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Obesity- The gateway to metabolic syndrome

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Abstract

Obesity can be referred to as the central player in the development and progression of metabolic syndrome. Although metabolic syndrome lacks a concise definition, insulin resistance, dyslipidemia and hypertension appear to occupy the front row with obesity at the driver's seat. With over one billion people across the world either overweight or obese the prevalence of metabolic syndrome is also multiplying at an alarming rate. Hence unraveling the underlying molecular aspects of obesity is slowly gaining momentum. One such evolving concept is considering the role of adipose tissue which is in a state of hypertrophy in obesity. In a condition of adiposity the adipose tissue no longer remains a passive storage site but acts an active endocrine organ. The physiology of adipose tissue has a key role in the pathogenesis of the metabolic syndrome and related cardiovascular disorders. This review discusses some vital aspects of the involvement of adipose tissue in obesity linked metabolic disturbances. The increased levels of inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor α (TNF- α), PAI-I (plasminogen activator inhibitor-I) and CRP (C-reactive protein) during obesity are believed to be released from the adipose tissue and thus termed as adipokines. Here we have discussed the role of some important adipose derived hormones leptin, adiponectin and resistin. Many more such adipokines or adipose derived hormones are coming into the picture thus exposing their potential roles in the treatment or prevention of obesity associated metabolic syndrome.

Key Words: Obesity, Metabolic syndrome, Adipokines.

INTRODUCTION

In the more recent years, metabolic syndrome has caused a revolution in vascular risk stratification and is slowly emerging as a well accepted concept among health science experts [1]. It is described as accumulation of several risk factors of CVD and type 2 diabetes mellitus within one individual. Metabolic syndrome has also been called dysmetabolic syndrome,

plurimetabolic syndrome, insulin resistance syndrome and syndrome X. These names indicate its multifaceted nature and hence the many definitions of metabolic syndrome [2].

1. WHO definition (1998): This definition applies to both the diabetic and non-diabetic populations. The definition suggests that metabolic syndrome involves glucose intolerance, hyperinsulinemia and diabetes, plus at least two other clinical or biochemical abnormalities [3].
- Abdominal obesity (waist: hip ratio >0.90 or body mass index [BMI] ⩾30 kg/m^2).
- Dyslipidaemia consisting of triglycerides ⩾1.7 mmol/l (150 mg/dl) or HDL-C <0.9 mmol/l (35 mg/dl).
- Hypertension (blood pressure ⩾140/90 mmHg or receiving antihypertensive medication).

2. The EGIR (*Groupe Européen pour l'étude de l'insulinorésistance*) definition: Applicable only to non-diabetic individuals , the definition assumes that the syndrome is indicated by a plasma insulin concentration found in the top quartile of the population plus two clinical or biochemical criteria that differ from those in the WHO definition [4].
- Waist circumference Men > 94 cm ,Women > 80 cm
- Triglycerides > 1.80 g/l or treatment
- HDL Cholesterol < 0.40 g/l
- Glycaemia ≥ 1.10 g/l
- Blood Pressure ≥ 140 / 90 mmHg

3. National Cholesterol Education Program Adult Treatment Panel III (ATP III) definition: In this definition, metabolic syndrome is diagnosed when at least three of the following are present [5]:
- Fasting plasma glucose ⩾110 mg/dl (6.1 mmol/l).
- Abdominal obesity (e.g., waist circumference >102 cm in men, >88 cm in women).
- Triglyceride level ⩾150 mg/dl (1.7 mmol/l).
- High-density lipoprotein cholesterol (HDL-C) level <40 mg/dl (1.0 mmol/l) in men and <50 mg/dl (1.3 mmol/l) in women.

4. IDF (International Diabetes Foundation) definition (2005): The definition uses the NCEP criteria, but considers waist measurement to be the main, and essential, parameter along with two other clinical or biochemical criteria [6].
- Waist circumference Men > 94 cm, Women > 80 cm
- Triglycerides > 1.50 g/l
- HDL Cholesterol : Men < 0.40 g/l ; Women < 0.50 g/l
- Glycaemia ≥ 1 g/l
- Blood Pressure ≥130/85 mmHg

All of these definitions of metabolic syndrome signify its multi-factorial nature thus making its management rather complicated. Hence unwinding the underlying mechanism of its cause can prove beneficial in prevention and treatment of metabolic syndrome.

