

# Obesity, Insulin Resistance, and Type 2 Diabetes: Associations and Therapeutic Implications

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*Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*

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**Abstract:** Obesity is a triggering factor for diabetes associated with insulin resistance. In individuals who are obese, higher amounts of non-esterified fatty acids, glycerol, hormones, and pro-inflammatory cytokines that could participate in the development of insulin resistance are released by adipose tissue. Besides, endoplasmic reticulum stress, adipose tissue hypoxia, oxidative stress, lipodystrophy, and genetic background have a role in insulin resistance. However, no effective drug therapy was developed for type 2 diabetes mellitus targeting these physiological factors. This is might be due to a lack of agreement on the comprehensive mechanism of insulin resistance. Therefore, this review assesses the cellular components of each physiologic and pathophysiologic factors that are involved in obesity associated insulin resistance, and may encourage further drug development in this field.

**Keywords:** obesity, insulin, insulin resistance, type 2 diabetes mellitus

## Introduction

Insulin is a hormone secreted by  $\beta$  cells of islets of Langerhans, controls the metabolism of carbohydrates, proteins, and fats by stimulating the absorption of molecules like glucose from the blood into fat, skeletal muscle cell, and liver.<sup>1</sup> A reduction in insulin signaling primarily in the insulin receptor substrate (IRS)/phosphoinositide-3-kinase (PI-3K)/protein kinase B (PKB) axis triggers insulin resistance that could affect the metabolic actions of insulin.<sup>2</sup> Insulin resistance is commonly linked with obesity, which is a pathophysiologic factor of type 2 diabetes mellitus (T2DM).<sup>3,4</sup> An extreme adipose tissue expansion due to an increase in nutrients intake and insufficient energetic expenditure is considered as Obesity. On the other hand, diabetes mellitus is a complex chronic illness manifested by a high level of blood glucose or hyperglycemia, resulting from deficiencies in insulin secretion, action, or both.<sup>5</sup> Obesity could cause chronic low-grade systemic and local inflammation that leads to the emergence of insulin resistance linked diabetes mellitus even though the mechanism is not clear.<sup>3,6</sup> In addition, insulin resistance and hyperinsulinemia can contribute to the development of obesity.<sup>6</sup> Therefore, the objective of this review is to highlight the mechanisms of obesity-associated insulin resistance in T2DM through induction of inflammation, adipocyte dysfunction, oxidative stress, endoplasmic reticulum stress (ER stress), aging, hypoxia, and change in genetic makeup. Because understanding the impairment of insulin signaling which is related to obesity-induced diabetes may lead to better pharmacological strategies not only for the treatment of but also for the prevention of obesity and T2DM.

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## Mechanisms of Obesity Induced-Insulin Resistance

Obesity escalates the pathogenesis of T2DM through stimulation of insulin resistance. T2DM treatment has been restricted by little understanding of insulin resistance. However, several studies described the association between mitochondrial dysfunction, inflammation, hyperinsulinemia, and lipotoxicity with insulin resistance.<sup>7</sup> Endoplasmic reticulum stress, oxidative stress, genetic background, aging, hypoxia, and lipodystrophy are also stated in the pathogenesis of T2DM through induction of insulin resistance. Nevertheless, none of those concepts has led to the discovery of effective drugs for T2DM. The reason might be lack of agreement for cross-linked mechanisms of insulin resistance in T2DM.<sup>7</sup> In the following sections, different physiological changes that are involved in obesity-associated insulin resistance will be discussed in part.

## Inflammation-Induced Insulin Resistance

Elevated levels of pro-inflammatory cytokines or an increased number of white blood cells in the blood or tissue are described by inflammation. Overstimulation of inflammatory process frequently leads to various abnormalities such as organ dysfunction and tissue injury. Obesity might cause chronic and low-grade inflammation that is involved in T2DM. In addition, adipose-specific cytokines (leptin, adiponectin, and inflammatory cytokines (tumor necrotic factor- $\alpha$  (TNF- $\alpha$ )) and interleukin-6 (IL-6)) are secreted by visceral adipocytes. An elevated amount of adipose tissue draining into the portal vein, chemokines, and IL-6 production can induce liver and systemic insulin resistance.<sup>7,8</sup>

