COMMENTARY

Adipose tissue inflammation and insulin resistance: all obese humans are not created equal

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In recent years, it has become widely accepted that obesity is characterized by a chronic low-grade inflammation of adipose tissue that predisposes affected individuals to insulin resistance, Type 2 diabetes and other disorders associated with the metabolic syndrome. On the other hand, a subset of obese individuals appears to be protected against insulin resistance and the disorders to which it predisposes. The comparison between such insulin-sensitive and insulin-resistant obese individuals offers a unique opportunity to identify key factors that either contribute to or prevent the development of insulin resistance in humans, without the confounding effect of a major difference in fat mass. In the previous issue of the Biochemical Journal, Barbarroja et al. reported that insulin-sensitive obese individuals show less inflammation in their visceral adipose tissue than a group of insulin-resistant subjects matched for BMI (body mass index). This finding reinforces the concept that inflammation in adipose tissue may be a cause of insulin resistance in most obese individuals, although it does not prove it. Further studies will be required for this purpose, as well as to identify the pathogenetic factors that determine whether or not adipose tissue of an obese individual becomes inflamed.

Key words: adipose tissue, AMP-activated protein kinase (AMPK), inflammation, insulin resistance, insulin-sensitive obese (ISO), metabolically healthy obese (MHO), obesity.

Obesity, when accompanied by insulin resistance, is an important risk factor for the development of such disorders as Type 2 diabetes, hypertension, atherosclerotic cardiovascular disease and NAFLD (non-alcoholic fatty liver disease). However, a subset of obese individuals appears to be protected against these diseases. In the scientific literature, they have been referred to as MHO (metabolically healthy obese), ISO (insulin-sensitive obese) or as having ‘uncomplicated obesity’ [1,2]. The ISO phenotype was first described in the 1980s [3,4] and has been the subject of a relatively small, but increasing, number of investigations. A study from NHANES (National Health and Nutrition Examination Survey) 1999–2004, indicated that among U.S. adults (>20 years of age) 30–40% of the obese population may be insulin-sensitive and metabolically healthy, depending on their sex and ethnicity [5]. Such individuals could offer a unique opportunity to delineate key factors that either contribute to or prevent the development of insulin resistance and metabolic disorders in humans without the confounding effect of increased body fat mass. The most common approach used to identify ISO individuals and their insulin-resistant counterparts has been the measurement of whole-body insulin sensitivity [e.g. via euglycaemic–hyperinsulinaemic clamp or HOMA-IR (homeostatic model assessment-insulin resistance)].

Using this approach, ISO individuals have been reported to have a similar BMI (body mass index), percentage of body fat and SAT (subcutaneous adipose tissue) mass, but less VAT (visceral adipose tissue), by CT (computerized tomography) scan, than IRO (insulin-resistant obese) subjects [6–8]. Thus, despite similar overall body fat as the IRO group, ISO individuals have lower fasting insulin and HbA1c levels, a normal glucose tolerance and they are not hypertensive [4,6,9]. In addition, they typically have less deposition of ectopic fat in their skeletal muscle and liver, a decreased prevalence of NAFLD [10] and lower levels of circulating hepatic enzymes [6,11], a finding suggestive of better liver function. Yet another distinguishing feature of ISO subjects is that they usually have lower circulating triacylglycerol [7–9,12–14] and NEFAs [non-esterified (free) fatty acids] [6] levels, and increased levels of circulating HDL (high-density lipoprotein) [7,8,13,14]. Collectively, these findings suggest that ISO individuals have an increased ability to store lipid in their SAT and that they store less of it in visceral fat, liver and muscle, organs in which the accumulation of intracellular lipids is associated with insulin resistance [15] (Figure 1). In this context, Puri et al. [16] recently reported that the expression of three lipid-droplet-associated proteins, Cidea [cell death-inducing DFFA (DNA fragmentation factor α)-like effector α], Cidec [cell death-inducing DFFA-like effector c] and perilipin, all of which appear to play a role in the sequestration of fat in the form of triacylglycerol in the adipocyte [16,17], is higher in adipose tissue of ISO than IRO individuals. This, plus the

Abbreviations used: AMPK, AMP-activated protein kinase; BMI, body mass index; DFFA, DNA fragmentation factor α; Cidea, cell death-inducing DFFA-like effector a; Cidec, cell death-inducing DFFA-like effector c; CRP, C-reactive protein; ERK, extracellular-signal-regulated kinase; FSP27, fat-specific protein 27; HDL, high-density lipoprotein; HIF, hypoxia-inducible factor; HOMA-IR, homeostatic model assessment-insulin resistance; IL, interleukin; IR-MO, insulin-resistant morbidly obese; IRO, insulin-resistant obese; ISO, insulin-sensitive obese; JNK, c-Jun N-terminal kinase; MCP, monocyte chemoattractant protein; MHO, metabolically healthy obese; NAFLD, non-alcoholic fatty liver disease; NEFA, non-esterified (free) fatty acid; NF-κB, nuclear factor κB; NIR-MO, non-insulin-resistant morbidly obese; SAT, subcutaneous adipose tissue; TNFα, tumour necrosis factor α; VAT, visceral adipose tissue.

