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Role of Visceral Adipose Tissue in Aging

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Abstract

Visceral fat (VF) accretion is a hallmark of aging in humans. Epidemiologic studies have implicated abdominal obesity as a major risk factor for insulin resistance, type 2 diabetes, cardiovascular disease, stroke, metabolic syndrome and death. Utilizing novel rodent models of visceral obesity, studies have demonstrated a causal relationship between VF and age-related diseases. In contrast, surgically removing large quantities of subcutaneous (SC) abdominal fat does not consistently improve metabolic parameters in humans or rodents, suggesting that SC fat accrual is not an important contributor to metabolic decline. There is also compelling evidence in humans that abdominal obesity is a stronger risk factor for mortality risk than general obesity. Likewise, we have shown that surgical removal of VF improves mean and maximum lifespan in rats, providing the first causal evidence that VF depletion may be an important underlying cause of improved lifespan with CR. Given the hazards of VF accumulation on health, treatment strategies aimed at selectively depleting VF should be considered as a viable tool to effectively reduce disease risk in humans. In summary, this review provides both corollary and causal evidence for the importance of accounting for body fat distribution, and specifically VF, when assessing disease and mortality risk.

1. Obesity and disease

The prevalence of overweight (body mass index >25) and obesity (body mass index >30) now affects nearly two thirds of Americans and has reached epidemic proportions in most of the developed world. Obesity increases the risk for several co-morbidities including type 2 diabetes (T2DM) [1], stroke [2], cardiovascular disease (CVD) [3], and metabolic syndrome [4]. In a report from the National Health and Nutrition Examination Survey III (NHANES III), by comparison with normal weight men, the odds of having metabolic syndrome increase in a dose-response manner from overweight (5.2), moderately obese (25.2), to severely obese (67.7) [5]. More recently, the risks associated with obesity have been extended to cancer [6,7] including, prostate [8], breast [9], liver [10], kidney [10], colon [11], ovarian [12], and endometrial cancers [13].

2. Abdominal obesity and disease risk in humans

The fundamental cause of obesity is a long-term imbalance in energy intake and expenditure (i.e., positive energy balance) leading to the increased body mass including the accumulation of subcutaneous (SC) and visceral fat (VF). Although general obesity is an important risk factor for many diseases, several human studies have demonstrated that VF accrual, which is the fat located in the viscera, as most strongly related to many health conditions, including CVD,

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insulin resistance and T2DM [14]. The mechanism(s) linking VF with the metabolic syndrome is not entirely clear, but it has been suggested to involve its anatomical location, leading to a 'portal' effect of greater free fatty acids (FFA) and glycerol release [15]. More recently, evidence has shown that adipose tissue is an active endocrine organ, capable of secreting many cytokines, often referred to as adipokines, that can promote inflammation and interfere with insulin action [16]. Furthermore, studies from our group and others have shown that SC and VF are biologically distinct, with VF demonstrating far greater pro-inflammatory characteristics than SC fat. In the remainder of this review, we will discuss 1) the epidemiologic and surgical data in humans linking VF and not SC fat to disease, 2) animal studies which demonstrate a causal relationship between VF, but not SC fat accumulation to metabolic decline with aging, 3) statistical and experimental data in humans and rodents linking VF accretion to mortality risk and lifespan, and 4) treatment strategies aimed at reducing disease risk by depleting VF stores.

2.1. Human Epidemiologic studies

The ability to prevent or delay the onset of disease is a critical determinant of lifespan. Some diseases are not treatable or preventable and have an inheritable component of risk. However, the leading causes of death and co-morbidities in humans, including CVD, stroke and T2DM are age-related conditions that can be largely prevented or delayed by lifestyle interventions [17]. Epidemiologic studies have revealed that a common yet preventable risk factor for these diseases is the accumulation of VF, which is a hallmark of aging in humans [18]. Using either waist circumference and/or waist-to-hip ratio as a proxy of abdominal obesity, numerous studies have found that VF is a stronger risk factor for insulin resistance, T2DM [19], CVD [20], stroke [21] and heart failure [22] than body mass index (BMI) or other fat depots. However, the hazards of abdominal obesity are not only limited to metabolic disorders, but also to cognitive decline, [23], Alzheimer's disease [24] and disability [25].

