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A review on metabolic syndrome

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***Abstract*---**Metabolic syndrome is considered a major reason for the emergence of chronic dreadful diseases. Obesity and wrong food habit are key factors for metabolic syndrome. Globally people are affected by glucose intolerance, central obesity, hypertension, and dyslipidemia. Diabetes is a major part of metabolic syndrome. Targeted anti-inflammatory therapy has been suggested for both prevention and treatment of many of the above-said syndrome especially diabetes. Diet is an important regulatory factor in the immune response. There is considerable evidence to suggest that malnutrition leads to immune suppression due to a susceptibility to infection. On the other hand, over-nutrition leads to immune activation due to a susceptibility to an inflammatory condition. Inflammation may have an important role in the development and progression of diabetes and its complications; however, the impact of experimental anti-inflammatory treatments on diabetes deterioration over time and cardiovascular outcomes is still elusive. Thus proper diet with some drug therapy not only resolves the issue but can prevent the progression of the disease at extreme levels.

***Keywords*---**metabolic syndrome, obesity, inflammation, diabetes, diet.

Introduction

Metabolic syndrome is becoming more prevalent in both developed and developing countries. There are several forms of metabolic syndrome, depending upon the combination of different components of the syndrome, which include glucose intolerance, central obesity, hypertension and dyslipidemia (hypertriglyceridemia, elevated non-esterified fatty acids and low HDL cholesterol). Several well-established studies suggest that metabolic syndrome increases the risk of cardiovascular disease, type 2 diabetes, stroke and cancer (1).

To explain the origin of metabolic syndrome, several explanations have been proposed. In some cases, an insulin-resistant state leads to other symptoms, while in other instances, obesity is the primary initiator (2). Many times diet rich in proteins and supplements of probiotics are found useful in management of the metabolic syndrome (2). Recent research has implicated a chronic low-grade inflammatory condition as a major factor in the occurrence of metabolic syndrome and its subsequent pathophysiology (3). However, the inflammatory state that accompanies the metabolic syndrome does not completely fit into the classical definition of acute or chronic inflammation, as it is not accompanied by infection; there is no massive tissue injury and the dimension of the inflammatory activation is also not large. Thus, an inflammatory process of low severity is called "low-grade inflammation" or "meta-inflammation". Meta-inflammation, or "para-inflammation," refers to an intermediate state between basal and inflammatory states (4).

Obesity is a condition of increased adipose tissue mass. Obesity can also be defined as an increase in body weight beyond the limits of physical requirement, as the result of an excessive accumulation of fat. Accumulation of fat, or triacylglycerol, is essentially the only way that body weight can become excessive, as other energy storage (5). Adipose tissue is a tissue entity that can, through hyperplasia and hypertrophy, vary enormously between individuals, more so than any other tissue. Adipose tissue is not purely a storage tissue for triacylglycerols, it acts as an endocrine organ also 4,5 releasing numerous chemical messengers (adipokines) that communicate and affect other tissues (6).

The definition of obesity cannot be simply made in terms of bodyweight because we should expect short people to be lighter than tall people. Therefore we need to standardize body weight against body height. The simplest expression for this is the body mass index (BMI) calculated as weight (kg) divided by height squared (m2). The definitions were further refined by the WHO with a BMI over 25 being defined as 'overweight' and over 30 as being 'obese' (7).

Acquired Causes of Obesity

Fundamentally, obesity is the result of excessive energy intake compared to energy expenditure (8). Cushing’s syndrome may cause obesity. It is also associated with truncal or visceral obesity, which can be difficult to differentiate from simple obesity. Although slight decreases in energy expenditure in clinical or subclinical hypothyroidism may contribute to weight gain, hypothyroidism is a

rare cause of obesity and much of the weight gain is due to water retention which is reversible after thyroid hormone treatment (9).