Moreover, visceral adipose depot and adipocyte size in humans are also related to insulin resistance.<sup>8</sup> The predisposition of visceral adipose tissue for elevated inflammation and the subsequent secretion of cytokines that alter insulin signaling may considerably contribute to insulin resistance in obesity. The levels of the macrophage-derived apoptosis inhibitor of macrophage protein that stimulates lipolysis in adipose tissue and responsible for local recruitment of adipose tissue macrophages are also increased with obesity.<sup>6,9</sup> Furthermore, saturated fatty acids (FAs), glucose, and changes in gut microbiota have been considered as triggers of metabolic inflammation through the stimulation of pattern-recognition receptors

(PRRs) such as; toll-like receptors (TLR), nucleotide oligomerization domain (NOD), and inflammasome.<sup>10,11</sup> These eventually increase pro-inflammatory cytokines production and immune cell recruitment like T lymphocytes and macrophages in metabolic tissues. These pro-inflammatory cytokines activate numerous kinases that interfere with insulin signaling and insulin action in adipocytes and hepatocyte.<sup>12</sup> Different studies reported that drugs that suppress inflammation improve insulin sensitivity and enhance glucose regulation in T2DM insulin-resistant patients.<sup>13,14</sup> For instance, salsalate, TNF- $\alpha$  inhibitors (etanercept, infliximab, adalimumab), IL-1 $\beta$  antagonists like canakinumab, thiazolidinediones, and metformin are found to be anti-diabetes drugs with anti-inflammatory properties.<sup>14</sup>

## Toll-Like Receptors in Insulin Resistance

Toll-like receptors (TLR) are found under the family of PRRs play an indispensable function in innate immunity and identify tissue injury by the danger-associated molecular patterns. Studies reported that, among the different types of TLR, TLR2 and TLR4 have a role in inflammation-associated insulin resistance during obesity.<sup>15,16</sup> In obese mice and humans with diabetes, the expression of TLR4 in adipocytes, hepatocytes, muscles, and in the hypothalamus is increased and negatively affects insulin sensitivity.<sup>15</sup> Another study also revealed that, during obesity, metabolic endotoxemia triggers the development of inflammation and metabolic disorders by activating TLR4 in metabolic tissues.<sup>16</sup> On the other hand, the abrogation of TLR4 leads to the reduction of oxidative stress by metabolic reprogramming of mitochondria in visceral fat, alleviating obesity-induced insulin resistance.<sup>17</sup> In addition, various TLR inhibitors have been developed to regulate excessive inflammation; these are; small molecule inhibitors, antibodies, oligonucleotides, lipid-A analogs, microRNAs, and emerging nano-inhibitors.<sup>18</sup>

## Mitochondrial Dysfunction in Insulin Resistance

A decrease in mitochondrial function might be associated with insulin resistance and T2DM since it facilitates the ectopic accumulation of fat in muscles and adipose tissues. Insulin resistance is linked substantially with an increased amount of triglycerides in muscle and liver in elder patients. These might cause a decrease in both

mitochondrial oxidative activity and ATP synthesis; both are indicators of a decrease in the function of mitochondria.<sup>19</sup> In other studies, a decrease in muscle mitochondria number by low expression of nuclear-encoded genes that control mitochondrial biogenesis, such as peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) coactivator 1  $\alpha$  (PGC-1 $\alpha$ ) and PGC-1 $\beta$  produces intramyocellular fat accumulation in the insulin-resistant subjects.<sup>19,20</sup> Accordingly, PGC-1 $\alpha$  has gained attention as a very attractive target for diabetic therapy due to its role in lipid and glucose metabolism. Pharmacological activation of PGC-1 $\alpha$  is thought to result in health benefits. Nevertheless, this notion has been challenged by growing evidence indicating that insulin resistance is increased when PGC-1 $\alpha$  is well beyond normal physiological limits.<sup>21</sup>

