Int J Pharm Bio Sci 2014 July ; 5 (3) : (B) 987 - 995

Review Article **Biochemistry**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

ROLE OF INFLAMMATION IN OBESITY RELATED METABOLIC DISORDERS.

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ABSTRACT

Globally, obesity is a major contributor to the burden of several chronic metabolic diseases, including type 2 diabetes mellitus and cardiovascular diseases. With changing life style, obesity has now become a global phenomenon affecting all socioeconomic groups, irrespective of age, sex or ethnicity. Morbid obesity and co morbidities of metabolic syndrome, such as hypertension, dyslipidemia and glucose intolerance are now increasingly recognized in young adults predisposing them to early cardiovascular diseases. Obesity is now viewed as a low grade inflammatory disease, characterized by increased levels of inflammatory markers like C-reactive protein, TNF-α, interleukins and other adipokines that promote insulin resistance in liver and skeletal muscle ultimately leading to the clinical expression of various metabolic disorders. Because of the reversibility of obesity related diseases with suitable interventional strategies, it is important to identify and treat the pro inflammatory state of obesity to prevent premature deaths due to metabolic diseases. The relationship between obesity, inflammation and metabolic disorders was investigated extensively in several populations. This review aims at giving a general view on the role of inflammation in obesity related metabolic disorders and summarizing the recent progress. Elucidation of the mechanisms that link obesity with inflammation and metabolic disorders will not only contribute to the understanding of the patho physiology of obesity, but also open to novel strategies for prevention and treatment of pro-inflammatory state of obesity and obesity related metabolic disorders.

KEY WORDS: **Obesity, inflammation, inflammatory markers and metabolic disorders**

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INTRODUCTION

The incidence of obesity worldwide has increased drastically during recent decades. Obesity has become the most common metabolic disorder in the world.[1] Consequently obesity and its related disorders, particularly Type 2 Diabetes mellitus (T2DM) and Cardiovascular diseases are now a serious threat to the current and future health of all populations in the world. . Many recent epidemiological studies have documented a rapid increase in the prevalence of obesity all over the world[2]. Studies in India had shown a rising prevalence of obesity particularly in adolescents3. WHO projects that by 2015, approximately 2-3 billion adults will be overweight and more than 700 million will be obese[4]. Potential causes of this growing epidemic of obesity include changes in the life style, dietary patterns and physical inactivity, and may also include as yet unidentified genetic and environmental determinants. Along with an increase in obesity there is a parallel increase in the prevalence of T2DM, hyperlipidemia, hypertension and cardiovascular diseases.[5] Obesity is also associated with an array of additional heath problems, like increased risk of sleep disorders, fatty liver disease, atherosclerosis, degenerative disorders including dementia, and some cancers. This cluster of pathologies has also started to emerge in children at young ages. The risk of many metabolic diseases including cardiovascular diseases, hypertension, diabetes mellitus, and certain cancers increases many folds in association with obesity[6]. Many recent studies have shown that obesity induces a subclinical chronic inflammation in adipose tissue[7]. A chronic, sub acute state of inflammation often accompanies the accumulation of excess lipid particularly in adipose tissue and liver. Experimental data provide evidence for a direct link between obesity and subclinical inflammation and support the concept that the metabolic syndrome and T2DM are at least in part are inflammatory conditions. Furthermore, elevated levels of inflammatory biomarkers are not only associated with the development of insulin resistance and future diabetes but with cardiovascular diseases as well. These findings suggest that subclinical inflammation may be a contributing factor not only to the etiology of these metabolic disorders but also their cardiovascular complications[8]. The link between obesity and inflammation has therefore raised an important question of whether obesity-induced inflammation plays a pathogenic role in the development and progression of these disorders. The correlation between the global epidemic of obesity and metabolic diseases has encouraged investigating into the potential molecular links between obesity and inflammation. In this review we will summarize the rapidly expanding body of evidence that support potential role of inflammation in the pathogenesis of obesity induced metabolic disorders like T2DM and Cardiovascular diseases and also review the inflammatory markers released from adipose tissue that could contribute to the development of insulin resistance and related metabolic disorders.

