponectin levels at 5 y post-BS. This study also found augmented basal glycerol release from isolated SAT adipocytes at 5 y, despite not finding changes in fasting plasma levels.

2.4. Summary of BS Outcomes on WAT

In summary, after bariatric surgery, SAT and VAT reduce their size progressively during the weight-loss phases. M1-like decrease and M2-like ATMs increase early after surgery; however, there are no data beyond the short term after BS.

Most pro-inflammatory cytokines begin to decrease early after surgery and continue to decline in the medium- and long-term. However, TGF-B or IL1B decrease only after one year of BS. There are controversial data on short-term TNFα and IL-8 levels after surgery as well as in anti-inflammatory cytokine levels in the short- and medium-term after surgery. Leptin levels drop rapidly soon after BS and then continue to decline during the follow-up; conversely, adiponectin and omentin levels rise after surgery. Resistin and visfatin dynamics show less agreement.

Regarding fibrosis, only one study reported no changes at short-term. Gender differences seem to affect basal and stimulated rates of lipolysis, which have been found decreased only in females at mid-term after BS. For its part, insulin inhibition of lipolysis was found consistently enhanced at medium- and long-term after surgery. Finally, autophagy increases and several angiogenesis-related molecules decrease at short-term, although there is a lack of reports on longer follow-up periods.

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