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Review

An update on metabolic syndrome: Metabolic risk markers and adipokines in the development of metabolic syndrome

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ABSTRACT

Background: Metabolic syndrome is a collection of physiological and biochemical abnormalities about 20–25% of adult population in developing countries is suffering from metabolic syndrome. Previous research demonstrated that adipose tissue plays an important role in energy regulation via endocrine, paracrine and autocrine signals as results of obesity due to accumulation of adipose tissue to excess that by time affects negatively both physical and psychological health and well being, it has been found that adipose tissues produces a variety of factors known as ***"adipokines"*** which play a key role in the development and progression of the disease and also hypothesized that adipokines are a possible link between obesity and the other risk components of the Metabolic syndrome. Many of the adipokines exert multiple actions in a variety of cellular processes leading to a complex array of abnormal characteristic of Metabolic syndrome. Abnormal production of these adipokines by expanded visceral fat during Adiposity contributes to a pro-inflammatory state. Increasing evidence suggests that aberrant production/release of adipokine from adipocyte i.e. adiponectin, leptin and resistin etc, may contribute to the health problems associated with Adiposity such as dyslipidemia, insulin resistance and atherosclerosis. This study conclusively have shown a significant role of adipokines secreted by adipose tissue and various metabolic risk markers play a important role in the development of Metabolic syndrome.

1. Introduction

Metabolic syndrome (MetS) is a globally epidemic disorder and the term Met.S is used to describe the clustering of clinical and metabolic risk markers. It is a strong, independent contributor to the onset of coronary heart disease and type 2 diabetes (T2D) [1]. The MetS is a cluster of risk factors i.e. abdominal Adiposity, dyslipidemia, high blood pressure, insulin resistance and proinflammatory states, strongly linked to cardiovascular disease (CVD).[2–8] (Table 1)

2. Diagnostic criteria for metabolic syndrome

Many definitions of MetS have been laid down by the World Health Organization WHO) [9]. European Group for the Study of Insulin Resistance (EGIR) [10]. National Cholesterol Education Programme and Adult Treatment Panel III NCEP-ATP III, 2001) [11]. NCEP was slightly updated by AHA/NHLBI in 2005 [12] and same year International Diabetes Federation (IDF) proposed a new definition [13], based on clinical criteria, which are very similar and it can be expected that they will identify many of the same individuals as having MetS. In the present study MetS was defined in accordance with the NCEP-ATP III criteria. The criteria for MetS were based on simple clinical and biochemical parameters. At least three out of five of the risk factors need to be present for clinical criteria for the MetS Whereas in case of adult Asian Indian women [14], cut-off point for waist circumference is > 80 cm and body mass index (BMI) is > 23 kg/m^2 (modified in various combination with components of NCEP-ATP III). Studies suggest that for people of Asian origin, as a group, the cut-off levels for the symptoms of MetS are different from non-Asians. This is one of the reasons why a single definition of the syndrome has not yet been established and why medical organizations use "any three of the five" measures for diagnosis.

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Table 1
NCEP-ATP III criteria, 2001 of the metabolic syndrome.

S. No.	Risk Factor	Defining Level
1.	Abdominal Adiposity, waist circumference, cm (inch)	
	Men	>102 (>40)
	Women	>88 (>35)
2.	Triglycerides, mg/dl	>150 (1.69 mmol/l)
3.	HDL cholesterol, mg/dl	
	Men	<40 (1.04 mmol/l)
	Women	<50 (1.29 mmol/l)
4.	Blood pressure, mm Hg (Systolic/Diastolic)	>130/85
5.	Fasting glucose, mg/dl	>110 (6.1 mmol/l)

3. Prevalence of metabolic syndrome

Looking at previous studies around the world, which included general population, aged from 20 to 25 and upwards, the prevalence varies from 20 to 25% (India), 28% (USA), 30.1% (Tehran), 33.4% (Turkey) and 39.3% (Saudi Arabia). High prevalence of the Met.S has been reported from Sub-Saharan Africa and Middle East countries; South Africa, Morocco, Oman and Iran showed prevalence of 33.5%, 16.3%, 21% and 33.7%, respectively. The prevalence rates are also high in Venezuela (31.2%) and urban Brazil (25.4%) [15,16]. The situation appears to be similar in South Asian countries. MetS prevalence rates as described earlier vary among ethnic groups as defined by the NCEP-ATP III criteria among Finnish and Native American men. Both studies involved subjects with comparable age ranges (42–60 and 44–49 years, respectively), with the Finnish study showing prevalence of only 14% compared with the prevalence in the Native American study of 43.6%. The prevalence varies from a low of 13.9% in black men to a high of 27.2% in Mexican American women [17]. These results of literature indicate that MetS is currently more prevalent and dangerous for large number of people around the world.