Obesity: A global health concern

Obesity is an excessive accumulation of energy in the form of body fat which impairs health and has reached epidemic proportions globally, with more than 1 billion adults overweight - at least

300 million of them clinically obese - and is a major contributor to the global burden of chronic disease and disability. Often coexisting in developing countries with under-nutrition, obesity is a complex condition, with serious social and psychological dimensions, affecting virtually all ages and socioeconomic groups.

Increased consumption of more energy-dense, nutrient-poor foods with high levels of sugars and saturated fats, combined with reduced physical activity, have led to obesity rates that have risen three-fold or more since 1980 in some areas of North America, the United Kingdom, Eastern Europe, the Middle East, the Pacific Islands, Australasia and China.

The prevalence of obesity is commonly assessed by using body mass index (BMI), defined as the weight in kilograms divided by the square of the height in meters (kg/m^2). A BMI over 25 kg/m^2 is defined as overweight, and a BMI of over 30 kg/m^2 as obese [7, 8].

Table 1. WHO classification of obesity

WHO Classification	**Popular Description**	**BMI (kg/m^2)**	**Risk of co-morbidities**
Underweight	Thin	<18.5	Low (but risk of other clinical problems increased)
Normal range	Normal	18.5 - 24.9	Average
Overweight		25.0	
• Pre-obese	Overweight	25 - 29.9	Increased
• Obese Class I	Obese	30.0 - 34.9	Moderate
• Obese Class II	Obese	35.0 - 39.9	Severe
• Obese Class III	Morbidly Obese	> 40.0	Very severe

Pathophysiology of obesity associated metabolic complications: role of adipose tissue

Over the last few decades obesity research has been characterised by a dramatic change in the overall understanding about the adipose tissue and its role in pathophysiology [9]. The secretory nature of adipocytes or fat cells which encompass 95% of total body cells has shifted the concept of white adipose tissue (WAT) as a mere energy storing organ to that of an extremely active endocrine tissue [10]. The large number of secreted proteins includes hormones, growth factors, enzymes, cytokines, complement factors, and matrix proteins, collectively termed as adipokines or adipocytokines [11-14]. Since in obesity the adipose tissue is in a state of hypertrophy this secretory activity of WAT is believed to be exaggerated and closely associated with obesity induced metabolic syndrome.

Amid all these secreted products cytokines or better described as pro-inflammatory cytokines are thought to be fore-runners in obesity associated metabolic syndrome. The two major mechanisms linking inflammatory adipocytokines to metabolic disturbances are oxidative stress and endothelial dysfunction (see Figure 1).

1. Oxidative stress:
Oxidative stress is a condition in which generation of reactive oxygen species (ROS) exceeds the capacity of the antioxidant defense system. Thus, oxidative stress can occur as a consequence of excess generation of ROS, depressed antioxidant capacity, or a combination of the two. Inflammation and oxidative stress are inseparably interconnected. The ROS generated activates the redox sensitive transcriptional factors NFκB and AP-1(activator protein 1) which in turn trigger the release of cytokines and adhesion molecules, whereas on the other hand production of ROS is an inherent property of activated immune cells (as in the case of inflammation). Also these ROS oxidize LDL to LDL-ox (oxidized LDL), which damages the artery wall and initiates the development of atherosclerosis [15].

2. Endothelial dysfunction:
Nitric oxide is the key endothelium-derived relaxing factor (EDRF) that plays a pivotal role in the regulation of vascular tone and vasomotor function. In addition to its vasodialatory effect, NO also protects against vascular injury, inflammation and thrombosis by inhibiting leukocyte adhesion to the endothelium, maintaining the vascular smooth muscle in a non-proliferative state, and limiting platelet aggregation [16].

Endothelial dysfunction is characterized by defects in the normal vascular relaxation response to mediators like acetylcholine or to increased blood flow. The basis for endothelial dysfunction involves a reduction in the amount of bioavailable nitric oxide (NO) [17, 18]. Thus endothelial dysfunction can cause progression of atherosclerosis.

