

# **Obesity and Insulin Resistance: A Review of Molecular Interactions**

**Running Title:** Obesity and Diabetes Mellitus

**Habib Yaribeygi<sup>1\*</sup>, Mina Maleki<sup>2</sup>, Thozhukat Sathyapalan<sup>3</sup>, Tannaz Jamialahmadi<sup>4,5</sup>, Amirhossein Sahebkar<sup>6,7,8\*</sup>**

<sup>1</sup> Research Center of Physiology, Semnan University of Medical Sciences, Semnan, Iran

<sup>2</sup> Chronic Kidney Disease Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>3</sup> Academic Diabetes, Endocrinology and Metabolism, Hull York Medical School, University of Hull

<sup>4</sup> Halal Research Center of IRI, FDA, Tehran, Iran

<sup>5</sup> Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

<sup>6</sup> Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

<sup>7</sup> Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

<sup>8</sup> School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

## **\*Corresponding Authors**

Amirhossein Sahebkar, Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad 9177948564, Iran. Tel: +985138002299; Fax: +985138002287; E-mail: sahebkar@mums.ac.ir; amir\_saheb2000@yahoo.com

Habib Yaribeygi, Research Center of Physiology, Semnan University of Medical Sciences, Semnan, Iran, Tel: +989355644190

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## **Abstract**

The prevalence of insulin resistance and diabetes mellitus is rising globally in epidemic proportions. Diabetes and its complications contribute to significant morbidity and mortality. Increase in sedentary lifestyle and consumption of more energy-dense diet increased the incidence of obesity which is a significant risk factor for type 2 diabetes. Obesity acts as a potent upstream event that promotes molecular mechanisms involved in insulin resistance and diabetes mellitus. However, the exact molecular mechanisms between obesity and diabetes are not clearly understood. In the current study, we have reviewed the molecular interactions between obesity and type 2 diabetes.

**Keywords:** Diabetes mellitus, obesity, oxidative stress, adipokine, adiponectin, adipocyte, Glut-4, insulin signal transduction.

## **Introduction**

The prevalence of diabetes mellitus (DM) globally is growing rapidly [1]. This chronic disorder has a negative effect on most metabolic pathways of the body, which results in generating toxic byproducts and tissues dysfunction [2]. Diabetes and its ensuing complications result in considerable morbidity and mortality [3, 4][5-7]. Type 2 diabetes (T2DM) is the most common form of DM which is associated with lower insulin sensitivity in peripheral tissues known as insulin resistance [7, 8]. Insulin resistance is a state of reduced insulin signaling efficiency through lower response to circulatory insulin by adipocytes and myocytes which in turn, disturbs normal metabolic pathways in these tissues [8]. Insulin signaling pathway is a complex cellular event involving various signaling molecules and the exact pathophysiology of insulin resistance is not completely understood yet. Overweight and obesity are some of the critical risk factors for the development of insulin resistance [8, 9]. There is growing evidence suggesting that obesity has deleterious negative impacts on insulin signaling pathways and increases the risk of insulin resistance [10-12]. However, the exact mechanism is not elucidated yet [13]. In the current study, we review about the possible interactions between obesity, insulin signaling pathways and DM. The current review aimed to shed light into the molecular mechanisms linking obesity and insulin resistance for developing new non-pharmacological preventive and therapeutic approach for the management of insulin resistance and DM.

## **Obesity**

Obesity is defined as a medical state of excess body fat accumulation, especially in certain body areas such as around the abdomen and hip [14]. In this condition, oral intake of food is higher than the energy expenditure in the body and thereby, metabolic mechanisms shift toward storing excess substrates as adipocytes [15]. Hence, obesity is now identified as an imbalance between calories consuming and calories expenditure by hypertrophy, hyperplasia or enlarging

the adipocytes [16]. Adipose tissue responds to this excessive intake of nutrients by increased storage of fatty acids in an enlarged mass of adipose tissue [16]. Obesity is a pathologic condition completely different from being overweight which only means weighing too much [14, 17]. While the overweight state commonly arises from the excess weight of various tissues such as muscles, bones, adipose tissues and higher amount of body water, obesity is referred to more bodyweight due to higher fatty tissues [17]. For example, a person with only seventy kg of bodyweight and high fatty tissues may be obese, but another person weighing 120 kg and having a normal amount of adipose tissues may not be obese [18]. However, the incidence of obesity is higher among overweight individuals [18].