4. Risk markers of metabolic syndrome

4.1. Adiposity

In fact, it is generally agreed on that increased body weight and particularly central/abdominal Adiposity is at the core of MetS [18]. It has been known for many years that body fat tends to be distributed in different patterns. That is, some people tend to store a larger amount of fat in their hips and buttocks, while others have more of their body fat in their abdomen. These patterns have in the past been termed gynoid and android Adiposity because of the general tendency of women to have more fat in peripheral sites (hips and buttocks) and men to store fat centrally (in their abdomen). However, it is clear that the distribution of body fat is much more complex than the rules of age and gender since the patterns of body fat distribution overlap considerably among men and women. It is now established that central Adiposity is associated with the various components of MetS and that Adiposity is even more predictive than total body weight of a predisposition to CVD. Central Adiposity also causes insulin resistance, a decrease of the typical responses of tissues to the hormone insulin.

4.2. Insulin resistance/Hyperinsulinemia

Insulin resistance is a central abnormality of the MetS or syndrome X or Reaven syndrome, originally hypothesized by Reaven [19], may be the link that causes the other factors to cluster together. Insulin resistance is associated with a plethora of metabolic abnormalities (dyslipidemia, hypertension, abnormal haemostasis, low grade inflammation, altered adipokine levels) and many of these abnormalities can directly or indirectly accelerate the atherogenic process and malfunctioning of glucose metabolism. Metabolic abnormalities result from the interaction between the effects of insulin resistance located primarily in the muscle and adipose tissue. The adverse impact of the compensatory hyperinsulinaemia on tissues that remain normally insulin sensitive [20,21].

Fat in normal women represents between 18% and 20% of body weight, whereas in men it represents only 10%–15%. The reason for this difference is that women at some point in their lives may nourish a fetus and then a baby from their own reserves, so women have to stock energy in the form of fat in anticipation of future pregnancies (and must stock even more energy during the last two trimesters of pregnancy). For various reasons, different fat distributions occur in women according to climate. In hot countries, the fat is localized on the buttocks (black Africans), on the hips (Mediterraneans), and around the navel (certain Asians). This distribution avoids covering the woman with a hot coat of fat that would be difficult to bear and inefficient for thermoregulation during hot periods. In cold countries, the distribution of fat is more uniform, which provides for better protection during rigorous winters. However the fat is distributed, its main function is for the survival of the species as it provides for survival of the woman and her offspring during times of scarcity. (see Fig. 1)

4.3. Diabetes

The risk for incident T2D is up to five times higher in individuals with the MetS compared with those without the syndrome [22,23], Interestingly, the presence of both the MetS and insulin resistance has an additive effect, as these patients exhibit a six to seven-fold

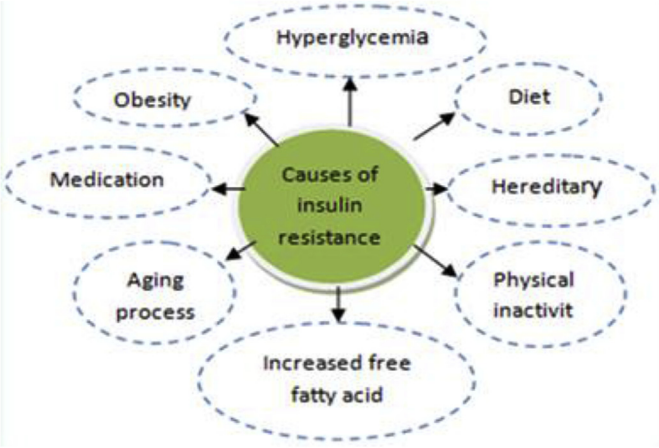

Fig. 1. Causes and consequences of insulin resistance.

increased risk for T2D [24,25], found that hyperinsulinemia was the strongest predictor of diabetes incidence. The presence of the MetS in women with gestational diabetes mellitus (GDM) substantially increases the risk of developing T2D. GDM alone significantly increases a woman's risk for subsequently developing T2D [26,27]. The conversion of GDM into T2D varies between 6 and 92% depending on diagnostic criteria, racial/ethnic background of the subject sample, and duration of surveillance [28]. The presence of the Met.S further increases the progression from GDM into T2D.