2.2. Liposuction of SC fat in humans

Several studies have reported on the metabolic consequences of surgically removing large quantities of SC fat by liposuction. The general premise of these studies is that absolute fat mass is the most important contributor to obesity-related complications such that large-scale removal of abdominal SC fat should improve several metabolic parameters including insulin sensitivity. Results from these studies have been contradictory with some showing beneficial effects of liposuction on insulin sensitivity [26–29] but not others [30,31] while one reported an improvement in the blood lipid profile, but not in insulin sensitivity [32]. It has been suggested that the conflicting nature of these studies is due to several uncontrolled confounders including the way that insulin sensitivity was assessed, failure to match properly for baseline parameters, poor control of behavioral confounders after the procedure and the removal of varying amounts of SC fat [33].

A study by Klein *et al.* [33] attempted to definitively address the potential of liposuction as a tool to treat obesity-related metabolic disorders by controlling for the aforementioned confounders. In a study consisting of 15 obese patients (8 non-diabetic controls and 7 T2DM patients) with similar BMI, several metabolic parameters were assessed before and 10–12 weeks after having ~10.5kg of SC abdominal fat removed. Utilizing the euglycemic-hyperinsulinemic clamp procedure, they found that liposuction did not significantly alter insulin action in muscle, liver, or adipose tissue, or plasma levels of C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), adiponectin, glucose, insulin, blood lipids and blood pressure. Therefore, surgically removing large quantities of SC abdominal fat does not appear to be sufficient to improve metabolic parameters, and suggests that SC fat is not an important component of obesity-related metabolic disorders in humans.

3. Animal models of obesity and disease

Human studies have clearly demonstrated that obesity, and specifically VF accrual is strongly associated with disease risk [14]. In order to better understand the pathophysiology of obesity in mammals, several strategies have been developed and implemented including, high-fat feeding in rodents [34] and dogs [35], seasonal models of obesity [36], transgenic mice [37] and spontaneous mutants such as *ob/ob* and *db/db* mice [38]. A common feature of obese animal models is a marked increase in VF and hyperinsulinemia, but similar to human studies, the distinct contribution of body fat distribution in these models cannot be directly elucidated. However, clever experimental strategies in animal models have been utilized which have overcome this inherent limitation and demonstrated a causal role for VF, rather than SC fat, in the etiology of insulin resistance, atherosclerosis and aging in mammals.

3.1. Transgenic Model of Visceral Obesity

Excess glucocorticoids are known to promote VF deposition and insulin resistance in obesity [39]. Since glucocorticoids can be produced locally by the enzyme 11 β hydroxysteroid dehydrogenase type 1 (11 β HSD-1), Masuzaki et al. [40] produced transgenic mice overexpressing this enzyme in adipose tissue. These mice were reported to be hyperphagic, despite elevated leptin levels, obese and displayed greater levels of corticosterone in fat. Most important, transgenic mice displayed exaggerated visceral obesity on a high-fat diet as compared to controls. Furthermore, transgenic animals demonstrated greater adipokine levels than controls, hyperlipidemia, glucose intolerance and hyperinsulinemia.

3.2. Fat transplantation models

Using a surgical approach, Ohman *et al.* [41] determined whether transplanting epididymal fat pads from C57BL/6J mice could affect vascular disease in atherosclerosis-prone apolipoprotein E-deficient (ApoE $^{-/-}$) mice. Plasma from ApoE $^{-/-}$ mice receiving fat transplants displayed elevated levels of leptin, resistin, and monocyte chemoattractant protein-1 (MCP-1) compared with plasma from sham-operated mice. Furthermore, mice transplanted with VF developed significantly more atherosclerosis than controls. In contrast, SC fat transplants did not accelerate atherosclerosis despite a similar degree of inflammation, suggesting that VF rather than SC fat-related inflammation accelerates atherosclerosis development in this model.

3.3. Surgical removal of visceral fat

Using a different surgical approach to demonstrate causality between VF and disease, we and others have selectively removed perinephric and epididymal fat pads from rats and mice and studied its impact on insulin action. Please refer to Table 1 for a summary of the metabolic effects of VF removal in rodents. In an initial study [42] from our lab, young moderately-obese Sprague-Dawley (SD) rats were randomized either to surgical removal of VF (VF-) or to sham operation (VF+). Since the VF that was removed accounted for only ~10% of total fat mass (FM), there was no difference between groups for body weight or total FM. Nevertheless, VF-rats demonstrated significantly reduced insulin levels, and during a glucose clamp, the rates of insulin infusion required to maintain plasma glucose levels and hepatic glucose production were reduced by 50%. More recently, we have shown that VF accretion is an important determinant of hepatic insulin resistance during pregnancy, which can be largely prevented by surgical removal of VF prior to mating [43], providing further evidence that VF directly impacts hepatic insulin action.