Obesity is closely associated with many pathologic states [19]. It has been frequently reported, the prevalence of various disorders such as cardiovascular disease, renal failure, neuro-behavioral illnesses, digestive diseases, respiratory disorders as well as metabolic complications are higher among the obese subjects than to healthy population [17, 20]. Hence, obesity has now considered as the main risk factor for these complications and lowering the bodyweight and readjusting the balance between feeding and energy expenditure is the main target of many non-pharmacological preventive and therapeutic approaches for managing these conditions [21-23].

### **Insulin signal transduction, insulin resistance and diabetes mellitus**

Insulin signal transduction (IST) is a complex molecular event involving various signaling molecules and enzymes (fig 1) [24]. Briefly, IST is activated by binding of appropriate substrates (insulin and insulin like growth factors (IGFs)) to the  $\alpha$  chain of insulin receptor (IR). IR is a transmembrane tyrosine kinase composed of two separate chains known as  $\alpha$  and  $\beta$  chains [25]. This binding to IR stimulates structural changes in the  $\beta$  chain by auto-phosphorylation in tyrosine residues followed by various downstream events such as

recruitment of various adaptor proteins i.e. insulin receptor substrates (IRSs), Shc protein (SHC-transforming) and APS protein (adapter protein with a PH and SH2 domain) [26, 27]. These events will provide a binding site for the insulin receptor substrates-1 (IRS-1) [27]. Activated IRS-1 then binds to the PI3K (phosphoinositide 3-kinase) to activate it. Activated PI3K will promote the conversion of PIP<sub>2</sub> (phosphatidylinositol 4,5-bisphosphate) to PIP<sub>3</sub> (phosphatidylinositol 3,4,5-trisphosphate) [28]. PIP<sub>3</sub> is a potent activator of PKB (protein kinase B, also known as Akt), which in turn facilitates glucose entering into the cells by localization of GLUT-4 (glucose transporter type 4) on the cellular membranes of adipocytes and myocytes, and inhibits glycogen synthase kinase leading to an increase in glycogen synthesis [28, 29]. In addition, there are other types of insulin-dependent kinases such as ERK1/2 (extracellular signal-regulated kinase 1/2), atypical PKC (protein kinase C), S6K1 (ribosomal protein S6 kinase beta-1), SIK2 (serine/threonine-protein kinase 2), AKT, mTOR (mammalian target of rapamycin) and ROCK1 (rho-associated protein kinase 1), AMPK (AMP-activated protein kinase) and GSK3 (Glycogen synthase kinase) which can similarly phosphorylate IRSs and promote the IST [27, 30].