4.4. Dyslipidemia

Insulin resistant state-inhibited lipolysis in the adipose tissue, leading to overproduction of FFAs in the plasma and increased FFA uptake by the liver. FFA leads to increased liver concentrations of TG and cholesterol esters. High blood TG concentrations in the form of VLDL induce cholesterol ester transfer protein (CETP) activity [29], which promotes transfer of TG from VLDL to HDL and a subsequent increase in HDL clearance and decreased HDL concentrations. It also promotes the transfer of TG into LDL in exchange for LDL cholesterol ester [30] The triglyceride-rich LDL can undergo hydrolysis by hepatic lipase or lipoprotein lipase, which leads to a small and dense, cholesterol depleted LDL particle (SD-LDL), components of atherogenic dyslipidemia are individually associated with a CVD risk [31].

4.5. Hypertension

Hypertension is becoming a public health emergency worldwide especially in developing countries, where studies have projected up 80% increase in the numbers of hypertensive subjects by the year 2025 [32] · Hypertension affects approximately 1 billion individuals worldwide and is an important worldwide public-health challenge because of its high frequency and increased risks of cardiovascular and kidney disease [33,34]. It has been identified as the leading risk factor for mortality, and is ranked third as a cause of disability adjusted life-years [35]. Hypertension is a common manifestation of the metabolic disturbances associated with insulin resistance and hyperinsulinaemia, a key factor of Met.S. Some studies using the hyperinsulinaemic-euglycaemic clamp technique have demonstrated that hyperinsulinaemia occurs in hypertension as a compensatory response to reduced insulin stimulated glucose uptake by skeletal muscle [36,37]. Evidences suggest that elevations in adipocyte derived resistin and leptin may contribute to the pathogenesis of hypertension in patients with insulin resistance [38,39].

5. Pathophysiology of metabolic syndrome

Adiposity increases the risk for various co-morbidities, and recent advances in the understanding of adipose tissue biology offer an insight into the complex pathophysiologic mechanisms (Fig. 2). Various endocrine and proinflammatory products from the visceral adipose tissue, which interact with the insulin signaling cascade, could be identified [40] Among these products, adiponectin protects from insulin resistance and cardiovascular disease [41], while free fatty acids, leptin, resistin and proinflammatory substances promote the development of insulin resistance [42]. Leptin, is primarily produced by the adipose tissue, regulates food intake and energy expenditure, fatty acid metabolism and hepatic glucose production [43]. Most common forms of Adiposity are characterized by high levels of circulating leptin and leptin resistance. Leptin reveals structural similarities with proinflammatory cytokines such as IL-6, which interferes with insulin action. Cells of the stroma vascular fraction in adipose tissue, and especially in

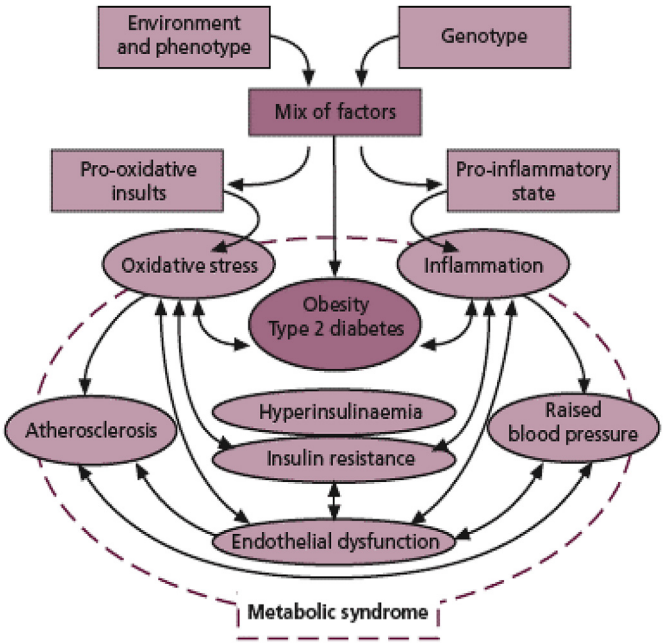

Fig. 2. Pathophysiology of metabolic syndrome.

visceral fat are an important source of IL-6 production [44]. TNF-α was extensively studied as a possible link between Adiposity, subclinical inflammation and insulin resistance. TNF-α impairs insulin action by inhibitory effects on the insulin signaling cascade and by suppressing the transcription of adiponectin [45]. Therefore, all the adipokines are interdependent, great interest and the cross talk among them plays an important role in pathophysiology of MetS.

