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What distinguishes adipose tissue of severely obese humans who are insulin sensitive and resistant?

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Abstract

Purpose of review—Despite a strong correlation between obesity and insulin resistance, 25% of severely obese (BMI >40) individuals are insulin sensitive. In this review, we will examine the factors in adipose tissue that distinguish the two groups, as well as reasons for believing the insulin-sensitive group will be less disease prone.

Recent findings—Obesity has been linked to the metabolic syndrome with an increase in visceral (intra-abdominal) compared to subcutaneous fat. Recent studies in which adipose tissue of insulin-sensitive and insulin-resistant patients with severe obesity were compared indicate that the insulin-resistant group is also distinguished by increases in oxidative stress and decreases in AMP-activated protein kinase (AMPK) activity. In contrast, changes in the expression of genes for SIRT1, inflammatory cytokines, mitochondrial biogenesis and function, and the two α -isoforms of AMPK showed more depot variation. Studies of how these and other changes in adipose tissue respond to bariatric surgery are still in their infancy.

Summary—Available data suggest that increases in oxidative stress, decreases in AMPK activity and SIRT1 gene expression, depot-specific changes in inflammatory, mitochondrial and other genes distinguish adipose tissue of insulin resistant from insulin-sensitive individuals with severe obesity.

Keywords

AMP-activated protein kinase; inflammation; insulin resistance; oxidative stress; SIRT1

INTRODUCTION

Mildly and moderately obese individuals (BMI 30–40) are predisposed to disorders such as type 2 diabetes, atherosclerotic cardiovascular disease, essential hypertension, nonalcoholic fatty liver disease (NAFLD), certain cancers, and neurodegenerative disorders including Alzheimer's disease [1[■]]. It has long been appreciated that some equally obese individuals do not show these disease predilections. In general, such individuals are more insulin sensitive and have relatively less abdominal fat (both visceral and subcutaneous) than their disease-prone counterparts [2,3[■],4]. The pathogenetic events that distinguish these patients

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Conflicts of interest

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are incompletely understood, although such factors as ectopic lipid disposition and low-grade inflammation in adipose tissue of the insulin-resistant obese group have been implicated. Diet and exercise can decrease both insulin resistance and inflammation in such obese patients. For instance, in a randomized prospective trial in middle-aged individuals with type 2 diabetes and mild obesity, diet and exercise have been shown to diminish coronary heart disease mortality [5]. However, their effectiveness in large populations over extended periods of time has been limited. Likewise, the long-term efficacy of pharmacological interventions remains to be demonstrated.

The same limitations apply to patients with severe obesity (BMI >40), although they too can respond to diet and exercise [6]. In contrast, bariatric surgery has shown substantial and lasting benefits. For instance, the Roux-en-Y gastric bypass procedure has proven effective in roughly 80% of such individuals in achieving sustained weight loss. In addition, it reverses type 2 diabetes, hypertension, and other disorder in many of these patients. Collectively, it and other procedures have been shown to diminish mortality because of atherosclerotic cardiovascular disease, an effect primarily observed in individuals in the two highest quintiles of plasma insulin (i.e. those with insulin resistance) [7[■]].

Interestingly, as is the case with their less obese counterparts [4], approximately 25% of severely obese individuals are insulin sensitive, as assessed by hyperinsulinemic–euglycemic clamps [8[■]] or homeostasis model of assessment (HOMA) [9[■],10[■], 11,12[■]]. Thus, a comparison of these patients and their insulin-resistant counterparts could provide useful information as to what distinguishes these two groups and potentially identify pathogenetic factors.

In this review, we will discuss the recent efforts to make such a comparison, based in large part on analyses of subcutaneous and visceral adipose tissue depots from the two patient groups taken at the time of bariatric surgery and in some instances afterward. The findings indicate that the insulin sensitive and resistant patients differ with respect to AMP-activated protein kinase (AMPK) activity and oxidative stress in all of their fat depots [12[■]] and in the expression of genes related to inflammation, mitochondrial function, SIRT1/Nampt, and many others [8[■],10[■],12[■],13[■],14[■]] in selected depots (Table 1). In addition, they suggest that differences in the abundance of lipid droplet proteins that regulate the storage and breakdown of triglycerides in the fat cell could play a key role [11].