Figure 1: Mechanisms linking obesity to the two major implications of metabolic syndrome viz. CVD and insulin resistance. ROS: reactive oxygen species, NO: nitric oxide

The reduced bioavailability of NO also affects the NO release stimulated by insulin. It is through the release of NO that insulin increases vasodilatation and improves the transport of glucose to

skeletal muscles, liver where it triggers the uptake of glucose. This explains how endothelial dysfunction can provoke insulin resistance [19].

Oxidative stress can also induce endothelial dysfunction by converting NO produced by eNOS (endothelial nitric oxide synthase) to peroxynitrite which cannot induce vascular relaxation and is itself a strong oxidant that can damage tissues [20].

Since it is these pro-inflammatory adipocyte hormones that mainly promote the progression of obesity into the manifestations of metabolic syndrome, administration or regulation of these adipocytokines can prove to be an attractive alternative for the treatment of metabolic syndrome [21].

Some important adipokines involved in obesity associated metabolic syndrome

1. Leptin

Leptin was discovered in 1994 and is product of the *ob-ob* gene. Although it is mainly secreted by the adipocytes, it is also expressed at lower levels in other tissues such as gastric epithelium, muscle and placenta. [22-24]. Plasma leptin concentrations positively correlate with subcutaneous, rather than intra-abdominal, fat tissue mass [26]. Obese individuals have higher leptin mRNA and protein levels than lean individuals indicating that adipocytes secrete leptin in direct proportion to adipose tissue mass as well as nutritional status [27, 28]. It has been evidenced that leptin plays crucial roles in regulation of food intake, body weight and energy balance via central and peripheral pathways [25]. Centrally leptin acts via the Ob-R receptors (JAK-STAT pathway) and inhibits anabolic peptides NPY (Neuropeptide Y) and AgRP (agouti related peptides). It also up-regulates pro-opiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART)-containing neurons which ultimately results in decreased food intake and increased energy expenditure. Plasma leptin levels and its actions change with the changes in body weight and body fat (Figure 2).

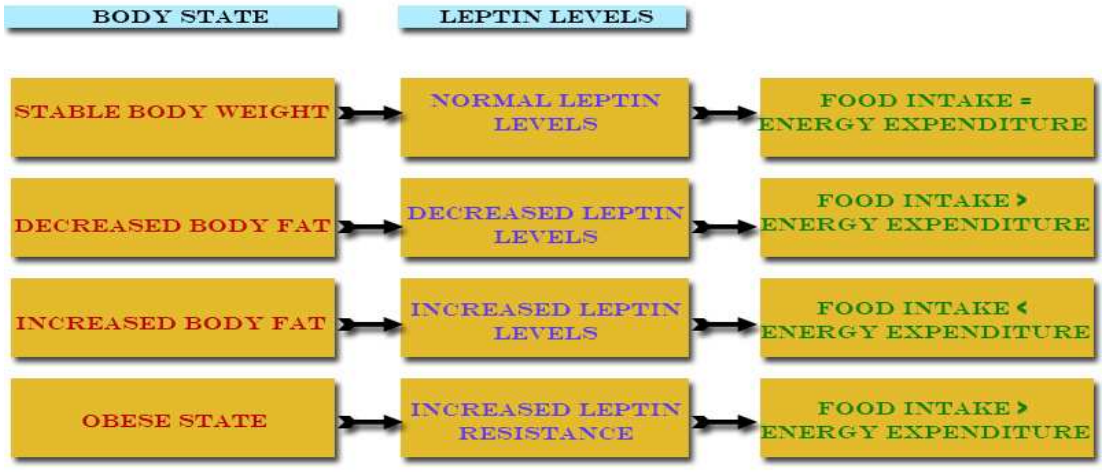

Figure 2: Changes in leptin levels and its actions corresponding to changes in body weight and body fat

Thus, obese individuals have higher circulating levels of leptin, indicating that leptin may play a role in obesity associated metabolic turbulences.

Leptin and Cardiovascular diseases

▪ Leptin increases generation of reactive oxygen species (ROS) in endothelial cells and stimulates secretion of pro-inflammatory cytokines such as tumor necrosis factor – α (TNF-α) and interleukin -6 (IL-6) both of which are promoters of hypertension and atherosclerosis [29].