6. Adipose tissue

Adipose tissue acts in an autocrine, paracrine or endocrine fashion [46] to control various metabolic functions and may contribute to the development of Adiposity mediated MetS. Adipose tissue functions can be classified into three aspects. First, it is related to lipid metabolism including TG storage and FA release. Second, it catabolizes TGs in order to release glycerol and FAs that participate in glucose metabolism in liver and other tissues. Finally, adipocytes secrete adipokines, which include hormones and cytokines [47] For these reasons, adipose tissue has an important influence on physiological processes such as development and growth of the adipocyte and energy homeostasis. There are two types of adipose tissue depending on its cell structure, location, color, vascularization and function: White adipose tissue (WAT) and brown adipose tissue (BAT). WAT is the primary site of energy storage in a lipid droplet of the adipocytes in the form of TGs, whereas BAT contains multilocular adipocytes or cells with various lipid droplets. It has a large number of mitochondria and is specialized in heat production and, therefore, energy expenditure. Nevertheless, in humans, BAT is present only in newborns for regulating thermogenic process [48].

Adipose tissue contains different cell types. Only one third of the tissue is constituted by adipocytes and the rest is represented by fibroblasts, macrophages, stromal cells, monocytes and pre-adipocytes [49]. Hormonal activity and transcription factors are responsible for differentiation of preadipocytes to adipocytes [50]. Nevertheless, the ability of differentiation of preadipocytes is always present in all species and depends on the body energy status

and the storage needs. White adipose tissue is further divided in visceral and subcutaneous adipose tissue.

6.1. Subcutaneous adipose tissue (SAT)

Subcutaneous adipose tissue is located underneath the skin and is responsible for the distinct body compositions of human males and females. This type of adipose tissue contributes to temperature regulation or thermal isolation (Guyton and Hall, 2000).

6.2. Visceral adipose tissue (VAT)

Visceral adipose tissue fills in space gaps between organs and maintains them in the adequate position (Guyton and Hall, 2000). Visceral fat mass and adipocyte size is associated with peripheral and hepatic insulin resistance (Cases and Barzilai, 2000).

Although it has been demonstrated that when removing visceral fat mass, but not subcutaneous fat mass, insulin sensitivity improves [51]. It does not imply that subcutaneous adipose tissue does not contribute to several metabolic abnormalities, particularly when weight gain occurs [52] Thus, an increase in abdominal fat mass, either visceral or subcutaneous, appears to be important for the pathogenesis not only of insulin resistance but also of dyslipidemia, glucose intolerance, hypertension, and cardiovascular risk [53,54].

7. Lipogenesis

Lipogenesis is the synthesis of esterified FAs, which form TGs from carbohydrates or other energy sources acquired in the diet. In rats, lipogenesis occurs in liver and WAT, whereas in humans, lipogenesis contributes mildly to the fat balance. Lipid accumulation in adipose tissue depends on circulating FA uptake [55]. FAs are provided by the enzymatic hydrolysis of TG contained in the chylomicrons by the lipoprotein lipase. After FAs enter the adipocyte, reesterification is necessary for lipid storage in TG form [56]. Several enzymes involved in adipose tissue lipogenesis are induced by insulin. These are fatty acid synthase (FAS), acetyl CoA carboxylase (ACC) and malic enzyme (ME). Newly synthesized FAs are used as substrates in TG synthesis [57]. Insulin-mediated stimulation of lipogenesis in response to nutritional status is the result of an increase in the enzyme activities involved in FA biosynthesis, as well as an increase in the gene expression of these enzymes [58].

8. Lipolysis

Regional adipose differences—the degree of expansion of particular adipose tissue beds is an important factor in the development of dyslipidemia. VAT has greater lipolytic activity than SAT, and fatty acids are directly delivered to the liver from this region via the portal vein. This leads to increased delivery of lipids to the liver and worsening IR in the liver, promoting TG synthesis and exacerbating dyslipidemia. Sam et al. found a significant link between visceral AT and dyslipidemia in patients with T2DM [59]. Expansion of VAT was associated with a greater number of VLDL and LDL particles in the circulation, even when controlling for BMI and SAT distribution. There are several differences between visceral and subcutaneous tissue, including the expression of different genes involved in insulin resistance and inflammation and, different patterns of adipokine secretion [60].