Metabolic Syndrome Criteria

The metabolic syndrome (previously known as syndrome X) has insulin resistance as its hallmark as indicated in the WHO classification of metabolic syndrome (10). The third report of The National Cholesterol Education Program (NCEP) Expert Panel also developed criteria (11) that are similar but can lead to differences in classification of various populations (12)(13). WHO Criteria for Metabolic Syndrome: Insulin resistance (Hyperinsulinaemia and/or Fasting Glucose >=6.1) + 2 of the following factors:

Table 1. Correlation between obesity inflammation and diet

Parameters	Men	Women
Body Mass Index	>= 30 kg/m2	>= 30 kg/m2
Or Waist Hip Ratio	>0.9	>0.85
Triglycerides	>1.7 mmol/L	>1.7mmol/L
HDL Cholesterol	<0.9 mmol/L	<1.0 mmol/L
Microalbuminuria	>2.5mg/mmol creatinine	>2.5mg/mmol creatinine
Blood Pressure	>=140/90 mmHg	>=140/90 mmHg

Obesity is a state in which there is an over-accumulation of subcutaneous and/or abdominal adipose tissue. This adipose tissue is no longer considered inert and mainly devoted to storing energy; it is emerging as an active tissue in the regulation of physiological and pathological processes, including immunity and inflammation. Adipose tissue produces and releases a variety of adipokines (leptin, adiponectin, resistin, and visfatin), as well as pro-and anti-inflammatory cytokines (tumor necrosis factor-α, interleukin [IL]-4, IL-6, and others). Adipose tissue is also implicated in the development of chronic metabolic diseases such as type 2 diabetes mellitus or cardiovascular disease. Obesity is thus an underlying condition for inflammatory and metabolic diseases. Diet or dietary patterns play critical roles in obesity and other pathophysiological conditions. A healthy diet and some nutrients are generally considered beneficial; however, some dietary nutrients are still considered controversial.

Adipose tissue has also been recognized as a heterogeneous tissue composed of several cell types: mature adipocytes, pre-adipocyte, fibroblasts, endothelial cells, mast cells, granulocytes, lymphocytes, and macrophages. When adipocytes increase in number (hyperplasia) and size (hypertrophy), various cytokines are secreted and contribute to the inflammatory process (14). The representative adipokines and cytokines are as follows

Table 2. Functions of Key Adipokines Secreted by Adipose Tissue

Sr.No	Example	Function	Response to obesity
1	Leptin	Regulates food intake and energy expenditure	↑
2	Adiponectin	Regulates glucose and lipid metabolism, insulin sensitivity,	↓
3	Visfatin	food intake	↑
4	Resistin	Insulin-mimetic effects	↑
5	Adipsin	Regulation of inflammation	↑
6	Tumor necrosis factor (TNF-α)	Enhance fat storage	↑
7	Interleukin (IL)-1	Pro-inflammatory inflammation, antagonism of insulin signaling	↑
8	IL-4	Pro-inflammatory, early mediator of inflammation	↓
9	IL-6	Anti-inflammatory, inhibition of pro-inflammatory cytokines	↑
10	IL-10	Pro-inflammatory regulates energy homeostasis and inflammation	↓
11	Vascular endothelial growth factor (VEGF)	Anti-inflammatory cytokine, host responses to systemic	↑
12	Transforming growth factor (TGF-β)	inflammation	↑
13	Plasminogen activator inhibitor-1 (PAI-1)	Stimulates vasculogenesis, angiogenesis, and T-cell cytokine	↑
14	Serum amyloid A (SAA)	production	↑
15	C-reactive protein (CRP)	Regulate cell growth, cell proliferation, cell differentiation and	↑

↑: increase, ↓: decrease

Obesity is associated with alterations in immunity, a chronic low-grade inflammation in which there are elevated circulating pro-inflammatory cytokines,

However, it is unclear how obesity precisely triggers inflammation. Several hypotheses have been proposed. One hypothesis is that the overload of nutrients in adipocytes induces intracellular stress, resulting in the activation of inflammatory cascades (15)(4).