Obesity and inflammation

Obesity was described as a low grade chronic inflammatory condition more than a decade ago[9]. A lot of research is going on to understand the role of obesity induced inflammation in the pathophysiology of various obesity related metabolic disorders and also to know whether inflammation is just a marker for underlying processes or it has got some role that affect both insulin sensitivity and related disorders. More data has now accumulated to reinforce the concept that obesity is an inflammatory state in humans resulting from chronic activation of the innate immune system, which can subsequently lead to hyperinsulinemia, insulin resistance, impaired glucose tolerance and even diabetes.[10] Obesity, insulin resistance and type 2 diabetes are closely associated with chronic

inflammation characterized by abnormal cytokine production, increased acute-phase reactants and other mediators and activation of a network of inflammatory signaling pathways[11]. Insulin regulates the uptake, oxidation and storage of fuel molecules in insulin-sensitive tissues like adipose tissue, skeletal muscle and also in macrophages. Obesity, in particular visceral obesity, is associated with resistance to the effects of insulin on peripheral glucose and fatty-acid utilization, often leading to T2DM[12]. Insulin resistance, together with the associated hyperinsulinemia and hyperglycemia, and the presence of pro-inflammatory mediators might lead to a state of vascular endothelial dysfunction, an abnormal lipid profile, hypertension and vascular inflammation, all of which promote the development of atherosclerotic cardiovascular disease. Subclinical, low-grade inflammation might have an important role in the pathogenesis of insulin resistance and type 2 diabetes mellitus. Population studies show a strong correlation between the levels of pro-inflammatory biomarkers, such as C-reactive protein, interleukin-6 and tumor-necrosis factor, and perturbations in glucose homeostasis, obesity and atherosclerosis. Insulin resistance might be partly precipitated or accelerated by an acute-phase reaction as part of the innate immune response, in which large amounts of pro-inflammatory. Mediators and insufficient amounts of anti-inflammatory mediators, such as adiponectin, are released from adipose tissue. Insulin resistance resulting from increased adipose tissue mass particularly in abdominal area has also been recognized as having an important role in inflammatory pathways. Insulin sensitive tissues particularly adipose tissue and skeletal muscle are proposed to lead to a worsening of the chronic , low grade inflammatory state . Resistance to insulin action promotes inflammation further through an increase in FFA concentration and interference with the anti-inflammatory effect of insulin. A chronic, sub acute state of inflammation often accompanies the accumulation of excess lipid in adipose tissue and liver, evidenced by changes in both inflammatory cells and biochemical markers of inflammation. These changes can be seen in the involved tissues and systemically in terms of elevated circulating levels of inflammatory markers[13]. Plasma concentrations of TNF-α, IL-6, C-reactive protein and other inflammatory mediators have been shown to be increased in the obese people [14]. The inflammatory process is most marked in the visceral fat depot as well as the vasculature, and is involved in the metabolic events which culminate in the insulin resistance and metabolic syndrome. The components of metabolic syndrome like obesity and hyperlipidemia comprise the major risk factors for cardiovascular diseases and type2 Diabetes mellitus.

An important feature of inflammation is infiltration of inflamed tissues by immune cells such as Neutrophils, Eosinophils and Macrophages. The recent finding that obesity is characterized by macrophage accumulation in white adipose tissue has added another dimension to our understanding of the development of adipose tissue inflammation in obesity macrophages in promoting insulin resistance[15]. However, no direct evidence has been offered to establish this connection thus far. In obesity, adipose tissue becomes inflamed due to filtration of adipose tissue by macrophages and also as excess production of inflammatory cytokines by adipocytes themselves. Inflammation of adipose tissue is a crucial step in the development of peripheral insulin resistance. In addition, in proatherosclerotic conditions such as obesity and dyslipidemia, macrophages accumulate lipid to become foam cells[16]. Adipocytes and macrophages share common features such as expression of cytokines, nuclear hormone receptors, and many other factors. Macrophages in adipose tissue are likely to contribute to the production of inflammatory mediators either alone or in concert with adipocytes, which suggests a potentially important influence of Macrophage infiltration of adipose tissue has recently been described in obese conditions in both mice and humans[17]. It has been suggested that expanding adipocytes or neighboring pre-adipocytes might begin to produce chemotactic signals leading to