OVERVIEW

Figure 1 depicts the events that occur in adipose tissue of the 75% of severely obese people who are insulin resistant. Key abnormalities appear to be impaired triglyceride storage and increased lipolysis by lipid droplets, mitochondrial dysfunction, inflammation, and increases in oxidative and endoplasmic reticulum stress [15]. Many of these abnormalities could be related to increased synthesis and release of chemokines from the adipocytes or more likely adjacent vascular cells that attract monocytes (CD68), T (CD4) and B lymphocytes, and neutrophils (MPO) from circulating blood [16] (Table 1). The resultant increases in the release of free fatty acid (FFA), reactive oxygen species (ROS), and inflammatory cytokines and the decreased release of adiponectin from the adipocyte are thought to act on peripheral tissues to cause such disorders as type 2 diabetes, atherosclerosis, and NAFLD. Not shown in the diagram is that in subcutaneous abdominal fat, the indicated changes may also be associated with decreased capillarity [13[■]] and impaired O₂ consumption and increased synthesis of type VI collagen [13[■],17], all of which could limit adipose tissue expansion. The nature of the initiating event(s) and the factors responsible for the above-mentioned changes are incompletely understood. What is clear is that many of the depicted events do not occur or are less prominent in adipose tissue of severely obese people who are insulin

sensitive. As will be discussed later, decreases in AMPK and probably SIRT1 activity are likely important pathogenetic factors.

FREE FATTY ACID AND LIPID DROPLET PROTEINS

An impaired ability to deposit triglycerides together with an increased release of FFA is one of the hallmarks of adipose tissue in severely obese people who are insulin resistant. Such abnormalities are not present in adipose tissue of equally obese people who are insulin sensitive. As reported by Puri *et al.* [11], these findings could be explained by differences in the abundance of three lipid droplet proteins, Cide A, perilipin, and FSP 27 (Cide C), all of which appear to regulate triglyceride storage and lipolysis in the lipid droplet so as to increase its size. They found that the expression of all three proteins was substantially greater in insulin sensitive than in insulin-resistant individuals with massive obesity. In addition, they observed that treatment of *ob/ob* mice which lack leptin with the thiazolidinedione or rosiglitazone increases Cide A, adiponectin, mitochondrial biogenesis, and lipid deposition in adipose tissue [11]. Others have found that such treatment activates AMPK in rodents *in vivo* [18] and that it does so at least by increasing the level of adiponectin, a known AMPK activator [19].

OXIDATIVE STRESS, INFLAMMATION, AND MITOCHONDRIA

Oxidative stress

Oxidative stress as reflected by lipid peroxidation, protein carbonylation, and DNA damage is increased in both adipose tissue and plasma of severely obese humans [20,21] and in particular those who are insulin resistant [12[■],22]. Studies in humans [21] suggest that adipose tissue is a major source of ROS in these patients. The relative contribution of increased NADPH oxidase activity, ROS generation by mitochondria, and decreased activity of antioxidant enzymes is uncertain. Elevated oxidative stress in adipose tissue is usually associated with insulin resistance and inflammation; however, the insulin resistance can occur in the absence of the latter. Thus, treatment of 3T3L1 adipocytes with glucocorticoids increases oxidative stress and causes insulin resistance even though it does not produce inflammation [23]. Such a situation presumably also occurs in humans with excess glucocorticoids (e.g. Cushing's syndrome) in whom central obesity and insulin resistance are concurrent events [24]. Interestingly, AMPK activity is diminished in visceral adipose tissue of these patients [24], just as it is in the adipose tissue of severely obese insulin-resistant patients without Cushing's syndrome [9[■],12[■]]. The basis for the decreased AMPK activity in the setting of Cushing's syndrome is not known. However, in light of the above-mentioned link between insulin resistance and oxidative stress in adipocytes [23], it is noteworthy that the lipid peroxide, 8-hydroxy nonenal (HNE), can bind to a specific lysine residue on the AMPK upstream kinase, LKB1, leading to its inhibition and secondarily that of AMPK [25].

Of further relevance to this discussion, studies in cultured 3T3L1 murine adipocytes have revealed that oxidative stress increases acutely when lipolysis is stimulated, and that this is associated with the activation of AMPK because of an increase in the AMP/ATP ratio caused by the energy demand of fatty acid re-esterification [26]. Interestingly, when AMPK activation was prevented in this setting, ROS release by the cell was markedly increased, raising the possibility that decreased AMPK activity could be a cause as well as a result of oxidative stress in the adipocyte. In keeping with this notion, a similar increase in ROS production has been observed in AMPK (-/-) endothelial cells incubated with palmitate [27].

