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Adipokines in Insulin Resistance: Current Updates

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Obesity is a chronic metabolic disease that affects both the pediatric and adult populations. Adipose tissue acts as an endocrine organ which secretes various adipokines involved in fat mass regulation and energy balance via modulating the metabolic signalling pathways. Altered secretion of adipokines promotes multiple complications, including insulin resistance. The primary mechanism of action that underlines the involvement of adipokines in the development of insulin resistance includes phosphorylation/de-phosphorylation of insulin receptor substrate-1 (IRS-1) facilitate by other signalling molecules like a suppressor of cytokine signalling 1 (SOCS-1). Adipokines mediated insulin resistance further contribute to the development of atherosclerosis, dyslipidemia, fatty liver disease, cancer etc. Thus, this review provides recent updates on the role of resistin, lipocalin-2, RBP-4, chemerin, TNF-alpha and IL-6 adipokines in the progression of insulin resistance.

Keywords: Adipose Tissue; Adipokines; Fatty Liver Diseases; Insulin resistance; Insulin Receptor Substrate-1 (IRS-1).

Obesity is emerging as an epidemic in both developed and developing countries. As per the current statistics, in the United States, approximately 42.4% adult men and women are affected with obesity [1], while for India a rise of 30.5% from the prevailing percentage has been forecasted by the year 2040 [2]. Obesity usually promotes type 2 diabetes mellitus, hypertension, atherosclerosis and cardiovascular diseases [3]. But, amid them, type 2 diabetes mellitus can be more severe due to insulin resistance in the liver, muscle cells and other peripheral tissues [4]. In this regard, it can be assumed that obesity is a metabolic disorder that further increases the diabetes burden apart from the pathophysiology of insulin. Over nutrition or high-calorie intake deposits lipids in the form of triglycerides in adipose tissue, resulting in obesity [5]. The severity of obesity is often accompanied by low exercise and stressful lifestyle [6]. In mammals, adipose tissue cluster pre-adipocytes, mature adipocytes, stromal vascular cells, macrophages and endothelial cells. However, adipose tissue is no longer considered as a mere fat storage depot; instead, it is now considered as an endocrine organ due to the secretion of adipokines such as adiponectin, leptin, visfatin, omentin etc., which regulate energy/metabolic homeostasis [7,8]. Deposition of excess energy causes adipose tissue

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dysfunction, which usually exhibits a low-grade chronic inflammation due to higher secretion of inflammatory and pro-inflammatory cytokines like IL-6 and TNF-alpha. This chronic inflammation favours insulin resistance by modulating various metabolic pathways [9]. The present review discusses the basic pathophysiology of adipokines with their current updates in the aetiology of insulin resistance.

Adipose tissue physiology

Adipose tissues are classified as brown adipose tissue (BAT) and white adipose tissue (WAT), originated from mesoderm and the mesenchymal stem cells during embryogenesis. BAT is rich in mitochondria; hence appear brown and predominantly involved in thermogenesis (heat production) via uncoupling proteins [7]. Conversely, WAT is organ-specific and is further divided into visceral (mesenteric, retroperitoneal, omental and pericardial) and subcutaneous (beneath the skin) adipose depots; thus obesity-related consequences are primarily regulated by WAT [10]. To store extra energy pre-adipocyte differentiates into mature adipocytes under the strict regulation of CCAAT/enhancer-binding proteins (C/EBPs) and peroxisome proliferator-activated receptor-gamma (PPARã) transcriptional factors [11]. This causes WAT expansion through a rise in adipocyte number (hyperplasia) and/or increasing adipocyte volume/ size (hypertrophy). The rise in adipocyte number favours severe obesity, while increased adipocytic volume contributes to obesity, overweight and diabetes. In- vivo studies showed that in adults, adipocytic numbers are usually constant; however, adipocytic volume increases [12]. This suggests the severity of obesity in the onset of type 2 diabetes mellitus in adult patients. Earlier, adipose tissue was considered as an inert fat storage organ, but the discovery of leptin revealed the endocrine functions of this organ, which secrete proteins/ hormones/factors/cytokines, collectively called as "adipokines" [13]. Obesity promotes altered secretion of adipokines, which work as endocrine, paracrine and autocrine way and modulate lipid (lipogenesis and lipolysis) and glucose metabolism [14]. A growing body of evidence proves the role of various adipokines in the pathophysiology of insulin resistance, which includes, resistin, lipochalin-2, retinol-binding protein-4 (RBP-4), chemerin, TNF-alpha and IL-6 [15,16].