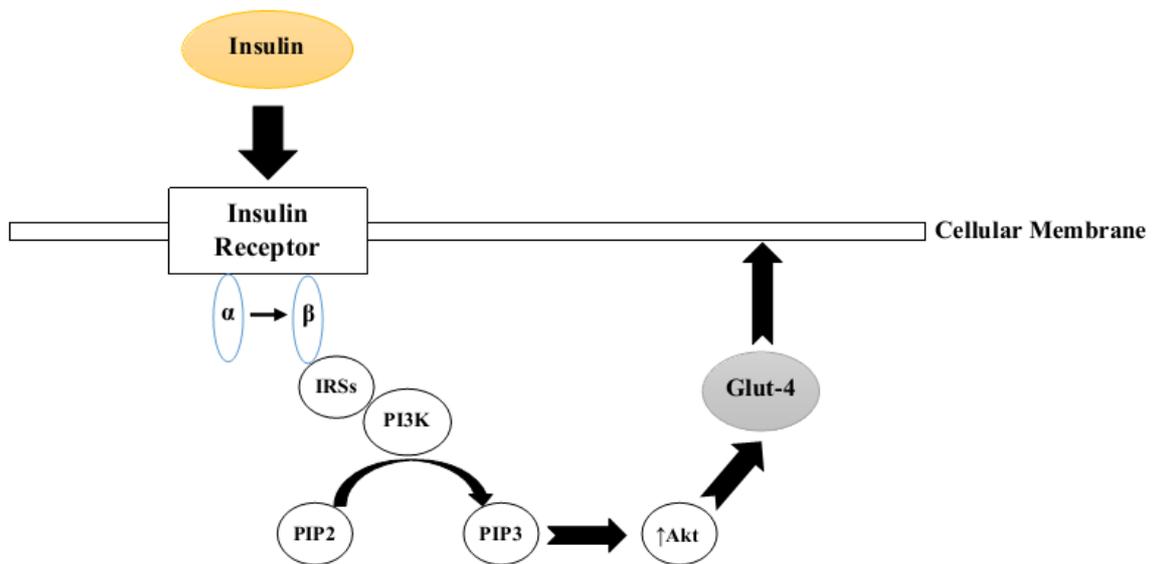


Figure 1: Schematic picture of insulin signaling pathways. It is initiated by binding the substrate (insulin) to its specific receptors and completed by Glut-4 localization into the cell membrane (IRSs= insulin receptor substrates, PI3K= Phosphoinositide 3-kinase,

PIP2= Phosphatidylinositol 4,5-bisphosphate, PIP3= Phosphatidylinositol 3,4,5-trisphosphate, Akt=protein kinase B, Glut-4= glucose transporter type 4)

Any disturbance in the IST steps will result in a drop of peripheral insulin sensitivity resulting in insulin resistance and increased likelihood of DM [24]. Most patients with diabetes especially type 2 diabetes (T2DM) have some degree of insulin resistance [24, 31]. T2DM is the most common type of diabetes [32]. Insulin resistance plays a crucial role in T2DM and gestational diabetes (diabetes occurring during pregnancy) [32, 33]. On the other hand, type 1 DM (T1DM) [32] results from autoimmune destruction of pancreatic beta cells [32][34][32, 35].

### **Obesity, Insulin Resistance and Diabetes Mellitus**

Obesity is an important risk factor which triggers various molecular pathways involved in the pathophysiology of insulin resistance and DM [10, 19]. In the following sections, we discuss the various molecular pathways by which obesity contributes to the development of insulin resistance and DM, especially T2DM.

#### **1. ER Stress**

Endoplasmic reticulum (ER) is a large intracellular organelle consisting of a network of tubules found in most eukaryotic cells except for red blood cells and spermatozoa. ER has many synthesizing, folding, secretory and transferring functions [36]. It produces almost all transmembrane molecules (lipids and proteins) and is responsible for most proteins secreted from the tissue such as insulin [37]. There are two types of ER known as smooth and rough or granular [36]. While rough ER is studded with many protein-producing structures known as ribosomes, the smooth ER lacks them [36]. Since ER membrane is continuous with the outer layer of nucleus membrane, it is involved in the folding of synthesized proteins in distinct types of sacs known as cisternae via different chaperones such as protein disulfide isomerase (PDI), endoplasmic reticulum protein 29 (ERp29), the Hsp70 family member BiP/Grp78, calnexin

and the peptidylpropyl isomerase family [36, 38]. In addition, ER is involved in the protein transport in special vesicles to the Golgi apparatus [38]. Moreover, smooth ER is included in the synthesis and release of lipids, steroids and phospholipids [36]. ER has other physiologic functions such as calcium storage [39].

ER stress or the so-called unfolded protein response (UPR), is a term mainly referred to any conditions in which a higher load of activities are imposed to the ER which will disturb its normal function [36]. ER stress is an adaptive cellular response which cells use to align the ER functional capacity with higher demand [36]. In the pathologic state, the normal process of protein folding is disturbed and physiologic capacity of tissues (such as beta-cells) for protein (e.g. insulin) synthesis and secretion are significantly reduced so that the misfolded proteins accumulate in the cell [36]. There is growing evidence that ER stress contributes to a variety of disorder such as insulin resistance and DM [40]. Chronic unfolded protein responses, which arise from ER dysfunction due to chronic ER stress, has a negative impact on beta-cell function, insulin release and insulin signaling [37, 41]. Prolonged ER stress also contributes to inflammation dependent beta-cell death by promoting different pro-apoptotic pathways in the pancreatic cells [37]. It can markedly reduce the pancreatic islets' capacity for postprandial insulin secretion and thereby impairing glucose homeostasis [37]. ER stress impairs IST activities such as Akt and IRSs and induce insulin resistance in adipocytes, hepatocytes and myocytes [37, 42-44]. ER stress is now considered as the main inducer for insulin resistance and DM [37, 41].