macrophage recruitment. The role of inflammation in obesity was considerably impacted by the demonstration of resident macrophages in adipose tissue[18]. There is also a novel evidence to suggest that adipose tissue is infiltrated by macrophages which potentially leads to altered secretion of pro inflammatory adipocytokines and dysregulated lipid homeostasis[19]. Recent studies have suggested that macrophages infilterate adipose tissue as a part of a scavenger function in response to adipocyte necrosis, which is indeed the initiating event in the process of macrophage infiltration. The proinflammatory cytokines, as well as free fatty acids, the latter as a result of lipolysis of neutral fat commence the process of inflammation by the activation of macrophages. Hypoxia has been proposed to be an inciting etiology of adipocyte necrosis. With obesity and progressive adipocyte enlargement, the blood supply to adipocytes may be reduced and the induction of adipocyte hypoxia in vitro results in the expression of a number of inflammatory cytokines[20]. The acute phase response is activated by ongoing inflammation, in which macrophages secrete proinflammatory cytokines in response to multiple stimuli[21]

Inflammatory markers

It has been proposed that inflammatory cytokines secreted by adipose tissue exert an endocrine effect conferring insulin resistance in liver, skeletal muscle, and vascular endothelial tissue, ultimately leading to both T2DM and cardiovascular disease. In particular, elevated production of adipocytokines, such as tumor necrosis factor and interleukin-6 (IL)-6, leads to an acute-phase response with increased hepatic production of C-reactive protein (CRP), a sensitive marker of low-grade systemic inflammation.[22] TNF-α, IL-6, and CRP not only directly promote insulin resistance, but also stimulate endothelial production of adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular adhesion molecule-1 (VCAM-1), critical mediators of endothelial dysfunction in capillary and arteriolar endothelium . Adipose tissue has been shown to express most of the proinflammatory mediators however it is only recently that inflammatory cytokines are detected in obese states and are postulated to be the causal in the development of metabolic complications[23]**.** Adipose tissue elaborates pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α, TNF-α is a multifunctional cytokine with different roles ranging from proliferation to inflammatory effects and mediation of the immune responses with greater secretion from the stromal vascular fraction than from adipocytes and with greater secretion from visceral than subcutaneous adipose tissue sites[24]. The role of adipose tissue in metabolic disorders has continued to evolve with the description of numerous secretory products from adipocytes. Several studies have shown positive association between several inflammatory markers and obesity [25]. The main source of inflammatory mediators within human adipose tissue are macrophages , although other cell types, including adipocytes, preadipocytes, vascular endothelial cells, T-lymphocytes, and the mesothelium may contribute. In many studies there was marked increase in inflammatory adipocytokine levels in obesity and was found to be associated with increased numbers of macrophages in adipose tissue of obese mice[26]. Macrophages have been identified as the primary source of many of the circulating inflammatory molecules that are detected in the obese state and are postulated to be causal both in the development of insulin resistance and in the progression to type 2 diabetes[27]. Clinical studies have confirmed a correlation between BMI and adipose tissue macrophage numbers, in human visceral adipose tissue[28]. Obesity induced inflammation results in an increased number of macrophage residents in human adipose tissue. Macrophages secrete pro-inflammatory cytokines such as TNF-α, IL-6, MCP-1 and contribute to the inflammatory process. Conversely, expression of adiponectin, insulin-sensitizing effectors is down-regulated during obesity decreasing its levels. Leptin could modulate macrophage activation and TNF-α production. IL-6 production by human adipose tissue increases during obesity[29]. It may induce