Resistin

Resistin a 114 amino acid (10 kDa) containing adipokine also called as an adipose tissue-specific secretory factor (ADSF) was discovered by Dr Mitchell A. Lazar in the year 2001 [17,18]. Resistin is a member of a cysteine-rich protein termed as resistin like molecule (RELM) and circulates as a hexamer and trimer. Hexameric form of this adipokine is more abundant, while trimeric form induces severe insulin resistance [19]. The mechanism by which resistin causes the insulin resistance includes the activation of suppressor of cytokine signalling-3 (SOCS-3), which attenuates insulin-arbitrate signalling in adipocytes [20]. In association with the toll-like receptor (TLR-4), resistin stimulates insulin resistance in different cells. In the hypothalamus, resistin directly binds with the TLR-4, which suppresses signalling pathways via stimulation of MyD88 and TIRAP adaptor protein accumulation and debilitates insulin response in the hypothalamus by phosphorylation of insulin receptor, AKT and ERK1/2. The activation of Resistin/TLR-4 pathway also upregulated the activity of SOCS-3 and protein-tyrosine phosphatase 1B (PTP1B) and thereby promote insulin resistance [21].

The fibroblast growth factor (FGF)-21 is an important hormone that regulates many metabolic activities. The FGF-21 works as insulin-sensitizing hormone as like of adiponectin. Study on the chronic intracerebroventricular mechanism revealed that resistin infusion in the brain of mice downregulates adiponectin synthesis via regulating its adaptor protein known as APPL1 in both hypothalamus and liver. Resistin also inhibits expression of FGF-21 receptors on the hypothalamus and the peripheral tissues, resulting in FGF-21 resistance. This effect of resistin was abolished in TLR4 knockout mice, suggesting the role of Resistin/TLR-4 pathways in FGF-2 resistance/ insulin sensitivity [22]. Further, studies on mice reported resistin/TLR-4 pathway for increased hypertension, insulin resistance [23] and breast cancer progression [24]. It has been evidenced that aerobic exercise prevents insulin resistance in type 2 diabetes mellitus via miR-382-3p/Resistin [25] and miR-492/Resistin axis [26]. Recent studies exhibit the role of resistin in endothelial related insulin resistance. Treatment of resistin on human umbilical vein endothelial cells (HUVC) showed

that oxidative stress in the endoplasmic reticulum promotes insulin resistance and impairment in the endothelium [27]. Also, tunicamycin induced oxidative stress in endoplasmic reticulum reported increased resistin mRNA in human THP-1 monocytes [28].

Lipocalin-2

The lipocalin-2 (Lcn2) is a 25 kDa adipokine also known as neutrophil gelatinase-associated lipocalin (NGAL), sidrocalin and 24p3 belong to the lipocalin superfamily and reported for altered glucose metabolism and insulin resistance [29]. Lcn2 is highly expressed in adipocytes, liver, kidney and on macrophages and regulates apoptosis and innate immunity [30]. The primary mechanism underlines the effect of Lcn2 on insulin resistance include the modulation of 12-lipoxygenase activity and TNF-á levels in adipose tissue [31]. The level of this adipokine increases during pre-adipocyte differentiation into mature adipocyte. With the help of a small cavity like hydrophobic structures Lcn2 binds and transport distinct lipophilic compounds like steroids, retinoids and arachidonic acids [32]. Study on LCN2"/" mice showed increased hepatic gluconeogenesis, debilitate lipid metabolism, impaired oxidation capacity of mitochondria, elevated inflammation favouring dyslipidemia due to diet-induced obesity, fatty liver disorders and insulin resistance [33].

Systems genetics analyses studies revealed the sex-specific role of Lcn-2. Overexpression of this adipokine in adipose tissue has been reported for elevated fat mass, glucose intolerance and insulin resistance only in females via mitochondrial dysregulation [34]. Studies using synthetic glucocorticoids and dexamethasone in the regulation of Lcn-2 expression in adipose tissue explore the role of sex steroids [35]. In postmenopausal women, 17-â-estradiol (E2) increases the Lcn-2 expression in subcutaneous adipose tissue. There are two estrogen receptors (ERá and ER-â), which facilitates the effects of steroids on adipose tissue, however, among them; ERâ plays a significant role in the binding of â-estradiol [36]. Synthetic dexamethasone increases ERâ pathway and decreases the ERá pathway and thus responsible for glucocorticoid-induced insulin resistance in human adipose tissue via Lcn-2 adipokine [37]. Many other studies also implicate the role of steroids in the induction of Lcn-2 induced insulin resistance [38,39]. Moreover, Lcn-2 showed inhibition of autophagy and insulin resistance induction in H9c2 cells derived from rat heart ventricle [40].