▪ Leptin has direct vasodilatory effects due stimulation of NO synthesis. However leptin increases release of endothelin -1 (ET-1), a vasoconstrictor secreted primarily by endothelial cells and also by macrophages, fibroblasts and cardiomyocytes which counteracts effects of NO inhibition [30]. Also as mentioned earlier the excitatory sympathetic activity of leptin is continued even in hyperleptinemia, this explains hypertensive conditions in obese subjects with high levels of circulating leptin.

▪ The proatherogenic action of leptin is likely attributable to a combination of its effects on various cell types. In endothelial cells as mentioned earlier leptin triggers oxidative stress and inflammatory responses, thus increases the production of monocyte chemoattractant protein-1 (MCP-1) and monocyte colony stimulating factor (M-CSF), thus contributing to the development of atherosclerosis [31,32] Leptin also promotes calcification of cells of the vascular wall and facilitates thrombosis by increasing platelet aggregation [33].

Leptin and insulin resistance

Leptin administration enhances the inhibitory action of insulin on hepatic glucose production (HGP) via complete suppression of hepatic glycogenolysis (leptin lowers the mRNA levels of gluconeogenesis enzymes). Also leptin has found to potentiate glucose uptake by insulin. However these pro-insulin effects of leptin are independent of the feeding state and are observed in normal physiologic levels of leptin [34]. In conditions of overfeeding and obesity the anti-insulin effects of leptin are observed.

▪ It was observed that after 3 days of overfeeding, the action of leptin on hepatic gluconeogenesis was blunted. Hepatic insulin resistance and leptin resistance was demonstrated after just 3 days of voluntary hyperphagia [36].

▪ Leptin increases the release of TNF-α from adipocytes. TNF-α has a direct effect on insulin resistance. Also leptin induces oxidative stress which also leads to insulin resistance via endothelial dysfunction [38, 29].

▪ In pancreatic ß cells, leptin causes the activation of phosphodiesterase 3B (PDE3B), which leads to marked inhibition of glucagon-like peptide-1–stimulated insulin secretion. However this effect in obese subjects has not been fully established [39].

Current drugs modulating leptin

4-phenyl butyric acid (PBA), and tauroursodeoxycholic acid (TUDCA), have the ability to decrease ER (endoplasmic reticulum) stress and act as leptin-sensitizing agents which has been indicated by research on mice fed with high fat diet [40]. Currently, 4-PBA is used to treat cystic fibrosis and urea cycle disorders, while TUDCA is used to treat liver diseases. Since both drugs are already FDA-approved, the researchers believe that it will be easy to move them quickly to human trials. Also there is a proposal of nanobodies (a unique form of antibodies that is characterized by a single antigen-binding domain and generally does not cross the blood–brain

barrier) may lead to an antagonist that could selectively inhibit peripheral activities of leptin [41]. This form of leptin antagonist might be clinically useful, as they can target peripheral adverse effect of leptin without inducing central weight gain.

2. Adiponectin

Adiponectin or adipocyte complement-related protein of 30 kDa (Acrp30) also known as AdipoQ, ApM1 and GBP28, is an adipocytokine exclusively expressed and secreted by adipose tissue [42, 43]. Adiponectin plays an important role in the regulation of insulin function and energy homeostasis [44, 45]. Though synthesized by adipocytes, circulating levels and adipose tissue gene expression are found to be lower in the obese and in type 2 diabetes subjects with respect to healthy controls [46-48] and negatively correlate with the body mass index (BMI), the plasma levels of glucose, insulin, triglycerides and the insulin-resistance [49]. Lower levels of circulating adiponectin in obese individuals can therefore be correlated directly to the progression of metabolic syndrome.

Adiponectin attenuates the inflammatory response induced by different stimuli by modulating signal transduction mechanisms in different cells and these anti-inflammatory properties of adiponectin could account for its beneficial effects on cardiovascular (Figure 3) and metabolic disorders, including atherosclerosis and insulin-resistance [50].

Adiponectin and cardiovascular diseases

Adiponectin and endothelial cells

Adiponectin has novel vascular actions to directly stimulate production of nitric oxide (NO) in endothelial cells via the phosphorylation of endothelial nitric oxide synthase (eNOS) by adenosine-monophosphate-activated protein kinase (AMPK) [51]. It inhibits the production of inflammatory adipokines like TNFα, IL-6 and indirectly CRP by interfering with the nuclear transcription factor kappa B (NF-κB) signaling. Thus it reduces expression of adhesion molecules like intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1 [52, 53].