9. Adipose tissue as an endocrine organ

For many years, adipose tissue regarded merely as a heat insulator and storage of free fatty acid (FFA) that could be release when needed. However after the identification of adipokines, adipose tissue is now recognized to play a central role in the pathophysiology of insulin resistance and MetS [61]. In recent years, it has become clear that adipose tissue is far more than a storage facility and thermoregulator and is in fact an active secretory organ of multiple mediators known as adipokines [62]. These adipokines include hormones (for example, leptin and adiponectin), inflammatory cytokines (for example, tumor necrosis factor α (TNFα), interleukin (IL)-6, omentin and visfatin) and other proteins (for example, plasminogen activator inhibitor (PAI)-1, angiotensinogen, resistin and apelin) [63].

The different fat depots (visceral vs. subcutaneous) are heterogeneous not only in terms of metabolic capacities, but also of adipokine secretion pattern. Fat depot-specific characteristics may be retained in strains derived from single human preadipocytes even after 40 population doublings [64]. Depot-related differences in secretion may have local repercussions on the adipose tissue by autocrine or paracrine mechanisms and/or may directly impact the liver for substances produced by intraperitoneal fat. When the contribution of each depot to systemic levels of adipokines is considered, it should be kept in mind that intra-abdominal fat only represents 15% of total fat in lean and obese individuals [65].

Maintenance of a normal amount of adipose tissue is essential because imbalance can cause serious health problems and dysregulated release of adipokines may lead to metabolic disturbances and inflammation. Virtually all known adipokines are markedly dysregulated in Adiposity and Met.S. Many adipokines implicated in the pathogenesis of inflammation and insulin resistance are overproduced with increasing adiposity, thereby promoting metabolic complications.

10. Adipokines in metabolic syndrome

Many of the adipokines exert multiple actions in a variety of cellular processes leading to a complex array of abnormal characteristic of Met.S. Abnormal production of these adipokines by expanded visceral fat during Adiposity contributes to a pro-inflammatory state. Increasing evidence suggests that aberrant production/release of adipokine from adipocyte i.e. adiponectin, leptin and resistin, may contribute to the health problems associated with Adiposity such as dyslipidemia, insulin resistance and atherosclerosis. Therefore, adipokines are potential candidates of insulin resistance, endothelial dysfunction and hypertension and reflect the importance of visceral Adiposity as a causal factor in metabolic and vascular disease.

10.1. Resistin

Resistin antagonizes the action of insulin and their expression is inhibited in Adiposity and insulin resistance [66]. Elevation of the insulin and TNF-α in Adiposity, have been found to inhibit resistin expression, which may explain the low levels of resistin found in the studies on Adiposity and diabetes. A mice study suggested that resistin selectively impairs the inhibitory action of insulin on hepatic glucose production [67]. Neutralization of resistin by specific antibodies resulted in decreased blood glucose levels and improved insulin sensitivity [68], thereby providing a more direct link between fat mass and insulin resistance but the physiological role of resistin and the mechanism by which it neutralizes insulin action, are still unclear. The expression of resistin gene is induced during adipocyte differentiation of 3T3-L1 cells and the resistin polypeptide was expressed and secreted by mature adipocytes [69]. The secreted protein was found to inhibit 3T3-LI adipogenesis and it was speculated that resistin was a feedback regulator of adipogenesis. However, the role of resistin on Adiposity-associated

insulin resistance has become controversial because additional evidence has suggested that Adiposity and insulin resistance are associated with decreased resistin expression [70,71]. Resistin exists predominantly as the hexamer, although our current understanding of the metabolic effects of either complex is limited. Studies demonstrating a causal role of resistin in glucose homeostasis are based on animal models with altered serum resistin levels. Infusion or over-expression of resistin leads to hyperglycemia, a response which to a large degree can be explained by increased hepatic glucose production [72]. Despite the significant interest generated by the discovery of resistin in 2001 (Steppan et al., 2001), very little is known about the intracellular signaling pathways by which resistin induces its metabolic effects although resistin has been shown to be important in regulating metabolic pathways in several tissues and organs including the hypothalamus, adipocytes and the liver. A consistent finding in vivo is that resistin suppresses liver and muscle AMPK activation [72–74]. However, in isolated mouse muscle this does not occur suggesting that the inhibitory effects of resistin on AMPK may require release of an unknown factor from other cell types [75].