Retinol Binding Protein-4 (RBP-4)

Retinol binding protein-4 (RBP-4) is another crucial adipokine that attributes in insulin resistance. Apart from adipocyte RBP-4 is also expressed in liver and macrophages [41]. Higher expression of this adipokine in the adipocyte is inversely associated with the GLUT-4 expression in the adipocyte. Thus, decreased GLUT-4 in adipocytes promotes higher expression of RBP-4, which inhibits insulin-mediated insulin receptor substrate-1 (IRS-1) phosphorylation that can contribute to insulin resistance [42]. During obesity, RBP-4 is preferentially produced by visceral fat depot than subcutaneous fat depot, suggesting the role of intra-abdominal adipose tissue in insulin resistance [43]. The thiazolidinedione, a peroxisome proliferator-activated gamma (PPARã) stimulating drug suppresses RBP-4 production in adipose tissue and thereby stimulate insulin sensitivity of tissues (skeletal muscle) [44]. However, RBP-4 mediated insulin resistance also play a pivotal role in the development of cardiovascular diseases (CVDs). Increased production of RBP-4 in adipose tissue stimulates the higher production of adhesion molecules like vascular cell adhesion molecule-1 (VCAM), intercellular adhesion molecule-1 (ICAM) and E-selectin in the endothelial cells, resulting in atherosclerosis-related CVDs and hypertension [45].

Of note, the prevalence of RBP-4 related insulin resistance is considered as a significant risk factor for the pediatric cardiometabolic system [46]. Also, RBP-4 in association with adiponectin and Fatty Acid–Binding Protein 4 (FABP-4) are reported to be associated with the increased rate of CVDs in male patients of type 2 diabetes mellitus [47], while in adolescent girls the increased CVDs are associated with waist circumference in overweight/ obese [48]. Thus, RBP-4 and insulin resistance suggest the role of sex hormones in the progression of CVDs and coronary artery diseases [49]. Furthermore, assessment of the levels of RBP-4 for ten years during childhood can help in the prediction of future cardiometabolic risks [50]. Apart from the CVDs elevated RBP-4 related insulin resistance can be correlated with the progression

of rheumatoid arthritis [51] and non-alcoholic fatty liver disease [52].

Chemerin

Chemerin is secreted from adipose tissue as an inactive pre-pro chemerin (163 amino acids). After the intracellular hydrolytic cleavage of N terminal polypeptide (20 amino acid), it releases in the serum as 18-kDa inactive pro-protein, which then converts into 16-kDa active chemerin by serine protease cleavage of the C-terminal portion [53]. The estimated concentration of chemerin in plasma and serum of mice was reported 0.6 and 0.5 nM, respectively, while in human 3.0 and 4.4 nM, respectively [54]. This adipokine is also called as tazarotene-induced gene 2 (TIG2) encoded by the retinoic acid receptor responder 2 (Rarres2) gene and acts as an endocrine, paracrine as well as an autocrine way [55]. Chemerin is a pro-inflammatory adipokine predominantly produced by white adipose tissue (WAT) and act as a ligand for G-protein-coupled receptor CMKLR1 [56]. Chemerin regulates the immune system (adaptive and innate), adipogenesis and metabolic homeostasis [57]. Overexpression of chemerin in adipose tissue causes insulin resistance in human skeletal muscles by modulating IRS-1, glucose uptake, Akt, glycogen synthase kinase 3 phosphorylation (GSK3P), nuclear factor-êB (NF-kB), p38 mitogen-activated protein kinase and extracellular signal-regulated kinase (ERK)-1/2 [58].

Non-alcoholic fatty liver disease (NAFLD) is a common phenomenon in obesity, which is closely associated with chemerin induced increased insulin resistance [60]. However, outdoor aerobic exercise improves the status of chemerin induced insulin resistance and thereby NAFLD [61]. Overexpression of CMKLR1 promotes insulin resistance. During low-grade inflammation (a common feature of obesity), both chemerin and CMKLR1 exhibit inverse expression, manifesting in the progression of insulin resistance [62]. Tumour necrosis factor-alpha (TNF-alpha) is a potent inflammatory cytokine that in association with chemerin induces insulin resistance. This effect of chemerin-TNF-alpha is overcome by the high-intensity interval training (HIIT), further suggesting the role of exercise in the prevention of insulin resistance [63]. However, another study in women with multiple sclerosis proves that the continuous chronic aerobic exercise lowers the chemerin, insulin and thereby suppresses insulin resistance [64]. Chemerin can be used as an adipokine marker for uremic insulin resistance in chronic kidney diseases at stages 3, 4, and 5 [65]. Moreover, a growing body of recent evidences revealed the role of chemerin induced insulin resistance in the development and the prognosis of polycystic ovary syndrome (PCOS) in adult women. A recent study on 45 patients with PCOS showed higher chemerin levels in obese PCOS group as compared to the lean PCOS, obese and the non-obese groups [66]. These finding described above and other recent studies [67-68] signify the role of chemerin induced insulin resistance in the progression of PCOS.