Adiponectin and foam cell transformation

Adiponectin suppresses macrophage to foam cell transformation by suppressing the expression of macrophage SR-As (class A scavenger receptors), resulting in the reduction of foam cell formation and decreasing the secretion of pro-inflammatory cytokines [54]. Foam cell formation is further reduced by adiponectin-induced down-regulation of acyl-coenzyme A:cholesterol acyltransferase-1 in macrophages, the enzyme that catalyzes the formation of cholesteryl esters [55].Also adiponectin induces anti-inflammatory cytokine IL-10 secretion from macrophages [56]. Accordingly, adiponectin limits the initiation of atherosclerotic plaque formation.

Adiponectin and smooth muscle cells

Adiponectin suppresses the proliferation and migration of smooth muscle cells (SMCs) induced by platelet-derived growth factor (PDGF) in the intima, thus interfering with the evolution of fatty acid streak.

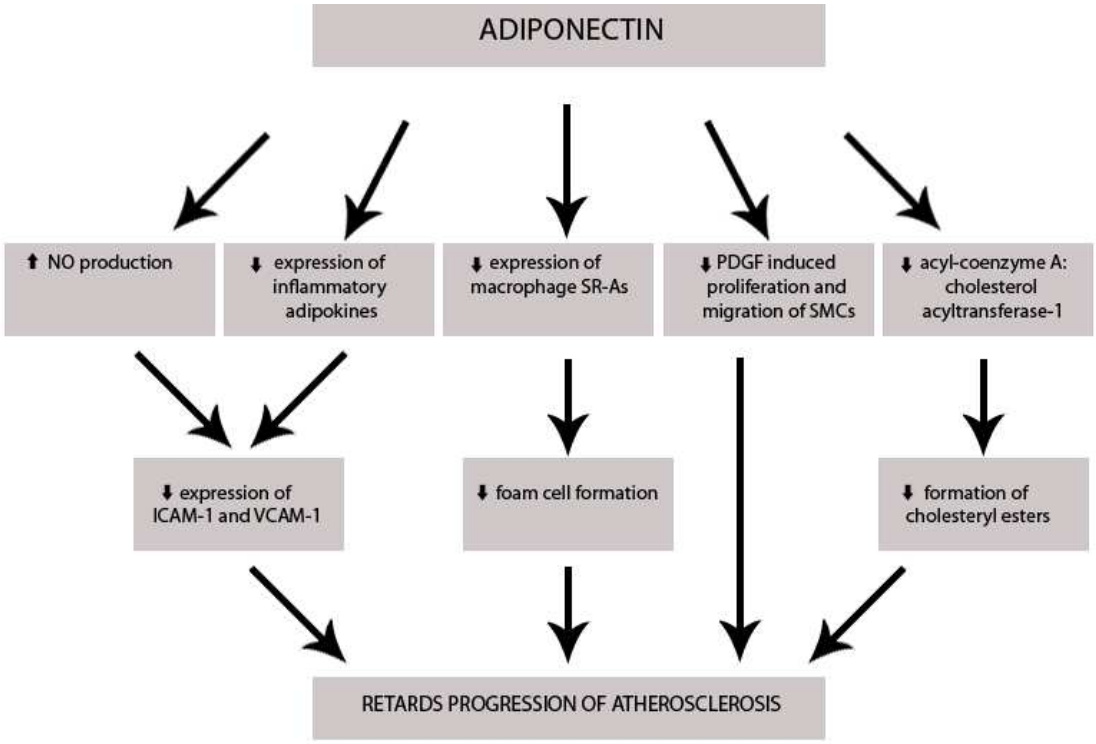

Figure 3: Cardioprotective effects of adiponectin

NO: nitric oxide; SR-As: class A scavenger receptors; PDGF: platelet derived growth factors; SMCs: smooth muscle cells; ICAM-1: intercellular adhesion molecule-1; VCAM-1: vascular cell adhesion molecule-1;

Adiponectin and insulin resistance

It has been observed that adiponectin reduces glucose levels in different animal models of obesity/diabetes mellitus and this hypoglycemic effect is not associated to stimulation of insulin secretion, whose levels are reduced in parallel with those of glucose, but to an increased insulin sensitivity [57].