Inflammation

Although inflammation may not always be necessary for the development of insulin resistance in adipose tissue (see above), insulin resistance in most obese individuals is typically preceded by increases in leukocyte infiltration and inflammatory cytokines [28]. The inflammation is also usually associated with increases in plasma FFA and oxidative stress and mitochondrial dysfunction in adipose tissue [29]. Another contributing factor could be an increase in circulating lipopolysaccharide (LPS), possibly related to alterations in the microbiome and the permeability of the gut, such as have been described in obese humans [29].

Recently, it has been proposed that inflammation in adipose and other tissues can be mediated by activation in macrophages of the inflammasome. An inflammasome is a multiprotein complex that mediates the cleavage and activation of caspase 1, which in turn leads to the maturation and release of the inflammatory cytokines IL-1 β and IL-18. Cytosolic NOD like-receptors such as NLRP3, together with an adaptor protein, ASC, have been shown to mediate these events in response to many stimuli. Based predominantly on the studies in cultured cells and gene knockout animals, a hypothetical mechanism for inflammasome activation and action in adipose tissue is depicted in Fig. 2 [30,31[■],32[■]]. Inflammasomes are induced in the macrophage in response to increases in such factors as fatty acids (palmitate), ROS, and potentially many others. To what extent their activation is initiated by fatty acids and ROS derived from adipocytes unable to store lipids in lipid droplets (see previous section) is unclear. As depicted in Fig. 2, autophagy removes damaged mitochondria and this could also diminish inflammasome formation and secondarily, the generation of inflammatory cytokines. The potential roles of AMPK and a closely related molecule SIRT1 in regulating inflammasome formation and other events that occur in adipose tissue in the setting of insulin resistance will be discussed in a later section. Suffice it to say, it has been proposed that decreased AMPK activity impairs the activity of the autophagosome, a key element in the autophagic process, and secondarily increases oxidative stress [30,32[■]]. As already noted, research on the inflammasome has been performed predominantly in cultured cells and experimental animals. Recently, however, Vandanmagsar *et al.* [31[■]] observed that in obese humans with type 2 diabetes, a 1-year diet and exercise intervention program decreased both insulin resistance and the expression of three elements of the inflammasome, NLRP3, ASC, and IL1 β -mRNA in subcutaneous adipose tissue.

Mitochondrial dysfunction

Mitochondrial dysfunction can precipitate and be a consequence of oxidative stress. Because of their relative paucity in white adipose tissue, the role of mitochondria in regulating adipocyte function has traditionally received little attention. More recently, diminished mitochondrial mass and function, as well as abnormally low levels of mitochondrial DNA were found in adipose tissue of *ob/ob* and *db/db* mice and were reversed by treatment with thiazolidinediones [33,34]. In humans, the scenario appears to be more complex. Mitochondrial DNA levels are diminished in adipose tissue of obese patients with type 2 diabetes [35]; however, it has been suggested that this is because of the presence of the diabetes phenotype [36]. In our own work, we found a reduced expression of the mRNA for PGC1 α , the master activator of mitochondrial biogenesis in omental fat of obese insulin-resistant patients compared to their insulin-sensitive counterparts [12[■]]. A similar finding was reported in subcutaneous fat in another study where omental fat was not concurrently examined [13[■]]. The integrity and function of mitochondrial DNA were not examined in either study.

AMPK AND SIRT1

AMPK has been implicated in regulating a variety of cellular functions including energy state, fuel metabolism, mitochondrial biogenesis, protein and ceramide synthesis, and cell growth and proliferation. In addition, its activation was initially shown to inhibit glucose, palmitate and TNF α -induced inflammation, insulin resistance, apoptosis, and oxidative stress in cultured human umbilical vein endothelial cells [27,37] and later in other cells, suggesting it plays an even broader role [1[■],38[■]]. Conversely, decreased AMPK activity has been observed in rodents with metabolic syndrome associated disorders including *ob/ob* and *db/db* mice, fat-fed rodents of many types, and ZDF rats, all of which are obese and insulin resistant [1[■]]. Furthermore, in the ZDF rat in which the primary defect is an absence of the leptin receptor, pharmacological AMPK activation has been shown to prevent the development of diabetes. In doing so, AMPK activation diminishes ectopic lipid deposition, inflammation, and apoptosis in pancreatic islets, strongly suggesting the decrease in its activity plays a key pathogenetic role [39].