A variety of physiological, pathological and pharmacological agents can induce ER stress [39], including obesity [40, 41, 43]. Interestingly, ER stress markers such as BiP, phosphorylated PERK and phosphorylated  $\alpha$ -subunit of eukaryotic translational initiating factor 2 (eIF2 $\alpha$ ) are up-regulated in the adipose tissue and the liver of obese subjects [43]. Besides, free fatty acids,

which are commonly raised in obesity, can induce ER stress in adipocytes and beta-cells [41, 45]. Hence, obesity is usually accompanied by some degree of ER stress [41, 46-48].

Obesity can act as a potent upstream event for insulin resistance and DM by promoting ER stress [40, 41, 43]. For example, obesity-induced ER stress in hepatocytes suppresses the normal IST via c-Jun N-terminal kinase activation and reduces the insulin sensitivity in liver tissue [37, 49-51]. Also, Kawasaki et. al, in 2012 demonstrated that obesity induces ER stress via promoting oxidative damages which in turn impairs insulin signaling in 3T3-L1 adipocytes [52]. They found that, ameliorating the ER stress by chaperones, improved insulin signaling in adipocytes [52]. Similarly, Park and coworkers in 2014 reported that the inhibition of cytochrome P450 4A (CYP4A) ameliorated obesity-induced ER stress which in turn, improved insulin sensitivity in mice [53]. Moreover, Liang et. al, in 2015 demonstrated that obesity dependent ER stress reduced insulin sensitivity by impairing the IR signaling in brain tissues of obese rats [54]. This evidence suggests that obesity induces insulin resistance at least partly via increasing the ER stress [55].

## **2. Oxidative Stress**

Oxidative stress is a condition of imbalance between free radical species and antioxidant defence system of the cells in favor of the free radicals [56, 57]. This pathologic state is due to the generation of more free radicals and weakening of the cellular antioxidative defence system in the biologic environment [57, 58]. All biologic molecules with an unpaired electron(s) are targets of the attack by the free radicals [59-61]. There is growing evidence that oxidative damage by free radical species negatively affects most steps of the insulin signaling pathway and increases the risk of DM [61]. It can impair normal IST at several points including Akt signaling, Glut-4 expression/translocation/localization, IRSs activation and p38-MAPK (p38 mitogen-activated protein kinases) pathways [61, 62]. Therefore, readjusting the balance between free radicals and antioxidant defensive system and lowering the rate of oxidative

damages is one of the important strategies for improving insulin sensitivity and preventing DM [62, 63]. Besides, any condition or agent which can induce oxidative stress, potentially increase the likelihood of DM [64].

Obesity and higher amount of adipose tissues are associated with an increased free radical generation and oxidative stress [15]. It interferes with molecular mechanisms involved in the free radical production at many levels [15]. Recent findings suggested that obesity is a potent inducer for pro-oxidant enzymes generating free radicals such as Nox<sup>1</sup>, Cox<sup>2</sup>, Lox<sup>3</sup>, Mpo<sup>4</sup>, Cytochrome-P450, eNOS<sup>5</sup> and Xox<sup>6</sup> [65-71]. Therefore, a higher rate of free radicals is produced under the influence of adipocyte tissues [65-71]. In addition, some evidence suggests a negative effect of obesity on the antioxidant defensive system [72-74]. An et. al. in 2018 demonstrated that, the rate of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) antioxidant enzymes activities were lower than the healthy state in individuals with a high body mass index (BMI) [72]. Similarly, Mohseni and coworkers in 2018 reported that SOD and CAT enzymes activity were diminished in obese children. This was accompanied by insulin resistance in these children [74]. They also demonstrated that by potentiating the cellular defensive antioxidative system reversed the obesity-induced insulin resistance and improved glucose homeostasis in obese children [74]. This suggests that obesity induces oxidative damages either by stimulating free radical production or weakening the antioxidant defence systems [65-74]. In addition, this evidence suggests that obesity can impair normal IST and induce insulin resistance by promoting oxidative stress [65-74].