▪ Stimulating glucose uptake by muscle and liver cells via the phosphorylation and activation of 5'-adenosine monophosphate activated protein kinase (AMPK) [51].

▪ Adiponectin decreases hepatic glucose production by inhibiting enzymes of gluconeogenesis, and thus contributes to reduction in blood glucose levels in normal and diabetic animals.

▪ Adiponectin inhibits the production of TNFα which directly produces insulin resistance via IRS1 associated decreased PI3 kinase activity in muscle [58].

Current drugs modulating adiponectin

Pharmacological interventions, namely, with PPAR-γ agonists or thiazolidinediones, appear to enhance adiponectin expression. Used clinically to treat Type 2 diabetes by improving insulin sensitivity, thiazolidinediones increase adiponectin mRNA expression and secretion in adipose tissue by activating the adiponectin promoter [59]. In a randomized, double-blind placebo-controlled trial conducted on patients with Type 2 diabetes, rosiglitazone therapy for 6 mg

resulted in a significant increase in circulating plasma levels compared with placebo [60]. Additionally, rosiglitazone therapy has been reported to selectively elevate plasma high-molecular-weight adiponectin in humans and rodents [61]. Pioglitazone exerts a similar effect on adiponectin levels [62] and increases the secretion of the high-molecular-weight (HMW) form of adiponectin [63]. Furthermore, PPAR-γ agonists appear to enhance the expression of AdipoR1 and AdipoR2 in skeletal muscle and adipose tissue and thereby may enhance adiponectin intracellular signaling pathways that promote glucose utilization and anti-atherosclerotic conditions [64]. In addition to PPAR-γ agonists, treatment with both angiotensin-converting enzyme inhibitors and angiotensin receptor blockers increased adiponectin concentrations in insulin-resistant hypertensive patients, without affecting BMI; however, the molecular mechanisms involved remain to be elucidated [65]. Recently, the Rimonabant in Obesity-Lipids (RIO-Lipids) study examined the effects of rimonabant, a selective cannabinoid-1 receptor blocker, on metabolic risk factors [66]. Rimonabant is believed to induce significant weight loss in obese patients via the activation of the endocannabinoid system through CB1, which plays an important role in both the central and peripheral regulation of energy balance, body weight, and food intake [67]. Rimonabant, at a dose of 20 mg daily, resulted in a significant increase in plasma adiponectin, at levels above those that could be explained by weight loss alone [65]. Finally, as the beneficial molecular properties of adiponectin continue to emerge, a recombinant form of adiponectin may become available for therapeutic use or, alternatively, an adiponectin receptor-specific agonist may be developed to optimize the favorable cellular effects of adiponectin.

3. Resistin

Resistin is a 12.5-kDa polypeptide is expressed and secreted by both brown and white adipocytes in proportion to fat size stores leading to impaired glucose tolerance and insulin action [68]. Resistin is not exclusively expressed in adipose tissue, but is also expressed in the gastrointestinal tract, adrenal glands, and skeletal muscle [69]. Furthermore, resistin expression was demonstrated to be regulated in a tissue- and gender-specific manner.

Circulating resistin concentrations have been shown to be increased in genetically obese rodents (*ob/ob* and *db/db* mice) as well as in high-fat-diet–induced obesity. Resistin immunoneutralization has been reported to improve hyperglycemia and insulin resistance in high-fat–induced obese mice, while recombinant resistin administration impairs glucose tolerance and insulin action in normal mice [70]. All these reports highlight the role of resistin in obesity linked metabolic syndrome.

Resistin and cardiovascular disorders

It has recently been found that resistin participates in the inflammatory response. In further support of its inflammatory profile, resistin has been shown to increase transcriptional events leading to an increased expression of several pro-inflammatory cytokines including IL-6, TNF-α etc. in an NF-κB mediated fashion. It has also been demonstrated that resistin upregulates intracellular adhesion molecule-1 (ICAM1) vascular cell-adhesion molecule-1 (VCAM1), all of which are occupied in chemotactic pathways involved in leukocyte recruitment to sites of infection [71].Therefore resistin may be a link in the well-known association between obesity, inflammation and cardivascular complication.