As already noted, AMPK activity is diminished in omental, subcutaneous, and epiploic fat of severely obese humans who are insulin resistant compared to equally obese individuals who are insulin sensitive. Why such a decrease in AMPK activity occurs and whether it is the cause or the result of the increases in oxidative stress and inflammation, and mitochondrial dysfunction is unclear. In support of a causal role, AMPK activation has been shown to inhibit inflammasome formation in macrophages [30,32[■]] as well as the conversion of monocytes to M1 macrophages [40]. In addition, as already noted, in various cell types, AMPK inhibits the adverse effects of such molecules as palmitate, TNF α , and LPS. On the other hand, both oxidative stress [25] and inflammation as well as fatty acids have been shown to diminish AMPK activity by their effects on protein phosphatases [38[■]] in cultured cells and rodents *in vivo*. Thus, the question of which events are causal in adipose tissue must be considered unresolved. Perhaps adding to the conundrum in humans, decreases in AMPK activity and increases in oxidative stress appear to be present in multiple fat depots of insulin-resistant patients, whereas changes in the expression of genes for specific inflammatory cells and other molecules (e.g. PGC1 α , various cytokines and chemokines, and adhesion molecules) are more depot specific [12[■]].

The sirtuins are a family of histone protein deacetylases that have long been linked to the anti-aging effect of caloric restriction in rodents and other species [41]. More recently, it has become apparent that sirtuins can activate AMPK and vice versa and that these molecules have many actions and target molecules (e.g. PGC1 α , FOXO, and p53) in common [1[■]]. Thus, downregulation of SIRT1 in adipose tissue (like that of AMPK) has been shown to increase obesity, macrophage accumulation, and inflammation in rodent fat [14[■],42[■]] and conversely, activation of both molecules has been shown to diminish inflammation in macrophages [40,43]. Likewise, decreased SIRT1 expression has been observed by several investigators in adipose tissue of obese humans who are insulin resistant (Table 1) and where studied, it was associated with increased macrophage infiltration [14[■]]. Also of note, both SIRT1 and AMPK have been linked to inflammasome formation (presumably in macrophages). As already noted, AMPK has been reported to inhibit inflammasome formation by effects on mitophagy and oxidative stress [32[■]]. In contrast, SIRT1 is cleaved and inactivated by caspase 1 of the NLRP3 inflammasome [42[■]]. Finally, decreases in the activity of both AMPK and SIRT1 have been linked to the development of obesity and insulin resistance in a wide variety of rodent models [1[■],42[■],44]. In fat-fed obese rats, increases in AMPK activity and SIRT1 abundance have been observed after gastric bypass surgery [45].

BARIATRIC SURGERY

Our understanding of type 2 diabetes has been radically changed by the effects of bariatric surgery, as durable and full remission can now be achieved in a matter of days with the gastric bypass procedure in contrast to a similar correction, but one that may take months after the adjustable gastric banding operation. Bariatric surgery reverses type 2 diabetes and other disorders associated with the metabolic syndrome including hypertension, dyslipidemias, polycystic ovary syndrome (PCOS), and non-alcoholic steatosis hepatitis (NASH), as well as asthma and gastroesophageal reflux disease (GERD), even prior to significant weight loss. In addition, as already noted, it diminishes long-term mortality because of coronary heart disease [7[■]] and the prevalence of solid tumors by over 70% within 5 years after surgery [46–48].

With respect to coronary heart disease, the greatest effect was observed in patients with higher insulin levels, suggesting that the major benefit likely occurred in the insulin-resistant population. However, in a preliminary study, we observed that recovery from diabetes (as measured by fasting glucose 3 months after surgery) correlated most closely with insulin sensitivity, that is, the more insulin-resistant patients had a less favorable outcome [49]. To our knowledge, other than these studies, the relation of the response to bariatric surgery to preoperative insulin resistance has not been systematically studied in humans.