Adipokines such as resistin, Lpn-2, RBP-4, chemerin, TNF-á and IL-6 secreted during obesity altered numerous metabolic signalling pathways that result in insulin resistance and related diseases. TLR-4: Toll-like receptor-4, Irs-P: Insulin receptor phosphorylation, SOCS-3: suppressor of cytokine signalling-3, FGF-21: Fibroblast growth factor, Lpn-2: Lipocalin-2, TNF-á: Tumour necrosis factor-á, ER-â: Estrogen receptor-â, RBP-4: Retinol binding protein-4, GLUT: Glucose transporter, IRS-1-P: Insulin receptor substrate-1-phosphorylation, GSK-3: Glycogen synthase kinase 3 phosphorylation, NF-kB: Nuclear factor-êB (NF-kB), ERK: Extracellular signal-regulated kinase, NOS: Nitric oxide synthase, NO: Nitric oxide, PTEN: Phosphatase and tension homologue, IR: Insulin resistance, IL-6: Interleukin-6, STAT-3: signal transducer and activator of transcription 3.

TNF-á

Tumour necrosis factor-á (TNF-á) is secreted by adipose tissue often considered as an adipocytokine. A 26 kDa transmembrane monomer of this adipokine converts into 17-kDa soluble TNF-á molecule by an enzyme TNF-á converting enzyme (TACE). It acts as an inflammatory cytokine that affects distinct cellular and biological functions including apoptosis, cell differentiation, energy metabolism and immune system [69]. TNF-á adipocytokine induces insulin resistance via decreasing the tyrosine kinase activity of the insulin receptor [70]. This causes altered signalling pathways that can induce insulin resistance and related diseases. One of such signalling pathway that modulated by TNF-á is Akt/eNOS (nitric oxide synthase)/NO. In mice with fed by a high-fat diet, overexpression of TNF-á in adipose tissue

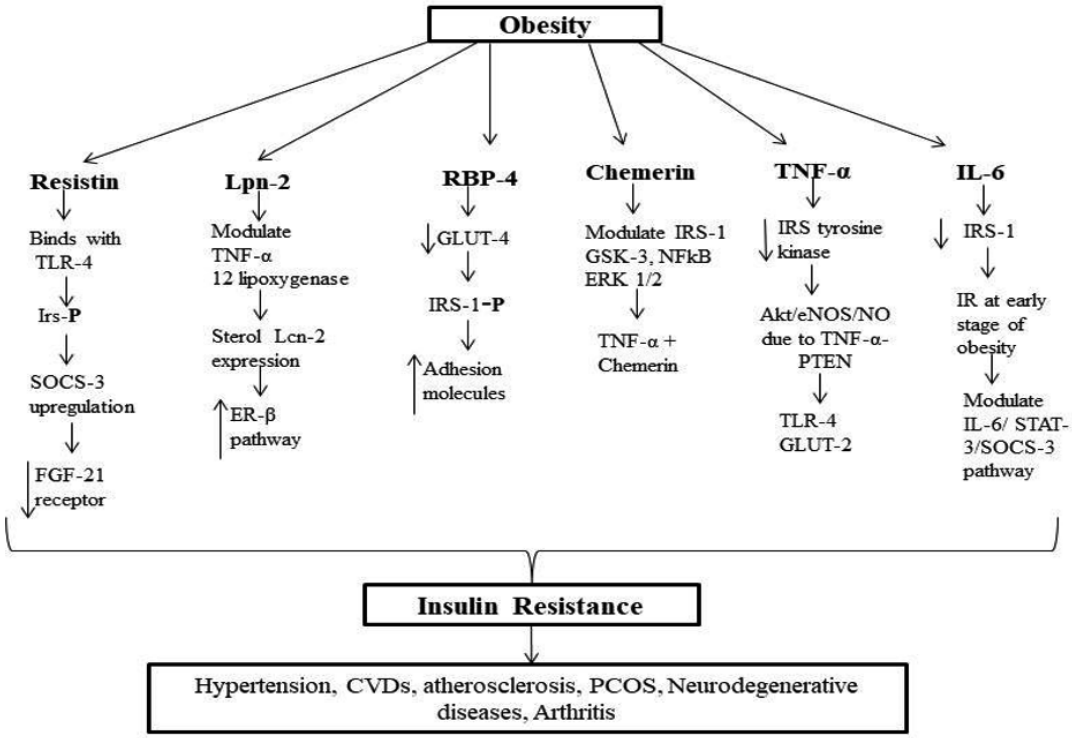

Fig. 1. Schematic diagram representing the role of adipokines in insulin resistance and related diseases