Resistin and insulin resistance

The role of resistin in mediating insulin resistance was studied in mice using various in vivo tests. Purified recombinant resistin was administered intraperitonially (i.p.) to C57B1/ 6J mice and glucose tolerance was measured. Peak blood glucose level increased in the resistin-treated mice, compared to control-injected mice. This was followed by a concomitant increase in insulin levels. These results, suggested impairment in glucose tolerance *in vivo* as a direct function of resistin administration. Resistin neutralization experiments in mice were carried out to further document the involvement of resistin in insulin resistance. Diet induced insulin-resistant obese mice when administered anti-resistin IgG therapy showed a significant decrease in blood glucose and reversibly reduced hyperglycaemia. Anti-resistin IgG-treated mice showed much improved insulin sensitivity compared to non-specific IgG treated mice [72]. These experiments clearly point out the involvement of resistin in mediating insulin resistance in diet-induced obesity. However the exact mechanism through which resistin induces insulin resistance is not clearly known, but resistin mediated inflammation may be one of the pathways.

Current drugs modulating resistin

Studies on db/db mice suggest that as compared to the obese mice (*db/db* mice) and age-matched lean controls, resistin protein expression was reduced by 58% in the obese mice with severe hyperinsulinemia. It was observed in this study that Metformin upregulates resistin expression via the improvement of hyperinsulinemia in obesity [73]. Also thiazolidinediones are found to suppress resistin release from adipocytes via its action on PPARγ receptors [74].

Some Novel Adipokines

1 . Chemerin

Chemerin is a novel adipokine that has been suggested to play an important role in the pathogenesis of metabolic syndrome. Chemerin, also known as tazarotene induced gene 2 (TIG2) and retinoic acid receptor responder 2 (RARRES2), is a recently discovered adipokine that has been reported to modulate immune system function through its binding to the chemerin receptor (ChemerinR, a G protein-coupled receptor) [75]. Expression of chemerin and its receptor increases during the differentiation of pre-adipocytes into adipocytes. A critical function of chemerin/ ChemerinR is to regulate adipogenesis and metabolic homeostasis in adipocytes in mice and humans [76].

Recent results also indicate that chemerin and ChemerinR could have an important biological role in the formation of white adipose tissue during normal development and in pathological states such obesity [76,77]. Chemerin downregulation during adipocyte maturation results subsequently in lower expression of perilipin, GLUT4 (insulin-regulated glucose transporter), adiponectin and leptin by mature adipocytes. This novel adipokine probably also modulates metabolic pathways in mature adipocytes. In agreement with this, the absence of chemerin expression results in a reduced basal and stimulated rate of lipolysis. On the other hand, nanomolar concentration of chemerin decreases intracellular cAMP (cyclic-adenosin monophosphate) leading to the assumption that chemerin might oppose the lipolytic action of catecholamines by reducing intracellular cAMP [76]. In summary, chemerin has a regulatory role in adipogenesis and adipocyte metabolism, and influencing chemerin and ChemerinR signaling,

might pave a way to novel therapeutic approaches in the treatment of obesity- related metabolic syndrome.

2. Fibroblast growth factor (FGF)

The fibroblast growth factor (FGF) family is composed of 22 members (FGF1 to FGF22) with a wide range of biological functions, including cell growth, development, angiogenesis, and wound healing [78,89]. FGF21 was first suggested as a metabolic regulator with potential anti-diabetic properties during a high throughput screening for agents capable of increasing glucose uptake in 3T3-L1 adipocytes [80]. Addition of recombinant FGF21 to adipocytes was found to stimulate insulin-independent glucose uptake by enhancing the expression of GLUT1 [80]. A recent study has demonstrated a profound synergy between FGF21 and the anti-diabetic agent rosiglitazone (a peroxisome proliferator–activated receptor γ[PPARγ] agonist) in stimulating glucose uptake [81]. Transgenic mice with over expression of FGF21 were resistant to diet-induced obesity and metabolic disturbance [80]. In both *ob/ob* and *db/db* obese/ diabetic mice, therapeutic intervention with recombinant FGF21 resulted in a reduction of blood glucose and triglycerides to near normal levels, without apparent mitogenicity, hypoglycemia, or weight gain [80]. Furthermore, chronic treatment of diabetic rhesus monkeys with FGF21 for a period of 6 weeks could provide efficient and durable glucose control and triglyceride lowering without obvious adverse effects [82].