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observation that ISO individuals have an increased proportion of large adipocytes in their SAT, as well as an increased expression of genes involved in adipogenesis and terminal differentiation of their adipocytes [i.e. PPAR (peroxisome-proliferator-activated receptor) γ1 and 2, and adiponectin], suggests that they may be more effective at sequestering fat than IRO individuals [13].

Another potential factor that may differentiate ISO from IRO individuals is inflammation (Figure 1). A causal link between obesity, inflammation and insulin resistance was first reported by Hotamisligil et al. [18] and Feinstein et al. [19]. Both groups observed that TNFα (tumour necrosis factor α), a pro-inflammatory cytokine overproduced by adipose tissue of obese subjects, can cause insulin resistance. Since then, it has become clear that adipose tissue of such obese individuals secretes a multitude of pro-inflammatory cytokines and chemokines such as TNFα, MCP (monocyte chemoattractant protein)-1, PAI (plasminogen-activator inhibitor)-1, CCL5 (CC chemokine ligand 5), IL (interleukin)-6, CRP (C-reactive protein) and chemerin. To a considerable extent, such inflammation may result from the attraction, infiltration and activation of immune cells by adipose tissue [20,21]. Thus several studies have reported an increased presence of macrophages in adipose tissue of obese humans and rodents compared with lean controls [22–25]. Despite these observations, the question remains as to whether this link between inflammation and insulin resistance is causal and, if so, whether there are obese individuals who do not manifest such a pro-inflammatory state. Findings from several studies suggest that this could be the case. Thus it was shown that ISO subjects have reduced circulating levels of inflammatory molecules, such as CRP [6–8], chemerin [6], IL-6 [6,8] and oxidized LDL (low-density lipoprotein) [8], and increased levels of adiponectin, an adipokine that activates AMPK (AMP-activated protein kinase) (see below) and has well known anti-inflammatory and insulin-sensitizing properties [6,10,14,26,27].

In the previous issue of the Biochemical Journal, Barbarroja et al. [28] reported for the first time that morbidly obese insulin-sensitive individuals show less inflammation in their VAT than BMI-matched individuals who are insulin resistant. To demonstrate this, they stratified 24 morbidly obese subjects (mean BMI of 56 kg/m²) undergoing bariatric surgery into IR-MO (insulin-resistant morbidly obese) and NIR-MO (non-insulin-resistant morbidly obese) groups, according to HOMA-IR, and assessed various markers of inflammation in their visceral fat. The study also included a control group of twelve non-obese subjects (BMI 18.5–24.9 kg/m²) with no alterations in lipid or glucose metabolism. Despite having similar BMIs, NIR-MO subjects had significantly less inflamed VAT than IR-MO individuals as suggested by: (i) lower mRNA and protein levels of the inflammatory cytokines IL-6 and IL-1β; (ii) lower mRNA levels of CD11b, PLAUR (plasminogen activator urokinase receptor), CSF (colony-stimulating factor)-3 and MCP-1, which the authors used as macrophage markers; and (iii) a decreased presence of macrophages, as shown by immunostaining of CD68. They also examined the possible involvement of key inflammatory pathways, such as JNK (c-Jun N-terminal kinase), ERK (extracellular-signal-regulated kinase) and NF-κB (nuclear factor κB), and found that JNK activation was similar in ISO and IRO subjects, whereas ERK and NF-κB activation appeared to be greater in the IRO individuals. Although very exciting, the latter results need to be viewed with caution as some experimental controls were not provided (protein loading controls for immunoblots, and supershift and competition assays for electrophoretic mobility-shift assays). It is also noteworthy that compared with the lean control group, the NIR-MO (ISO) subjects did not appear to be metabolically healthy, as evidenced by their higher HOMA-IR values and increased levels of serum triacylglycerol, glucose and insulin, and lower levels of serum HDL. In addition, similar to their intermediate insulin resistance and metabolic disturbances, this group showed an intermediate level of inflammation in VAT. These questions aside, very similar results were reported almost simultaneously by Kloting et al. [6]. These authors observed greater levels of inflammation in VAT of
IRO than ISO subjects, and noted that this was associated with impaired insulin-stimulated glucose uptake in adipocytes isolated from omental fat. They also noted increased inflammation in abdominal SAT in the IRO individuals, although to a lesser extent than in visceral fat, in keeping with previous reports [6,29,30]; however, none of those studies included a lean control group. Even when overall and SAT fat mass are comparable, VAT mass is typically larger in IRO than in ISO subjects [6–8]. Thus the results do not appear to support the notion that VAT inflammation is independent of the level of expansion of adipose tissue as suggested by Barbarroja et al. [28]. On the other hand, modest inflammation in SAT seems to occur in IRO individuals [6,29,30] even when its mass is not increased compared with that of ISO individuals [6–8]. As noted above, SAT expansion could be limited in such patients due to decreases in Cidea, Cidec/FSP27 or perilipin [16], and such a failure to expand could lead to inflammation and eventually insulin resistance (Figure 1). Recently, Khan et al. [31] have reported that in various rodent models of obesity, adipose tissue shows signs of fibrosis, which restrains the expansion of adipocytes and is associated with inflammation and insulin resistance. Furthermore, that study demonstrated that a knockout of type VI collagen in ob/ob mice both increased the expansion and decreased inflammation in adipose tissue and increased whole-body insulin sensitivity [31]. More recently, a positive correlation between adipose tissue collagen VI mRNA levels, BMI and inflammation has been found in humans [32]. It has been proposed that the mechanism that triggers this sequence of events could be a rapid expansion of adipose tissue that, together with insufficient growth of the microvasculature, leads to hypoxia and the activation of the transcription factor HIF (hypoxia-inducible factor)-1α [33]. Initial studies suggest that ISO individuals may be protected against such adipose tissue hypoxia as shown by lower mRNA expression of HIF-1α in their adipose tissue [6]. Whether they are also protected against adipose tissue fibrosis remains to be determined.