## Endocrine Mechanisms of Insulin Resistance

Energy storage depots for triglycerides synthesis is the essential role of adipocytes. They also act as endocrine cells, thereby secrete many peptide hormones and cytokines such as TNF- $\alpha$ , plasminogen-activator inhibitor-1, which involves maintaining the level of angiotensinogen and its proteolytic product that controls vasoconstriction; and leptin, which participates in energy mobilization.<sup>22</sup> In addition, active steroid hormones, including estrogen and cortisol can be produced by adipose tissue. Over such produced molecules, adipocytes retain the capacity to perform their local functions and systemic metabolism in different organs like muscle, brain, liver, gonads,  $\beta$ -cells, lymphoid organs, and blood vessels. This assumption increases several possibilities for the further association between adipocyte function/mass and insulin resistance.<sup>22</sup> For instance, in the T2DM mouse model, leptin enhanced insulin resistance and hyperglycemia.<sup>23</sup> Impaired leptin signaling may contribute to low adiponectin expression in obese individuals. Increased leptin signaling can therefore be a focus for therapies aimed at raising adiponectin expression, increasing insulin sensitivity, and improving the cardiometabolic profile of obesity.<sup>24</sup>

## Adipokines Role in Insulin Resistance

Patients with T2DM and insulin resistance often exhibit signs of impaired metabolism, deposition, and concentration of lipids in the skeletal muscle and blood.<sup>25</sup> An

abundance of free FAs in the plasma reduces insulin-regulated glucose metabolism, whereas a low level of lipid in the plasma enhances insulin function in the adipocytes, liver and skeletal muscle cells. Increasing plasma FAs in humans and rodents reduce insulin activation of IRS-1-linked PI-3K activity in skeletal muscle. Insulin resistance associated with lipid has also been shown to be linked to defects in translocation of glucose transporter 4 (GLUT4).<sup>26</sup> In addition, various adipokines (such as adiponectin, TNF- $\alpha$ , resistin, and IL) are involved in this disease state.<sup>27</sup> Thus, an increase in the level of adiponectin enhances insulin sensitivity while resistin exhibits insulin-antagonistic effects. Resistin induces insulin resistance through inhibition of glucose transport in vitro and increases hepatic glucose production and fasting blood glucose concentrations in vivo.<sup>26</sup> A study found that trelagliptin succinate reduced the content of resistance secreted by fat cells, suggesting that trelagliptin can reduce insulin resistance in fat cells.<sup>28</sup>

## Neural Mechanisms of Insulin Resistance

Studies revealed that our brain receives information from insulin and leptin, the transducer of adiposity signals, and integrates this input with signals from nutrients such as FAs. Thereafter, the brain sends signals to regulate the metabolism of macromolecules and feeding behavior to maintain homeostasis of fuel metabolism and energy stores.<sup>29,30</sup> Peripheral metabolism of glucose is controlled by both leptin and insulin. Peripheral and brain IRs are very crucial for normal insulin function, even though glucose homeostasis in mice with reduced hepatic IRs is altered by the central administration of insulin. Moreover, hypothalamic IRs function inhibition results in impaired hepatic glucose metabolism and insulin resistance. Interestingly, leptin and insulin both enhance the expression of suppressor of cytokine signals-3 (SOCS-3) and sensitivity to both leptin and insulin is increased in mice with reduced SOCS-3 neuronal expression.<sup>31</sup>

## Excessive and Ectopic Lipid Deposition Induced Insulin Resistance

The storage capacity of single adipocytes is limited, although they have a highly advanced ability to sequester fat.<sup>32,33</sup> Following a short-term high-fat diet enlarged adipocytes trigger insulin resistance in the absence of much

macrophage infiltration into adipose tissue.<sup>34</sup> Hence, excess lipid in adipose cells results in insulin resistance even without inflammatory responses. This might be justified as, excessive and ectopic lipid accumulation in adipocytes, liver, muscle, and outside may cause insulin resistance through metabolically toxic product formation. For instance, ceramide production has been increased by saturated FAs, which in return contributes to insulin resistance.<sup>34,35</sup>

In addition, the level of hepatic diacylglycerol shows a strong association with systemic insulin resistance, especially in nonalcoholic fatty liver disease. These lipids may activate signaling pathways that negatively impact insulin signal transduction like one or more of the protein kinase C proteins. Incomplete FA oxidation products may also affect the steps in the insulin signaling cascade or the pathways it controls.<sup>35</sup>