In contrast to the reversal of diabetes, the increase in insulin sensitivity after bariatric surgery appears to occur much more slowly. Insulin sensitivity, measured with a frequently sampled intravenous glucose tolerance test (IVGTT), was not statistically changed 1 month [21] or 3 months [50] after gastric bypass surgery. In patients who were weight stable more than a year after surgery, insulin sensitivity was equal to that of normal lean individuals and greater than that of weight-matched obese patients [21,51]. In short, the resolution of diabetes occurs within a few days after surgery, in line with the rapid return of insulin levels to normal, whereas insulin resistance recovers far more slowly. As reviewed elsewhere, the latter could be related to the fact that inflammation and oxidative stress both in adipose tissue and systemically take many months to an excess of a year to dissipate [21,52].

CONCLUSION

Although the majority of severely obese individuals who undergo bariatric surgery are insulin resistant, 25% of such patients are insulin sensitive. The latter are characterized by higher levels of AMPK and lipid droplet protein expression in adipose tissue. They also have less oxidative stress in all of their fat depots and a decreased expression of inflammatory genes that is more depot-selective.

Bariatric surgery reverses metabolic syndrome associated disorders such as type 2 diabetes within days, but only decreases insulin resistance, inflammation, and oxidative stress more slowly (months) in parallel with weight loss. How AMPK and SIRT1 change has not been studied. Whether the insulin sensitive and resistant patients have different risks for cardiovascular disease preoperatively is not known, although recent data indicate that cardiovascular mortality over 20 years after surgery is higher in patients initially in the highest quintiles of plasma insulin (i.e. the insulin-resistant group).

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 92).

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KEY POINTS

- Most patients with severe obesity are insulin resistant; however, approximately 25% are insulin sensitive.
- AMPK activity is diminished, and oxidative stress is increased in both subcutaneous abdominal and visceral fat of the insulin-resistant subgroup.
- The expression of inflammatory and other genes also differs in adipose tissue of the insulin sensitive and resistant patients; however, in contrast to the alteration in AMPK and oxidative stress, the differences are depot specific.
- Bariatric surgery readily reverses type 2 diabetes and other metabolic syndrome-associated disorders in these patients. In addition, it subsequently diminishes cardiovascular events and mortality.

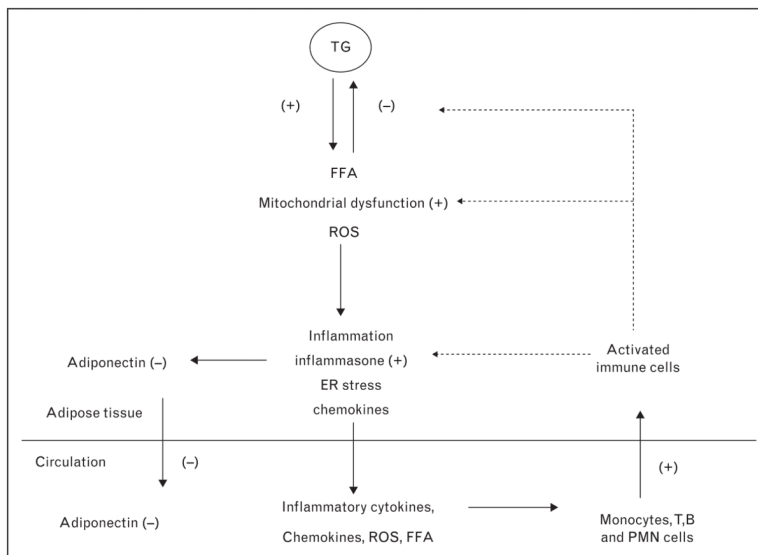


FIGURE 1. Pathophysiology of adipose tissue in an obese, insulin-resistant individual. Adipose tissue consists of the adipocyte and cells present in the stroma including those in the microvasculature, resident macrophages, and other inflammatory cells taken up from the circulation. It is assumed that mononuclear cells taken up are predominantly converted to type 1 macrophages that produce inflammatory cytokines. As discussed in the text, decreases in AMPK and SIRT1 activity, such as that found in the adipose tissue of insulin-resistant patients with massive obesity, very likely contribute to these events. An early occurrence is presumably a decrease in lipid droplet proteins that simultaneously diminish fatty acid deposition and increase free fatty acid (FFA) releases from the lipid droplet. This could account for observed increases of FFA and reactive oxygen species in the cytosol of the adipocytes; however, this remains to be proven.