hepatic CRP synthesis and may promote the onset of cardiovascular complications. Both TNF-alpha and IL-6 can alter insulin sensitivity by triggering different key steps in the insulin signaling pathway. In rodents, resistin can induce insulin resistance, while its role is still a matter of debate in humans. Adiponectin inhibits liver neoglucogenesis and promotes fatty acid oxidation in skeletal muscle. In addition, adiponectin counteracts the pro-inflammatory effects of TNF-α on the arterial wall and probably protects against the development of arteriosclerosis. In obesity, the pro-inflammatory effects of cytokines through intracellular signaling pathways involve the NF-kappa B and JNK systems. Genetic or pharmacological manipulations of these effectors of the inflammatory response have been shown to modulate insulin sensitivity in different animal models. In humans, it has been suggested that the improved glucose tolerance observed in the presence of statins is likely related to their anti-inflammatory properties. Thus, it can be considered that obesity corresponds to a sub-clinical inflammatory condition that promotes the production of pro-inflammatory factors involved in the pathogenesis. It has been proposed that inflammatory cytokines secreted by adipose tissue exert endocrine effects influencing insulin resistance in liver and skeletal muscle ultimately leading to the clinical expression of both type2diabetes mellitus and cardiovascular diseases[30]. TNF-α is able to induce not only its own synthesis, but is also a powerful regulator of other cytokines, e.g. stimulating the production of IL-6 .Elevated levels of TNF-α, and interleukin-6, leads to an acute phase response with increased hepatic production of CRP, a sensitive marker of low grade systemic inflammation[31.] CRP is an acute-phase reactant mainly produced in the liver. Recent studies have shown that CRP can also be produced by fat cells [38], which raises the possibility that CRP may simply be a marker of obesity in people who go on to develop diabetes. Fibrinogen is an acute-phase reactant involved in clotting and has been previously linked to incident diabetes [32]. IL-6 is made by leukocytes and other tissues that play a role in glucose homeostasis, including pancreatic islet cells, hepatocytes, adipocytes, and skeletal muscle cells, and is associated with incident diabetes[33]. NF-α, IL-6, and CRP not only directly promote insulin resistance, but also stimulate endothelial production of adhesion molecules such as E-selectin, intercellular adhesion molecule-1 , and vascular adhesion molecule-1, critical mediators of endothelial dysfunction in capillary and arteriolar endothelium[34]. Recent observations on the interference of insulin signal transduction by inflammatory mechanisms are of great interest, because obesity is a proinflammatory state. It is possible that other factors, such as genetic factors, may also contribute to the inflammatory stress in obesity. These factors may be important in ethnic groups like Asian Indians, who may have increased amounts of upper abdominal fat despite a normal body mass index. Because excessive nutritional intake probably accounts for the inflammation at least in obesity induced insulin resistance, the most rational way to suppress such inflammation is through caloric restriction. The other lifestyle change that affects inflammation is exercise. Exercise results in a fall in the indices of inflammation, such as plasma CRP concentration. The mechanism underlying this effect of exercise is not known. However, it is noteworthy that lifestyle change is a very effective way to reduce the rate of development of diabetes in a pre diabetic population, as shown by the diabetes prevention study.

Role of inflammation in the development of atherosclerosis and cardiovascular diseases.

The interplay between inflammation and lipid metabolism in obesity has-been studied extensively to understand the development of metabolic syndrome and mechanisms of atherogenesis. Adipose tissue which was previously viewed as a relatively inert tissue involved only in the storage of energy in the form of triglycerides, is now considered as an active endocrine tissue highly implicated in cell function and regulation through a complex network of endocrine, paracrine and autocrine signals and is a source of adipocytokines, like

leptin, adiponectin, resistin, interleukin -6, tumor necrosis factor -α etc. Adipose tissue participates in the regulation of several physiologic and pathologic pathways such as metabolisms, immunity and inflammation. Metabolic, inflammatory and innate immune processes are also coordinately regulated by lipids[35]. Hyperlipidemia in obesity is responsible in part for inducing peripheral tissue insulin resistance and dyslipidemic state characterized by increased plasma triglyceride and apolipoprotein B levels and decreased HDL – cholesterol contributing to the development of atherosclerosis. Considerable evidence implicates deranged adipocyte metabolism and altered fat topography in the pathogenesis of glucose intolerance in T2DM[36]. Fat cells are resistant to insulin's antilipolytic effect, leading to elevated plasma Free fatty acid levels. Chronically increased plasma free fatty acid stimulates gluconeogenesis, induces hepatic and muscle insulin resistance, and impairs insulin secretion in genetically predisposed individuals. These FFA-induced disturbances are referred to as lipotoxicity. Dysfunctional fat cells produce excessive amounts of insulin resistance-inducing inflammatory and atherosclerotic-provoking cytokines and fail to secrete normal amounts of insulin-sensitizing adipocytokines. Enlarged fat cells are insulin resistant and have diminished capacity to store fat. Most type 2 diabetics possess too much fat with an abnormal distribution of fat. Excessive fat deposition is seen in muscle, liver, and visceral adipocytes and have large insulin-resistant fat cells whose capacity to store triglycerides is compromised. Dysfunctional fat cells produce excessive amounts of adipokines that cause insulin resistance, inflammation, hypercoagulability, dyslipidemia, and possibly hypertension. When viewed in this context, it is clear that the glucose intolerance of T2DM results at least in part secondary to a disordered fat cell metabolism. Because the derangements in adipocyte metabolism are present in normal glucose-tolerant people as well as in insulin-resistant, genetically predisposed individuals , and in people with IGT it can be considered that disordered lipid metabolism represents the primary disturbance in the pathogenesis of Type2 diabetes mellitus [37].The influence of inflammatory markers on lipid metabolism is so complicated and present information is still not very clear. Further studies on these mechanisms are needed. However, documented data have demonstrated that the mechanisms through which the inflammation effects lipid metabolism at various levels in various tissues and organs and also alters the expression and secretion of various inflammatory markers. Further identification and verification of these pathways might provide novel potential strategies and drug targets for dyslipidemia therapy. A number of prospective studies have documented the inflammatory markers and diabetes association[38].