## Genetic Factors Related Insulin Resistance

Not only insulin receptors and IRS-1 gene polymorphisms affect insulin signals, but also polymorphisms of other genes such as; uncoupling protein gene,  $\beta 3$  of the adrenergic receptor gene and GLUT-4 gene associated with visceral obesity may promote insulin resistance.<sup>36</sup> A study revealed that T2DM patients and their relatives showed reduced total-body glucose disposal stimulation by insulin compared to control subjects. This glucose disposal impairment was mainly associated with the reduction in insulin-mediated storage of glucose in the form of glycogen. The rate of total-body glucose disposal in subjects with normal fasting glucose concentrations is also affected by the levels of GLUT-4 mRNA and GLUT-4 protein.<sup>37</sup>

## Endoplasmic Reticulum Stress Induced Insulin Resistance

Study revealed that ER stress and unfolded protein response are the central factors for T2DM, post-burn insulin resistance, and stress-induced diabetes pathogenesis.<sup>38</sup> Protein synthesis and folding of secreted and membrane-bound proteins take place in the ER. Enhanced unfolded and/or misfolded proteins in the ER lumen may be caused by the depletion of calcium stores from the ER. The presence of a high level of misfolded proteins results in the activation of signaling pathways to restore homeostasis and may lead to insulin resistance.<sup>38</sup>

## Adipose Tissue Hypoxia-Induced Insulin Resistance

Studies showed that, in obese animals, hypoxia response in adipose tissue is common. The results of most studies on adipose tissue hypoxia have revealed the presence of a strong association between adipose tissue hypoxia (ATH) and major chronic disorders like obesity pathogenesis. ATH may stimulate cellular mechanisms for leptin elevation, mitochondrial dysfunction, macrophage infiltration, chronic inflammation, adiponectin reduction, ER stress, and adipocyte death in obese individuals.<sup>39</sup> In addition, inhibition of adipogenesis and triglyceride synthesis by hypoxia may be a new mechanism for elevated FAs in the blood during obesity. Therefore, ATH may represent a combined cellular mechanism for many metabolic disorders and insulin resistance in patients with metabolic syndrome. ATP also involves in the pathogenesis of insulin resistance and inflammation-induced obstructive sleep apnea.<sup>40</sup> An inverse association has been also observed between increasing body mass index and decreasing insulin receptor expression in visceral adipose tissue (VAT) of obese humans. VAT-specific insulin receptor downregulation is an early event in obesity-related adipose cell dysfunction that enhances systemic insulin resistance in both obese humans and mice by decreasing insulin receptor mRNA stability by activating micro RNA-128 (miR-128) that lowers insulin receptor expression in adipocytes.<sup>41</sup>

## Aging and Insulin Resistance

Obesity enhances the aging of adipose tissue, a process only now beginning to come to light at the molecular level. Studies in mice reveal that obesity increases reactive oxygen species formation in fat cells, shortens telomeres, and eventually results in inactivation of the p53 tumor suppressor, inflammation, and the elevation of insulin resistance.<sup>42</sup> Inflammation and insulin resistance in adipose tissue is increased by transgenic overexpression of p53 and cyclin-dependent kinase inhibitor 1a (Cdkn1a). In a similar study, p53 which is derived from adipocytes and macrophages contributes to adipose tissue aging in obese animals. This is because p53 is activated in response to shortened telomeres in aging cells. Mice without telomerase (Tert) produce shorter telomeres with successive generations and ultimately become infertile by the fourth to sixth generation (G4–G6).<sup>42,43</sup>

## Conclusion and Perspectives

The associations of obesity, insulin resistance, and T2DM are often discussed and have resulted in many hypothesized mechanisms. Further efforts in this area may lead to improved drug development.

## Abbreviations

ATH, adipose tissue hypoxia; DM, diabetes mellitus; FA, fatty acid; GUT, glucose transporter; IRS, insulin receptor substrate; IL, interleukin; IR, insulin receptor; IRS, insulin receptor substrate; SOCS, suppressor of cytokine signaling; T2DM, type 2 diabetes mellitus; TLR, toll-like receptors; TNF- $\alpha$ , tumor necrosis factor-  $\alpha$ ; VTA, visceral adipose tissue.

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