Borst et al. [44] studied the impact of VF removal on insulin action and skeletal muscle glucose transport in male SD rats. VF removal in rats tended to improve glucose tolerance (15% reduction in glucose AUC) and significantly lowered some pro-inflammatory adipokines in

serum. Most striking, VF- animals displayed increased insulin-stimulated glucose transport in excised soleus and digitorum longus muscle as compared to sham-operated controls. Overall, these studies provide verification that VF is a potent modulator of both hepatic and peripheral insulin action.

Our group [45] and others [46] have also demonstrated a protection from T2DM in rodents with VF removal. In our study, 2 month-old Zucker Diabetic Fatty (ZDF) rats were assigned to receive either a sham operation (ZDVF+), or surgical removal of VF (ZDVF-) [45]. Despite no differences in plasma glucose or FFA levels, ZDVF- rats had a marked reduction in fasting insulin levels by ~50%. In addition, during a glucose clamp, ZDVF- rats demonstrated a greater glucose infusion rate and insulin suppression of glucose production than controls. Furthermore, when rats were monitored longitudinally, the development of diabetes, as determined by fasting glucose, was delayed in ZDVF-rats but not in sham-operated rats.

Using a mouse model of diet-induced obesity and T2DM, Pitombo *et al.* [46] assessed the impact of VF removal on glucose metabolism, insulin signaling and serum adipokine levels. Control mice became diabetic and hyperinsulinemic, but VF removal partially restored metabolic parameters. In addition, VF removal completely attenuated the impairment of insulin signaling observed in muscle from control animals and lowered serum adipokines to near normal levels. Taken together, these studies demonstrate the ability of VF removal to prevent T2DM in both a spontaneous and diet-induced obesity-prone rodent model.

3.4. Expansion of SC adipose tissue improves metabolic parameters

Kim *et al.* [47] hypothesized that a major link between obesity and insulin resistance is due to a limited ability to expand SC adipose tissue leading to the expansion of other fat depots and ectopic fat deposition in skeletal muscle and liver. In order to test this hypothesis, they overexpressed adiponectin in *ob/ob* mice. They observed that mice lacking leptin while overexpressing adiponectin showed a dramatic improvement in the metabolic profile including normalized glucose and insulin levels and lower triglyceride levels. They also displayed reduced macrophage infiltration in adipose tissue and systemic inflammation. Most striking, the transgenic mice were morbidly obese, weighing nearly 100g by 20 wks of age as compared to *ob/ob* littermates that weighed nearly 40g less. Furthermore, transgenic mice had much greater fat mass including SC fat mass, but less relative VF (VF% of total body wt) than *ob/ob* mice and less triglycerides in muscle and liver. In summary, these data illustrate an interesting paradox which is in line with other studies showing no metabolic benefit to SC fat removal. Specifically, massive expansion of the SC fat depot is not harmful but instead appears to be beneficial for insulin action by preventing ectopic and VF deposition.

4. Abdominal Obesity and Mortality Risk in Humans

Several studies have reported that obesity, generally defined as a BMI >30, increases the risk of disease specific and all-cause mortality [48–51] and reduces life expectancy [52]. Fontaine *et al.* [52] reported that Caucasian men and women who reached a BMI >40 between the ages of 20-29 years, could expect a reduction in remaining years of life expected by approximately 6 and 12 years, respectively. Obesity has not only been linked to a reduced life expectancy but also to accelerated aging as demonstrated by obese women having telomeres that were 240 bp shorter than lean women of a similar age [53].

Since abdominal obesity, as assessed by waist circumference or the waist-to-hip ratio in large population studies, has emerged as a stronger predictor of disease risk than BMI, studies have begun assessing the mortality risk posed by abdominal obesity [54–56]. Wannamethe *et al.* [57] found that a particularly high waist circumference (>102 cm), waist-to-hip ratio (top quartile), and a composite of waist circumference and sarcopenia were the strongest predictor

of mortality in men. More recently, a large cohort study in Europe reported that general (BMI) and abdominal adiposity (waist circumference; waist-to-hip ratio) are both strong predictors of mortality risk but that the importance of abdominal obesity was most striking among persons with a low BMI [58].