In humans and rodents, plasma resistin concentrations are positively correlated with BMI [76]. In an animal study expression of resistin in visceral and subcutaneous adipose tissue is controversial. The present data on resistin in human samples is conflicting. Some reports have shown that resistin levels are elevated in individuals with Adiposity and diabetes [77–79]. Recent study showed that 420C/G polymorphism of resistin gene directly correlated to its high circulating level and metabolic risk factors specifically markers of obesity (WC, WHR and BMI) and atherosclerosis (TG, TC, BP), so it may have an important role in the development of metabolic syndrome and cardio metabolic diseases in adult women [80] Furthermore, a recent meta-analysis, which was conducted to evaluate the significance of serum resistin levels in hypertensive patients, shows that serum resistin level in hypertensive patients is significantly higher than normotensive individuals [81].

10.2. Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is a cytokine produced by several cells (fibroblasts, endothelial cells, monocytes, adipocytes, etc) [82]. The in vivo release of IL-6 by whole-body AT could contribute to 15–35% of the systemic IL-6 in humans [83]. The IL-6 receptor belongs to the class I family of cytokine receptors, which uses Janus kinases (JAKs) as intracellular signaling pathways. Circulating levels and AT production of IL-6 are increased in Adiposity [82]. IL-6 could be implicated in insulin resistance and its complications. In mice fed a high-fat diet, the increased production of IL-6 by AT induced hepatic insulin resistance. This hepatic insulin resistance could be mediated, in part, by the increased expression of suppressor of cytokine signaling (SOCS)-3, a protein that binds and inhibits the insulin receptor and also targets IRS proteins for proteosomal degradation [84], Consistent with this report, mean plasma concentration of IL-6, but not of TNFα, leptin or MCP-1, was found to be 50% higher in the portal vein than in the radial artery of obese subjects and this portal vein IL-6 concentration correlated directly with systemic C-reactive protein concentrations [85], Also, IL-6 expression varies between adipose tissue sites: expression is higher in visceral than in peripheral adipocytes, and 90% of IL-6 expressed in adipose tissue is produced by cells other than adipocytes [86]. Overall, the association of IL-6 and insulin resistance seems complex and IL-6 alone might not be an appropriate marker of insulin resistance or Met.S [87,88]. Fasting plasma IL-6 concentration was negatively correlated with the rate of insulin-stimulated glucose disposal in Pima Indians [89]. Circulating IL-6 level is increased in obese and insulin resistant subjects [90] and is significantly higher with greater expression in VAT [91].

Studies in myotubes have demonstrated that these effects require activation of AMPK-activated protein kinase [92,93]. However, the exact mechanism by which IL-6 activates AMPK to promote glucose uptake and fatty acid oxidation is not yet understood. IL-6 has also helped us understand the link between Adiposity and insulin resistance. The strong correlations between adipose tissue mass and the secretion of many adipokines has led to the suggestion that reducing total adipose mass may be a strategy for the treatment of Adiposity-related diseases. However, due to the severe metabolic consequences of adipose tissue ablation as observed in lipoatrophic patients, directly modifying adipokine gene expression and release into the circulation may be more viable. IL-6 is an inflammatory biomarker that is positively correlated with obesity, glucose intolerance, and insulin resistance. The production of IL-6 is 3 times higher in visceral adipose tissue than in subcutaneous adipose tissue [94,95].

10.3. Tumor Necrosis Factor-alpha (TNF-α)

TNF-α is more expressed in visceral than in subcutaneous fat and abundantly produced by macrophages than adipocytes cells [96]. The degree of TNF-α mRNA adipose tissue expression is positively correlated with percentage body fat, body mass index, hyperinsulinemia, indicating that the amount of TNF-α present in adipose tissue may be related to insulin resistance [97], but weight loss decreased TNF-α level [98]. It significantly increases the expression of IL-6 [99], but reduces the expression of resistin in 3T3-L1 adipocyte cells [100]. It is unknown whether increased expression of TNF-α may modulate leptin expression. Neutralization of TNF-α has differential effects on critical adipokines and body composition indices; thus it improves inflammatory markers and total adiponectin in patients with the Met.S without improving insulin sensitivity. A number of studies have demonstrated that TNFα can impair insulin signaling in hepatocytes and adipose tissue [101,102]. Chronic treatment with TNFα decreases insulin-stimulated glucose uptake in rat skeletal muscle. In addition, studies using a soluble TNFα receptor-IgG chimeric protein restored insulin-induced insulin receptor and IRS-1 phosphorylation in Zucker rats in fat and skeletal muscle. Most effects of TNF α on AT are mediated by the TNFα receptor 1 subtype (TNFR1) and subsequent activation of various transduction pathways [103]. Furthermore, the targeted deletion of TNF-α or its receptors increased insulin sensitivity and glucose tolerance in obese rodents in some [104]. In obese type 2 diabetic humans, TNF-α neutralization does not appear to improve glucose tolerance or insulin sensitivity, however, in individuals without established type 2 diabetes prolonged treatment does improve insulin sensitivity [105].