### **3. Beta-cell dysfunction**

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<sup>1</sup> NADPH oxidase

<sup>2</sup> Cyclooxygenases

<sup>3</sup> Lipoxygenase

<sup>4</sup> Myeloperoxidase

<sup>5</sup> Endothelial nitric oxide synthase

<sup>6</sup> Xanthine oxidase

Most cases of T2DM have some degree of beta-cell dysfunction [75]. There is also a lower functional mass of pancreatic islets producing insulin in patients with DM [76]. Any factor that can affect the normal function of beta-cells can disturb the normal glucose homeostasis and increase the risk of DM [77, 78]. There is growing evidence indicating that obesity is a risk factor for impaired beta-cell function and can significantly reduce their mass and efficiency [79-81]. This demonstrates that obesity induces various molecular pathways involved in beta-cells apoptosis such as inflammation, ER stress and oxidative damages thereby, reducing their functional capacity [82-84].

However, there are some controversies regarding the effects of obesity on beta-cells [85]. Some recent evidence suggests that obesity induces beta-cell regeneration and stimulates beta-cell expansion in a compensatory mode [85-89]. They state that beta-cell mass increases adaptively in response to a higher demand for glucose production and secretion in obese subjects [87]. This obesity-induced beta-cell proliferation suggests that we do not have a complete understanding of the impacts of obesity on pancreatic islets yet [90]. It seems that obesity has a bi-directional relationship with beta-cells. Obesity may reduce the functional capacity of beta-cells by promoting various pathophysiologic molecular pathways as well as induce beta-cell proliferation in a compensatory mode in response to a higher demand for insulin.

#### **4. Mitochondrial Dysfunction**

Mitochondrial dysfunction is a key feature commonly observed in tissues in the diabetic milieu [91, 92]. Mitochondrial dysfunction negatively affects various molecular pathways and cellular functions in DM such as beta-cell function, insulin secretion, insulin sensitivity, glucagon secretion and glucose metabolism [92-95]. Therefore, improving mitochondrial efficiency is one of the main potential therapeutic targets for the management of patients with diabetes [6,

93, 95-97]. On the other hand, any factor which can induce mitochondrial dysfunction can be a potential risk factor for the development of insulin resistance and DM [8, 98, 99].

There is growing evidence suggesting that obesity is accompanied by some level of mitochondrial dysfunction [16, 100, 101]. Obesity can impair mitochondrial function through several pathways such as oxidative stress and inflammation [16]. Overfeeding (as commonly seen in obese subjects) can overwhelm the Krebs cycle and the mitochondrial respiratory chain capabilities for the normal metabolism of nutrients. This will impose a higher workload to the mitochondria leading to mitochondrial dysfunction and oxidative stress which in turn, impairs insulin signal transduction resulting in insulin resistance [16]. Also, inflammation is another link between obesity and mitochondrial dysfunction. Obesity-induced inflammatory responses negatively modulate mitochondrial function resulting in impaired insulin sensitivity [16]. Obesity also reduces mitochondrial mass and the number of active mitochondria [102]. Ritov et al. in 2005 demonstrated that subsarcolemmal mitochondria were reduced in muscles of obese subjects and was associated with insulin resistance [102]. Most aspects of mitochondrial biology such as fusion, biogenesis, energetic processes and oxidative events are under the influence of obesity which negatively modulates mitochondrial function [103, 104]. Recently, Constantin-Teodosiu et al. in 2019 found that the number of mitochondrial DNA (mtDNA) copy, which is raised by exercise and lowering the bodyweight, is related to the level of insulin sensitivity [105]. They reported that obesity induces insulin resistance by decreasing the mtDNA number while lowering the bodyweight reversed these events [105]. Therefore, insulin resistance observed in the obese subjects is at least partly related to obesity-induced mitochondrial dysfunction [93, 106, 107].