5. The controversy of body fat in caloric restriction-associated longevity

Studies dating back to the early 1900's by Moreschi and Rous, and later by McCay and Tannenbaum [59,60], respectively, were the first to demonstrate that a reduction in food intake was capable of increasing lifespan and inhibiting tumor formation in rats [61]. Nearly a century later, calorie restriction (CR) remains the only known behavioral intervention capable of delaying the onset of many age-related diseases and extending maximal longevity [62,63]. This finding has since been extended to several diverse organisms including yeast, nematode, water flea, fruitfly, dog, and cow [60,62,64–66].

The fact that limiting calorie intake has such profound effects on mammalian aging and disease is intriguing, because it suggests that the rate of biological aging is intimately related to energy metabolism. In the laboratory, CR is generally implemented by limiting food intake 20–40% of *ad libitum*-fed controls [67]. Thus, the beneficial effects of CR have historically been attributed to a reduction in food intake [68–70]. However, this simplistic view has recently been called into question since CR is not only characterized by less food intake, but also by concurrent changes energy balance, body mass, and body composition [71,72]. Since adipose tissue has been historically viewed as an inert storage depot for triglycerides, this robust phenotypic change had been widely discounted as merely a byproduct of reducing food intake [68,69,73]. It was not until 1960 that a reduction in fat stores was proposed as an important mediator of CR [74]. Since many believed CR worked by slowing metabolism or retarding growth and development, this hypothesis was never fully embraced at the time, although it was neither discounted until 20 years later.

5.1. Evidence against a role for body fat in determining lifespan

In 1980 and 1984, respectively, two historic studies were published which essentially discredited the “Reduction of Body Fat Hypothesis” for many years. The first by Bertrand and colleagues [68] reported that fat mass was not related to lifespan in *ad libitum*-fed rats, but was paradoxically associated with a greater lifespan in calorie-restricted rats. The later study by Harrison *et al.* [73] found that calorie-restricted *ob/ob* mice were longer lived than *ad libitum*-fed wild types, despite having nearly twice as much body fat. Indeed, these studies made a compelling case against a role for body fat in the determination of lifespan. However, the conclusions of these studies have since been criticized and debated [69,72]. There has also been controversy regarding the role of body fat in both spontaneous and transgenic long-lived mutants. For instance, several models of growth hormone (GH) deficiency or resistance including the Ames dwarf, Snell dwarf, and the GHR $-/-$ mouse have reduced body size and live substantially longer than controls. However, these mice all have a high percentage body fat, although to the best of our knowledge, body fat distribution in these models has not been reported.

5.2. A paradigm shift

Since the discovery of leptin in 1994 [75], the view of adipose tissue as an inert storage depot began to change. Indeed, evidence began to mount that obesity and specifically VF is associated with a low-grade inflammation due to the increased secretion of numerous pro-inflammatory cytokines from adipocytes and their associated macrophages [76,77]. Many of these cytokines also referred to as “adipokines” including leptin, TNF- α , IL-6, heparin-binding epidermal growth factor (HB-EGF), and vascular endothelial growth factor (VEGF) among others, may

play an important role in many disease pathologies by promoting angiogenesis, inflammation, cell proliferation, and insulin resistance [77,78]. Considering this new perspective of fat, coupled with studies from our group linking age-related changes in body composition with insulin resistance, we hypothesized that the ability of CR to improve insulin action is by reducing VF.

5.3. VF removal in rats mimics the benefits of CR on insulin action

Since CR limits the accumulation of VF and preserves hepatic insulin action with aging in mammals [79] and extends lifespan in a variety of species [80], we suspected that the ability of CR to prevent insulin resistance with aging was due to the attenuation of VF, rather than other fat depots. To directly test this hypothesis, we studied four groups of rats: VF-, SC- (equivalent SC fat removed), SO (sham-operated controls), and CR (CR+sham operated) [45]. Post-absorptive plasma insulin levels were nearly 50% greater in the SC- and SO rats as compared to CR and VF- animals. During a glucose clamp, VF- rats had an 80% increase in the rate of glucose infusion, significantly greater glucose uptake, and 50% increase in the ability of insulin to suppress hepatic glucose production compared to SC- and SO rats. Most striking, the dramatic improvement in insulin action with VF, but not SC fat removal, closely resembled the effects of prolonged CR, suggesting that decreased VF could largely account for the beneficial effects of a reduction in food intake. Additionally, our earlier studies had shown a causal role for VF in age-related metabolic decline [72] leading us to revisit the body fat and longevity hypothesis by proposing that the ability of CR to improve longevity is by reducing VF.