Adipose tissue TNF-α concentration is correlated with Adiposity and insulin resistance in patients with and without type 2 diabetes [106]. In obese women, TNF-α messenger RNA expression in adipose tissue is correlated with fasting plasma glucose, insulin, and triacylglycerol concentration [107]. TNF-α increases adipocyte lipolysis, and this appears to be mediated at least in part by its effects on perilipin [108,109]. Thus, TNF-α may increase systemic insulin resistance by promoting the release of fatty acids from adipose tissue into the bloodstream to act on tissues such as muscle and liver. The increases in serum proinflammatory cytokines, such as TNF-a is probably related to the enhanced production by the expanded adipose tissue mass. It has been suggested that resident monocytederived macrophages in the adipose tissue are a major source of pro-inflammatory cytokines [110]. Recently published study shown high TNF α level in coronary artery disease [111]. Moreover, recent study showed TNF-a/IL-10 ratio may also be

responsible for other disease like coronary artery disease in north Indian population [112].

10.4. Adiponectin

Adiponectin is a powerful inducer of proinflammatory cytokines produced by adipose tissues and macrophages [113]. The most abundant protein, adiponectin has anti-inflammatory properties affecting the nuclear factor (NF-κB) pathway and it is also a potent enhancer of insulin action on peripheral tissues [114]. The current understanding is that adiponectin acts as an endogenous insulin sensitizer by decreasing glucose levels and inducing the burning of lipid tissue in muscle and liver without increasing insulin levels. Adiponectin plasma levels are between 5 and 30 mg/L in lean subjects and represent 0.01% of plasma proteins. It is present in the blood stream in three main forms: trimer, hexamer and high molecular weight (HMW) 12-18-mer adiponectin [115]. Insulin-sensitizing action of adiponectin results from AMPK-mediated reduction of hepatic gluconeogenesis and increase of muscle glucose transport. Adiponectin also enhances energy consumption and fatty acid oxidation in liver and muscle, and reduces their tissue triglyceride content; thereby further enhancing insulin sensitivity in vivo [116]. AdipoR1 and AdipoR2 serve as major receptors for adiponectin in vivo. They belong to a new family of receptors predicted to contain seven transmembrane domains but to be structurally and functionally distinct from G-protein coupled receptors. AdipoR1 is abundantly expressed in muscle, whereas AdipoR2 is also expressed in liver [117].

Prospective studies in humans have shown that increased plasma concentrations of adiponectin are strongly and independently associated with reduced risk of incident type 2 diabetes in apparently healthy individuals and in Pima Indians [118,119]. HMW adiponectin rather than total adiponectin appears to be an important biomarker for the Met.S, being primary responsible for increased insulin sensitivity, reduced abdominal fat, high basal lipid oxidation and a more favorable lipoprotein subclass profile. Thus, lower level of HMW adiponectin could play a pathogenic role in the development of this syndrome [120].

Hypoadiponectinemia has been found in a variety of human metabolic and cardiovascular disease states including type 2 diabetes mellitus (T2DM), lipodystrophy, nonalcoholic hepatic steatosis, essential hypertension, and coronary artery disease even after body mass index (BMI) is matched. Genetic hypoadiponectinemia caused by a missense mutation has been reported. The patients carrying this mutation also exhibit a much higher propensity to develop the Met.S [121]. As the decrease of adiponectin precedes the development of insulin resistance and myocardial infarction in humans, low levels of adiponectin are likely to be a causal component of those disorders. Adiponectin mRNA expression varies according to tissue site, being lower in visceral than in subcutaneous tissue [122]. Adiponectin also affects hepatic glucose production by decreasing the mRNA expression of two essential gluconeogenesis enzymes: phosphoenolpyruvate carboxykinase; and glucose-6-phosphatase.In addition to its effects on insulin sensitivity, adiponectin has a vascular-protective effect early in the atherogenesis process by interfering with the regulation of adhesion molecule expression on vascular endothelial cells. The transformation of macrophages into foam cells [123], and by modulating smooth muscle cell proliferation). Also, adiponectin could reduce the inflammatory response induced by TNFα, as shown by studies in vitro where macrophage activity and TNFα production were diminished in macrophages treated with adiponectin [124].