positively modulates phosphatase and tension homologue (PTEN) and suppresses Akt/eNOS/NO signalling pathways in a vascular wall, leading to insulin resistance [71]. Thus, TNF-á/PTEN pathway can be targeted as a therapeutic to treat insulin resistance and vascular complications in obesity. During diabetes, in hepatic cells, TNF-attenuation improves the insulin receptor substrate 1 (IRS-1) via phosphorylation [72] at serine residues 636/639 and inhibiting the tyrosine phosphorylation of IRS-1. This phosphorylation/dephosphorylation is governed by c-jun N-terminal kinase (JNK) and an extracellular signal-regulated kinase (ERK) phosphorylation [73]. Apart from the IRS-1, toll-like receptors TLRs and GLUT-2 pathways modulate other signalling pathways that results in insulin resistance [74,75]. Further, the PPAR á/ã agonist aleglitazar [76], GW501516 [77] and TACE selective inhibitor JTP-96193 [78] have been reported for the inhibition of TNF-á arbitrate inflammatory reactions and insulin resistance. However, through independent pathways, insuin resistance due to this adipocytokine induces neuroinflammation in immortalised hypothalamic neuronal cells, which may promote neurodegenerative diseases [79].

IL-6

Interleukin-6 is a pro-inflammatory cytokine secreted by many different cell types and tissues, including adipose tissue, which regulates growth and development of distinct tissues and plays a significant role in the immune response [80]. This adipocytokine contributes to low-grade chronic inflammatory state responsible for adipose tissue dysfunction via altered lipid and carbohydrate metabolism, coronary artery diseases (atherosclerosis), CVDs diabetes and insulin resistance [81]. The mechanism of action by which this cytokine imparts its role in insulin resistance involves inhibitory effects on the gene transcription of PPAR gamma, GLUT-4 and IRS-1. This causes a reduction in IRS-1, insulin-stimulated tyrosine phosphorylation. In hepatocytes, SOCS inhibit insulin receptor signalling that stimulates insulin resistance [82, 83]. Obesity-related insulin resistance due to IL-6 promotes impaired adipogenesis in subcutaneous fat in humans, suggesting the role

of IL-6 in the modulation of signalling pathways [84]. By emphasizing the role of IL-6 in T cells, it has been corroborated that through a classical signalling pathway IL-6 stimulates inflammation and insulin resistance at the early stages of obesity development [85]. However, studies in humans showed an association between the amount of IL-6 and the size of the visceral adipose tissue favours insulin resistance [86]. Further, IL-6 in association with signal transducer and activator of transcription 3 (STAT3) modulates a variety of signalling pathways that imparts their role in insulin resistance/sensitivity and related diseases. It has been reported that the treatment of myo-Inositol in rat PCOS model downregulates the insulin resistance in association with IL-6-STAT-3 signalling pathway [87]. Whereas, atmospheric fine particles (PM2.5) increases the IL-6 levels in rat liver and suggest an essential role in the regulation of type 2 diabetes mellitus through IL-6/STAT3/SOCS3 pathway [88]. Pu-erh tea extract mitigates insulin resistance and non-alcoholic steatohepatitis through IL-6/STAT3 signalling pathway in mice [89]. However, the blocking of IL-6 receptor improves insulin sensitivity in patients with rheumatoid arthritis and non-diabetic [90].

CONCLUSION

Dysfunctional adipose tissue secretes altered levels of adipokines that are associated with many health problems, including insulin resistance. Adipokines imparts their deleterious effects in the development and the progression of insulin resistance mostly through IRS-1/STAT-3/SOCS signalling pathways. Recent findings exhibit the role of adipokine induced insulin resistance as a major risk factor for the development of chronic diseases like neurodegenerative diseases, non-alcoholic fatty liver disease, chronic kidney diseases, cardiovascular diseases etc. However, determining the role of adipokines in the aetiology of insulin resistance may provide new opportunities for developing novel therapeutics for obesity arbitrates insulin resistance.

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