5.4. VF removal in rats improves longevity

As previously mentioned, VF accretion is a common hallmark of aging, and we have demonstrated metabolic benefits to VF removal [79], and that decreased VF largely accounts for the improvement in insulin action with CR [45,79]. Therefore, it seemed plausible that the beneficial effects of CR on longevity may be due to the attenuation of VF [72]. Quite surprisingly, very few rodent studies have found a role for body fat in the determination of lifespan. In the most widely cited report by Bluher *et al.* in 2003, fat-specific insulin receptor knockout (FIRKO) mice showed a modest reduction in body mass, but were markedly leaner than controls, demonstrating a 50% reduction in fat mass and lived nearly 20% longer than controls. Using a mathematical approach, Wang *et al.* [81] found that CR and body weight had independent effects on mortality rate in male Wistar rats, such that statistically, body weight accounted for approximately 11% of the CR effect on mortality rate. However, this study may have underestimated the importance of body fat and specifically VF, since body composition was not measured.

In order to definitively demonstrate that VF modulates longevity, we prospectively studied lifespan in 3 groups of rats: *ad libitum* fed (AL), 40% CR and VF- rats [82]. CR rats demonstrated the greatest survival among all experimental groups (Fig. 1). Statistical analysis revealed a significant increase in both mean and maximum lifespan for VF- rats as compared to AL fed animals and VF removal accounted for ~20% of the effect of CR on longevity. Furthermore, the hazard rate of death in the VF- group was 0.49 (51% reduction) and in the CR group was 0.13 (87% reduction) compared to the AL-fed group. This effect of VF *per se* was even more remarkable when considering that VF- rats had similar food intake, body weight and body fat as AL controls. In fact, VF- animals were 220g heavier, had nearly 115g more body fat and a percentage body fat nearly double that of CR rats. Furthermore, the only fat pads removed were the epididymal and perinephric fat pads, which do not drain into the portal vein in rats. This raises the possibility in humans that VF depletion may be even more beneficial since VF depots in humans have direct portal access and hence a greater potential to harm the liver. An illustration of the proposed link among VF, age-related diseases and lifespan can be

found in Fig. 2. In summary, these data provide the first causal evidence implicating VF depletion as an important underlying cause of improved lifespan with CR.

6. Treatment studies

6.1. Leptin and β 3-agonist administration

Our group and others have demonstrated various treatment strategies for VF and/or its complications. In an initial study [83], we administered leptin by osmotic minipumps for 8 days to rats, since this fat-derived peptide had been shown to play an important role in energy homeostasis. Remarkably, we found that leptin administration led to a more dramatic decrease in VF than pair-fed controls, which were moderately food restricted, but body weight and total FM were not different. Furthermore, leptin-treated rats demonstrated the greatest enhancement in hepatic insulin action. Likewise, because the effects of leptin function primarily through the β 3-adrenoreceptor, we performed an analogous experiment designed to decrease VF to a similar extent by β 3-adrenoreceptor agonist or CR [84]. Compared to controls, hepatic insulin sensitivity was increased similarly (~3 fold) in CR and β 3-treated animals, further demonstrating that a pharmacologic reduction in VF can improve insulin action.

6.2. 11 β -hydroxysteroid dehydrogenase inhibitors

As previously mentioned, the enzyme 11 β HSD-1 converts inactive cortisone into active cortisol in cells and excess glucocorticoids promote VF deposition. When this enzyme was overexpressed in adipose tissue in mice, animals developed visceral obesity and diabetes [40]. Therefore, it seemed intuitive to Hermanowski-Vosatka and colleagues that pharmacologic inhibition of 11 β HSD-1 might serve as a therapeutic target for the metabolic syndrome. When a selective and potent 11 β HSD-1 inhibitor was given to DIO mice, they observed a reduction in body mass, retroperitoneal fat pad weight, as well as serum insulin, glucose and lipids [85]. Similarly, this inhibitor resulted in improved glucose tolerance in a mouse model of T2DM and attenuated vascular plaque formation in ApoE^{-/-} mice [85].

6.3. Prevention of systemic inflammation

Mounting evidence supports a role for adipose tissue-derived pro-inflammatory cytokines in the pathogenesis of diabetes and atherosclerotic diseases. Therefore, Ohmon *et al.* [41] administered pioglitazone, which has been shown to reduce MCP-1 levels and fat inflammation, to ApoE^{-/-} mice that received a VF transplant or sham-operated controls. Pioglitazone treatment lowered MCP-1 levels and macrophage content in the VF transplant and reduced atherosclerosis development in VF-transplant mice, but not in sham-operated mice. Likewise, in obese mice, short-term treatment with a pharmacological antagonist of chemokine (C-C motif) receptor 2 (CCR2) lowered macrophage content in adipose tissue and systemic inflammation, resulting in improved insulin action [86]. Therefore, drugs which can interfere with the infiltration of macrophages into fat, and specifically VF, may provide an effective strategy for the prevention of cardiovascular complications and metabolic syndrome due to abdominal obesity.