Another possible mechanism that could initiate inflammation in adipose tissue of ISO individuals is dysfunction of AMPK. AMPK is best known as a fuel-sensing enzyme that responds to decreases in a cell’s energy state by increasing processes that generate ATP, such as fatty acid oxidation, and decreasing others that consume ATP (e.g. lipid and protein synthesis) and that can be down-regulated without compromising cellular viability [34]. AMPK activation also has been shown to mediate angiogenesis in the setting of ischaemia [35–37] and to decrease inflammation, oxidative stress and insulin resistance in many cells when exposed to elevated levels of glucose, NEFAs and inflammatory cytokines (reviewed in [38]). Likewise, decreased AMPK has been observed in many rodents with a metabolic syndrome phenotype and agents that activate AMPK, including thiazolidinediones, metformin and adiponectin, have been shown to increase insulin sensitivity and diminish inflammation [38,39]. Recently decreased AMPK activity has been observed in adipose tissue [40,41] and isolated adipocytes [40] of mice on a high-fat diet, and knocking-down AMPK has been reported to enhance NEFA- and LPS (lipopolysaccharide)-induced inflammation in cultured macrophages [41]. A substantial body of evidence suggests that the anti-inflammatory effects of AMPK occur through inhibition of NF-κB signalling [41–43]. In as yet unpublished results that were presented at Obesity Society meetings [44,45], we found that AMPK activity is inversely correlated with markers of inflammation in SAT and VAT of morbidly obese humans (mean BMI of ∼45 kg/m²). Furthermore, AMPK activity was significantly greater in both SAT and VAT of ISO than in IRO subjects. Likewise, in complementary studies with cultured 3T3-L1 adipocytes, we found that down-regulation of AMPK results in increases in oxidative stress [45,46] and monocyte adhesion [45], suggestive of a pro-inflammatory state. Collectively, these findings suggest that decreased AMPK activity in adipose tissue could be a feature that distinguishes ISO and IRO humans. Whether it is a primary event that leads to inflammation and insulin resistance (Figure 1) or if it is the result of inflammation in adipose tissue infiltrated with immune cells, remains to be determined.

In conclusion, the study of Barbarroja et al. [28] reinforces the concept that inflammation of adipose tissue is a major contributor to the development of obesity-associated insulin resistance. Perhaps more importantly, it suggests that some obese individuals have adipose tissue that is better equipped to deal with calorific excess. Further investigations are required to elucidate the exact mechanism(s) that protect this unique subset of obese individuals against adipose tissue inflammation, insulin resistance and other metabolic disturbances.

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