## **5. Adipokines and Adiponectin**

Adipose tissues have many endocrine activities [108]. It means that adipocytes are no longer considered to be dormant cells that only stores fat and energy, but also can produce, store or release of many active biologic molecules as well as proinflammatory cytokines [108]. Adipokines and adiponectin are two separate classes of peptides with potent modulatory effects on insulin sensitivity. They are produced and secreted by adipose tissues into the circulation [109]. After the discovery of leptin as the first adipokines in 1994, hundreds of these molecules have been detected which are all produced by adipocytes and are closely involved in insulin sensitivity and glucose homeostasis [110, 111]. These adipocyte-derived peptides can disturb insulin signal transduction and induce insulin resistance and DM [112]. Some of these adipokines can improve insulin sensitivity [111, 113]. It has been suggested that while some adipokines impair insulin sensitivity by inducing inflammation, adiponectin improves insulin sensitivity through its anti-inflammatory effects [113, 114]. Adipokines can be classified as insulin-sensitizers (i.e. visfatin, adiponectin and fibroblast growth factor-21 (FGF-21)) and insulin-antagonizers (i.e. TNF- $\alpha$ , interleukin (IL)-6 and resistin) [66, 115]. In addition to these classifications, adipocytes-derived cytokines can modulate insulin sensitivity through mechanisms not completely elucidated yet [116].

While adipose tissue of lean individuals secretes anti-inflammatory mediators (e.g. adiponectin, transforming growth factor-beta (TGF $\beta$ ), apelin, IL-1 receptor antagonist, IL-10, IL-4, IL-13) obese adipose tissue mainly secretes proinflammatory cytokines [117]. In addition to adipokines, there are other potent inflammatory cytokines such as TNF- $\alpha$ , IL-1, IL-6, visfatin, resistin, angiotensin II and plasminogen activator inhibitor which produced are secreted by adipose tissue of obese subjects [117, 118]. All of these mentioned inflammatory mediators have a negative impact on insulin sensitivity and significantly increases the risk of DM [119, 120]. Hence, more adipose tissue, especially visceral adipose tissue, translates to more inflammatory responses thereby increasing insulin resistance [117, 121, 122]. Denis et

al. in 2017 found that higher chemokines and cytokines in plasma of African American women were related to an increased risk of insulin resistance and development of DM [122]. Besides, Rakotoarivelo et al. in 2018 demonstrated that subcutaneous and visceral adipose tissues have a varying profile of inflammatory cytokines in obese individuals in a different pattern compared to non-obese individuals [123]. Similarly, Kang and colleagues in 2016 reported that higher production of some cytokines such as leptin and resistin in visceral adipose tissues is closely associated to lower insulin sensitivity [124]. They found that, serum levels of adipocyte-derived cytokines, as well as mRNA and protein expressions, are predictors of DM in obese individuals [124]. This evidence strongly suggests that inflammatory responses are a major link between obesity and insulin resistance [122-124].

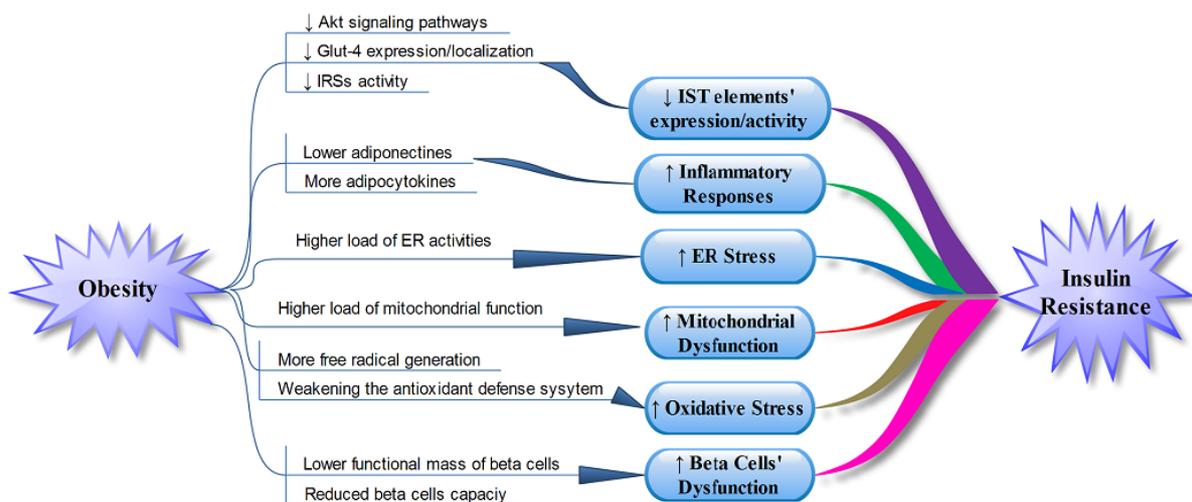


Fig 2: Possible molecular pathways involved in obesity-induced insulin resistance