Recently, the increase in adiponectin after weight loss was found to be correlated with serum lipid improvement, independent of insulin sensitivity changes [125]. Studies of isolated human explants or adipocytes suggest there are no differences in adiponectin secretion from visceral or subcutaneous depots [126]. Further evidence suggesting that adiponectin expression may be reduced in states of Adiposity was provided by Spiegelman and colleagues [127], who observed decreased adiponectin mRNA in adipose tissue from obese (ob/ob) mice and humans.

This observation may represent one feature of visceral adipose tissue (VAT) biology that leads to its strong association with negative health outcomes and may also explain the finding that even after controlling for BMI and fat mass individuals with higher VAT have lower adiponectin levels than subjects with less VAT [128]. Adiponectin exhibits insulin-sensitizing, fat-burning, cardioprotective, anti-inflammatory and anti-oxidant properties, thereby thwarting several pathologies belonging to the Met.S.

Adipocytokines (Leptin and Adiponectin) contribute to the development of metabolic syndrome in post menopausal women, attriubuting to adverse effects on glucose and lipid metabolism. Recently study showed that all the metabolic risk markers, anthropometrical markers, FPG, insulin, IR, serum leptin level and L:A ratio are significantly high in postmenopausal women with MetS as compared to postmenopausal women without MetS [129].

10.5. Leptin

Leptin is produced mainly by mature adipocytes, although production in minor extents from other tissues such as placenta, fundus of the stomach, skeletal muscle and liver has been reported [130]. Leptin concentrations have been shown to be directly proportional to the amount of body fat. Its concentration were found to correlate with insulin, insulin resistance, glucose and measures of adiposity [131], with marked sexual dimorphism as females have higher leptin concentrations than males.

The concept of “leptin resistance” or alternate concept “hypothalamic leptin insufficiency” has been challenged and is still unclear in humans and may involve multiple mechanisms. One mechanism may be the induction of leptin on suppressor of cytokine signaling-3, which blocks the intracellular pathway of leptin [132], Another mechanism for leptin resistance may diminish the transport of leptin across the blood-brain barrier and to endoplasmic reticulum stress, which inhibit leptin signaling [133]. As body weight increased, leptin signaling protected the β-cell from adverse effects of over nutrition such as lipid accumulation, thus improving β-cell function [134], Although, leptin receptor-mediated Janus Kinase-signal transducers and activators of transcription (JAK-STAT) signaling is essential for regulation of food intake and body weight, leptin-stimulated Phosphoinositol-3-Kinase signaling appears to be important for regulation of glucose metabolism.

Circulating leptin levels parallel adipose tissue mass but also reflect immediate changes in nutritional status as they decrease soon after the beginning of fasting [135]. The secretion is also dependent on the fat depot, being higher in the subcutaneous than in the visceral depot [136]. Subcutaneous fat is responsible of 80% of total leptin production. This was shown in cultures ex vivo where the production of leptin was higher in subcutaneous adipocytes than in those of deeper origin. Leptin plasma concentration [137], and mRNA expression in adipose tissue [138] are directly related to Adiposity severity, as an increase of fat mass is associated with an increase of leptin, which makes leptin an indicator of total fat mass. Leptin has been identified as a key factor in the longterm regulation of body weight [139]. Impairment of leptin transport and signalling may result in leptin resistance, probably a primary risk factor for obesity [140,141].

Taken all together, these observations suggest a potentially leptin improves insulin sensitivity through activation of AMP

protein kinase (AMPK), which controls cellular concentrations of malonyl-CoA, thereby inhibiting acetyl-CoA carboxylase (the enzyme involved in malonyl-CoA transformation) [142]. As a result, there is a decrease of intracellular malonyl-CoA and a decline of lipogenesis associated with increased fatty-acid beta-oxidation. Therefore, while leptin deficiency very likely contributes to insulin resistance when adipose tissue is lacking, leptin resistance is a main feature of human Adiposity. So far, the precise role of leptin in insulin resistance remains unclear. Finally we have concluded our study and found that TNF-alpha, resistin, IL-6 and Leptin levels were found higher in Metabolic syndrome populations of North India.

Conflicts of interest

None.

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Appendix A. Supplementary data

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