7. Perspectives

Numerous epidemiologic studies have implicated abdominal obesity as a major risk factor for insulin resistance, T2DM, CVD, stroke, metabolic syndrome and death. Utilizing novel models of visceral obesity, several studies have demonstrated that the relationship between VF and aging is causal while the accrual of SC fat does not appear to play an important role in the etiology of disease risk. Treatment strategies including pharmacologic agents (leptin, β 3-agonists) can improve glucose tolerance by effectively reducing VF. Compelling evidence also supports a role for inhibitors of macrophage infiltration into fat (thiazolidinediones, CCR2

antagonists), and hence systemic inflammation, for the treatment of insulin resistance and vascular disease. Therefore, two lines of investigation worth pursuing include (1) understanding the secretory biology of VF to identify the important mediators of the metabolic syndrome, and (2) the development of drugs designed to modulate body fat distribution. In summary, these studies highlight the consistent relationship of VF with disease and mortality risk in humans, evidence for causation in animals, the distinct metabolic capacity of VF, the importance of accounting for body fat distribution in disease risk and VF depletion as a potential treatment strategy to prevent or delay age-related diseases.

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Figure 1.

Survival curve of the three groups of rats (AL-fed, dashed line; VF-removed, dotted line; and CR, solid line). CR rats had the greatest mean and maximum lifespan but VF removal only was sufficient to extend lifespan as compared to AL controls and accounted for nearly 20% of the CR effect on lifespan. Figure is from Muzumdar *et al.* [82] and is presented with permission from *Aging Cell*.

Figure 2.

The proposed link among VF, age-related diseases and lifespan. The accumulation of VF, which is a hallmark of aging, is hypothesized to pose a greater risk for the development of insulin resistance and other features of the metabolic syndrome than other fat depots due to its anatomical location, high lipolytic rate and secretion of inflammatory adipokines. Some specific perturbations to tissues by increased VF include hepatic insulin resistance, impaired glucose uptake by skeletal muscle and increased basal lipolytic rate and FFA release by adipose tissue. The long-term consequence of VF-induced metabolic decline includes enhanced risk for several age-related diseases such as CVD, T2DM, Alzheimer's disease and certain cancers. Therefore, VF accretion would be expected to increase mortality risk and reduce lifespan.

Table 1

Effect of Visceral Fat Removal on Metabolic Parameters in Rodents

Study	Species/strain	Glucose/Insulin	Cytokines	Lipids	Insulin Action
Barzilai et al. [42]	Male SD rats	↔ Glucose ↓ Insulin 49%	↓ TNF-α 75% and ↓ Leptin 60% expression in SC fat NA	↔ FFA ↔ Glycerol ↓ FFA 66% ↓ TG 18%	↓ Insulin infusion rate 53% ↓ IGFBP-1 68% NA
Kim et al. [87]	Female SD rats (MSG treated)	↔ Glucose ↔ Insulin	NA	↔ Cholesterol ↔ FFA	↑ Glucose infusion rate 80% ↑ Glucose uptake 30%
Gabriely et al. [45]	Male SD rats	↔ Glucose ↔ Insulin 39%	NA	↓ FFA 44% during clamp	↑ Glucose production 50% ↑ Glucose infusion rate ↔ Glucose uptake
Gabriely et al. [45]	Male ZDF rats	↓ Insulin 50%	NA	↔ FFA	↓ Glucose production 20% ↓ GTT AUC 15% ↑ Insulin-stimulated glucose transport in muscle 24–31%
Borst et al. [44]	Male SD rats	↔ Insulin	↓ IL-6 53%, TNF-α ↓ Adiponectin 30% ↓ Resistin 26% harr:Leptin	NA	↑ Insulin action 45%
Pitombo et al. [46]	Male Swiss mice	↓ Glucose 35% ↓ Insulin 45%	↓ TNF-α 40% ↓ IL-6 60% ↑ Adiponectin 40%	NA	↑ GIR 32%, ↓ HGP 42% harr:Glucose uptake
Einstein et al. [43]	Female pregnant SD rats	↔ Glucose ↔ Insulin	↔ IL-6 harr:Adiponectin	↓ Hepatic TG 60% ↓ FFA 38%	