More importantly, FGF21 administration led to significant improvements in lipoprotein profiles, including decreased LDL and elevated HDL cholesterol, and beneficial changes in the circulating levels of several cardiovascular factors [82]. Also FGF21 has also been shown to improve pancreatic β-cell function and survival by activation of extra cellular signal–regulated kinase 1/2 and Akt signaling pathways [83]. The multiple beneficial effects of FGF21 on glucose and lipid metabolism and insulin sensitivity suggest that this small–molecular weight polypeptide might represent a promising therapeutic agent for the treatment of diabetes and other obesity-related metabolic disorders [82,83]. Although these animal-based studies are certainly of pharmacological interest, the physiological role of FGF21 remains poorly understood.

3. Neprilysin [84]

Neprilysin (NEP) is a zinc containing metalloendopeptidase which cleaves several bioactive peptides involved in the regulation of vascular function. NEP degrades vasodilator peptides (substance P, bradykinin and the natriuretic peptides and vasoconstrictor peptides (endothelin-1 and angiotensin). In human microvascular endothelial cells, fatty acids and glucose increase NEP activity, and inhibition of NEP in animal studies results in increased insulin sensitivity, suggesting that NEP may be related to the metabolic syndrome.

Dual NEP/ACE Inhibitors are more effective in regulating blood pressure than ACE inhibitor alone, suggesting NEP has a predominant effect on vasoconstricting peptides. Omapatrilat (NEP/ACE-I): has profound insulin-sensitizing properties and increases insulin stimulated glucose uptake both at the whole body level and in the insulin responsive tissues, indicating a potential role of NEP in the metabolic syndrome.

This hypothesis was tested at the University of Leeds (Division of diabetes and cardiovascular disorders) on cell, animal and human based models. In a diet induced animal model, male

C57BL/6J mice were fed with a high-fat diet, which resulted in decreased glucose tolerance and insulin resistance in obese mice. Results of this *in vivo* model suggested that plasma levels of NEP measured after 15 weeks of high fat diet feeding were significantly higher in obese mice as compared to lean mice. Also the epididymal and mesenteric fat in obese showed 4 to 9 folds higher levels of NEP as compared to lean, mice. In a study of 318 healthy white European males, plasma NEP measured by activity assay was significantly higher in subjects with the metabolic syndrome. NEP levels were found to be approximately 8-fold higher in those with metabolic syndrome as compared with those without the syndrome. High NEP levels correlated with high triglycerides, decreased HDL levels and raised blood pressure.

These findings show an association of NEP with the metabolic syndrome that seems to be mediated by obesity. These data also indicate that NEP is a novel adipokine that links increased fat to insulin resistance and vascular risk.

CONCLUSION

In this review we have tried to highlight the role of obesity in the pathogenesis of metabolic syndrome, a pandemic gaining steady momentum. Increased adipocyte activity and release of inflammatory mediators and their interplay seems to be the link. From a regulatory standpoint, the lack of a universal definition, the lack of a single etiologic factor or central pathophysiologic abnormality identified as mediating the constellation of features, uncertainty regarding study end points, heterogeneous study population, existing treatments, and regulatory precedent for established risk factors all suggest that some challenges will have to be solved before any new or existing drugs will be approved for the indication of metabolic syndrome. In February 2007, the US Food and Drug Administration (USFDA) stated in a draft guidance document that “it does not necessarily consider the metabolic syndrome to represent a distinct disease entity”. However, the USFDA concluded that “a therapeutic product intended to treat metabolic syndrome should normalize or improve all components of the syndrome, independent of weight loss, and ultimately be shown to prevent the development of diabetes and reduce CVD morbidity and mortality”. Although this is a very high aspiration from one drug, drugs modulating adipokine actions is an attractive option to impede the progression of obesity to type 2 diabetes mellitus and cardiovascular complications.

Future directions

Research suggests that aggressive treatment of cardiovascular risk factors associated with metabolic syndrome may prevent 80% of clinical cardiovascular events [85]. With the recent discovery of adipose tissue hormones, a palette of novel therapeutics targeting metabolic syndrome has emerged. Further elucidation of biology and mechanisms of adipokines promises newer discoveries resulting in paradigm shift in the appraisal of role of adipocyte in multi-component diseases.

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