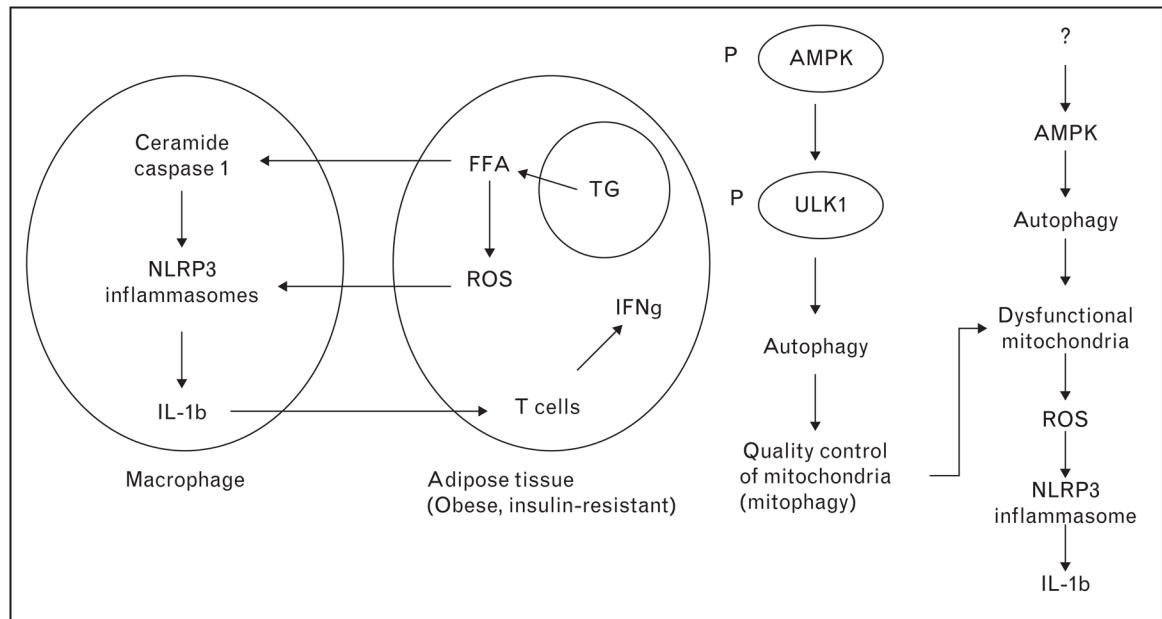


FIGURE 2.

Hypothetical mechanisms for the activation of inflammasomes in adipose tissue of obese insulin-resistant individuals (adapted with permission [30]). The identity of the factor(s) that decrease AMPK activity in cells in which inflammasomes are found is uncertain, although oxidative stress could be a factor. Not shown here is that activation of caspase 1 in the inflammasome complex cleaves and presumably inactivates SIRT1. ULK1, a regulator of the autophagy lysosome is phosphorylated and activated by AMPK.

Table 1

Summary of reported key differences in proteins and genes in adipose tissue of obese insulin-resistant vs. obese insulin-sensitive patients

	Subcutaneous fat	Omental fat
(a) Protein (Xu <i>et al.</i> [12 [■]])		
p-AMPK/AMPK	–	–
Nampt	0	–
Protein carbonylation	+	+
(b) Gene expression		
Xu <i>et al.</i> [12 [■]]		
CD4	+	+
CD68	0	+
MPO	0	+
CCL5	0	+
p-Selectin	0	+
SIRT1	0	0
Nampt	0	–
PGC1 α	0	–
Angiotensinogen	+	+
AMPK α 1	–	0
AMPK α 2	+	0
Klötting <i>et al.</i> [8 [■]]		
SIRT1	–	–
IL-6	+	+
IL-8	0	+
Nampt	0	+
Hardy <i>et al.</i> [10 [■]]		
CCL2, 3, 4, 8	0	+
IL-8	0	+
Goossens <i>et al.</i> [13 [■]]		
PGC1 α	–	ND
Gillum <i>et al.</i> [14 [■]]		
SIRT1	–	ND

In study by Xu *et al.* [12[■]], seven of the eight patients in the insulin-resistant group and three of eight in the insulin-sensitive group were diabetic (not insulin treated). Patients with diabetes or a family history of diabetes were excluded by Klötting *et al.* [8[■]]. + and – indicate a factor in increased or decreased. 0, no change; ND, not determined.