## 6. Insulin Signal Transduction Elements

The previous sections demonstrate that obesity can impair insulin signaling pathways by the aforementioned mechanisms. In addition, we have evidence to demonstrate that obesity can exert direct insulin antagonizing effects via impairing expression/localization/activities of various critical elements of IST [125-127]. For example, it may reduce Glut-4 expression/localization [125, 127-129], induces IRs polymorphism and disturb its

phosphorylation/activity [127, 130, 131] or impair PI3/Akt signaling pathways [127, 132, 133]. These direct effects potentially impair insulin signaling pathways and thereby, reduces insulin sensitivity.

Kahn and coworkers in 1993 demonstrated that high-fat diet dependent obesity down-regulated Glut-4 expression in rats [125]. Seraphim and colleagues in 2001 provided data demonstrating that obesity altered Glut-4 expression which in turn reduces insulin sensitivity [129]. MacLaren et al. in 2008 demonstrated that obesity has strong effects on the genes involved in insulin sensitivity such as PI3, Akt2 and Glut-4 [127]. Atkinson et al in 2013 suggested that obesity induces insulin resistance by reducing Glut-4 expression which was reversed by Glut-4 overexpression in high-fat diet mice [126]. Kubota et al. in 2016 provided further evidence indicating that obesity-induced insulin resistance is related to the altered expression/localization of IRs in the hepatic cells [131]. Saravani and coworkers in 2017 found that central obesity is associated with an altered profile of Glut-4 and IRs expression in adipose tissues in an Iranian population of obese subjects [130]. This evidence suggests that obesity can negatively modulate the expression, localization or activity of various IST elements [127, 130-133]. These effects have a negative impact on insulin sensitivity and increase insulin resistance. Hence, we can conclude that the negative effect on genes involved in insulin signaling is another possible pathway by which obesity impairs insulin sensitivity and induces insulin resistance.

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### **Conflict of Interests**

All the authors declare that they have no conflict of interest in this study.

**Table 1.** Possible molecular interactions between obesity and insulin resistance (ER= endoplasmic reticulum, IST=insulin signal transduction, Glut-4=glucose cotransporter type 4, IRSs=insulin receptor substrates, Akt=protein kinase B)

<b>Molecular mechanisms</b>	<b>Effects on insulin sensitivity</b>	<b>References</b>
ER Stress	Overwhelms ER capacity, induces ER stress and thereby, impairs normal process of protein assembly/release	[37, 40, 41, 43, 49-55]
Oxidative Stress	Strongly stimulates upstream events inducing oxidative damages, and so promotes oxidative stress-dependent insulin resistance	[65-74]
Beta-Cell Dysfunction	Reduces functional mass of beta-cells by promoting apoptosis and impairs beta-cell function	[79-81]
Mitochondrial Dysfunction	Disturbs normal mitochondrial functions and induces mitochondrial dysfunction leading to improper insulin secretion and lower levels of insulin sensitivity	[93, 106, 107]
Proinflammatory Mediators	Promotes inflammatory responses and thereby inflammation-induced insulin resistance	[117, 119-122]
Insulin Signal Transduction Elements	Negatively modulates insulin signaling pathways by disturbing the expression/activities of IST elements as Glut-4, IRSs, Akt and etc.	[127, 130-133]

## **Conclusion**

The prevalence of insulin resistance among obese subjects is higher than the non-obese population. This observation led to the hypothesis that "obesity induces diabetes mellitus" which was confirmed by experimental and clinical evidence. However, the precise molecular interactions between obesity and insulin resistance are not well elucidated. Based on the current knowledge, we propose that obesity can impair insulin signaling pathways via at least six molecular mechanisms such as promoting ER stress, inducing oxidative damages, enhancing inflammatory events, impairing the IST elements' activity, lowering the pancreatic beta-cell efficiency and by developing mitochondrial dysfunction.

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