Role of inflammation in the development of insulin resistance and diabetes mellitus

Inflammation activates intracellular signaling pathways and inhibits insulin signaling. Chronic inflammation produces insulin resistance in diverse tissues as liver, skeletal muscle, fat and vascular smooth muscle cells by the activation of serine / threonine phosphorylation of elements of the insulin receptor signaling system, especially Insulin receptor substrate-1[39]. Insulin affects cells through binding to its receptor on the surface of insulin-responsive cells. The stimulated insulin receptor phosphorylates itself and several substrates, including members of the insulin receptor substrate (IRS) family, thus initiating downstream signaling events[39]. The inhibition of signaling downstream of the insulin receptor is a primary mechanism through which inflammatory signaling leads to insulin resistance. Exposure of cells to inflammatory markers or free fatty acids stimulates inhibitory phosphorylation of serine residues of IRS-1[40]. This phosphorylation reduces both tyrosine phosphorylation of IRS-1 in response to insulin and the ability of IRS-1 to associate with the insulin receptor and thereby inhibits downstream signaling and insulin action[41]. Several studies have shown that insulin acts as anti inflammatory hormone. Long term severe hyperglycemia is found to be associated with marked increase in inflammatory mediators and when

hyperglycemia is treated with insulin, it resulted in a rapid decrease in the concentration of inflammatory mediators[42]. Thus, insulin has a comprehensive anti-inflammatory effect. several studies also has shown that insulin suppresses several proinflammatory transcription factors and the corresponding genes regulated by them, which mediate inflammation. An impairment of the action of insulin because of insulin resistance would thus result in the activation of these proinflammatory transcription factors and an increase in the expression of the corresponding genes. Among the proinflammatory cytokines, TNF-α is well described to disturb insulin signaling .Circulating TNF-α and adipose tissue TNF-α gene expression is increased in insulin resistance[43,44]. The mechanisms involved in over expression of TNF-α associated with obesity and molecular signals underlying TNF-induced metabolic dys-regulation need to be investigated further.

CONCLUSION

In conclusion, the inflammatory state of obesity induces insulin resistance and hyper insulinemia, both of which are the common preceding factors of altered glucose tolerance, hyperlipidemia and atherosclerosis leading to increased levels of inflammatory markers linking all of these abnormalities to the development and biochemical manifestations of various metabolic disorders like Type 2 diabetes mellitus, Cardiovascular diseases etc. inflammatory markers may be utilized to predict the risk for Cardiovascular diseases and can motivate individuals for lifestyle interventions. The studies on the interactions between metabolic and inflammatory pathways will be useful in future therapeutic strategies and may yield novel approaches to prevent metabolic diseases like type2diabetes mellitus, Cardiovascular disease and others . The effective administration of anti-inflammatory agents in the treatment of obesity induced insulin resistance and atherosclerosis is only the beginning of a promising approach in the management of these metabolic disorders. However, it remains important to focus on ways to increase adherence to lifestyle interventions of exercise and diet to reduce metabolic disease risk due to obesity. National programmes targeting public awareness, education and practicing healthy lifestyle are the keys to alleviate the economic and health care burden of the obesity-related disorders to the nation.

Conflicts of interest: none

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