1. The excessive nutrients may cause the accumulation of misfolded and/or unfolded proteins in the endoplasmic reticulum (ER), which activates the unfolded protein response (UPR) pathway (4) The UPR pathway essentially depends on three main ER sensors; a PKR-like eukaryotic initiation factor 2α kinase (PERK), inositol-requiring enzyme 1 (IRE-1), and activating transcription factor 6 (ATF-6) (16). These activated sensors could increase the activity of the C-Jun amino-terminal kinase (JNK) and inhibitor of IκB (IKK-β), serine-phosphorylation of insulin- receptor substrate protein 1 (IRS-1), and the nuclear factor κB (NFκB) pathway, leading to the enhanced expression of pro-inflammatory cytokines (17).
2. The second hypothesis suggests that the overloading of adipocytes with fat overwhelmingly increases the infiltration of macrophages. These processes may cause the subsequent differentiation and activation of cytotoxic T cells, which initiate and propagate inflammatory cascades (18).
3. The Third hypothesis suggests that as adipose tissues enlarge, tissues become relatively hypoxic. Hypoxia within adipose tissue may activate inflammatory pathways(19) (20).
4. The last hypothesis is that overloaded adipocytes can themselves directly activate immune pathogen- sensors that cause chronic inflammation (21).

Dietary Factors That Affect Inflammation Related To Obesity

Diet is an important regulatory factor in the immune response. There is considerable evidence to suggest that malnutrition leads to immune suppression due to a susceptibility to infection. On the other hand, over-nutrition leads to immune activation due to a susceptibility to an inflammatory condition. Therefore, optimal nutrition is required for a healthy immune balance.

Carbohydrates

Carbohydrates are a main dietary energy source and can be evaluated according to the glycemic index (GI) and glycemic load (GL) values. GI is a ranking of foods based on their postprandial blood glucose responses and a measure of carbohydrate quality (22).

Dietary fat

The high-fat diet causes excessive body fat accumulation and impairs the immune system. Many different fatty acids, including polyunsaturated (PUFA), saturated, and trans-fatty acids have been studied for their effects on inflammatory status (23). PUFA: The omega-6 (n-6) PUFA and omega- 3 (n-3) PUFA families are precursors of eicosanoids, which play an important role in the immune response. Trans and saturated FA: Observational and interventional studies suggest that trans- or saturated FAs are significantly related to the immune response (24).

Vegetables and fruits

Variable fruit consumption was inversely correlated with blood levels of CRP (25)

Other Nutrients

Some vitamins and minerals have been shown to have a beneficial effect on oxidative stress and immune responses. Cross-sectional and interventional studies have consistently demonstrated that vitamins and minerals are associated with levels of inflammatory markers.

Adipose Tissue Inflammation Is Crucial in the Development of Obesity-Induced

Insulin Resistance

Obesity is a pro-inflammatory condition in which hypertrophied adipocytes and adipose tissue-resident immune cells (primarily lymphocytes and macrophages) both contribute to increased circulating levels of pro-inflammatory cytokines. The obesity-associated state of chronic low-grade systemic inflammation, termed "metabolic inflammation," is considered a focal point in the pathogenesis of insulin resistance and T2D in humans (15)(26)(27) Besides lipid-filled mature adipocytes, the tissue is also composed of various stromal cells, including preadipocytes, endothelial cells, fibroblasts, and immune cells. During the progression of obesity, both the adipocyte and the stroma vascular fractions are changed: adipocytes grow larger, secrete predominantly pro-inflammatory cytokines, and are insulin resistant; coincidently, the nature of WAT immune cells is also modified (28). The complex alterations in adipose tissue secretion of cytokines, adipokines, and chemokines and immune cell composition are observed in adipose tissue-related pathologies such as obesity.

Anti-inflammatory Agents in the Treatment of Diabetes and Its Vascular Complications

The association between hyperglycemia and inflammation and vascular complications in diabetes is now well established. Antidiabetes drugs may alleviate inflammation by reducing hyperglycemia; however, the anti-inflammatory effects of these medications are inconsistent and it is unknown whether their beneficial metabolic effects are mediated via modulation of chronic inflammation. Recent data suggest that immunomodulatory treatments may have beneficial effects on glycemia, b-cell function, and insulin resistance. However, the mechanisms underlying their beneficial metabolic effects are not always clear, and there are concerns regarding the specificity, safety, and efficacy of immune-based therapies. Herein, we review the anti-inflammatory and metabolic effects of current antidiabetes drugs and of anti-inflammatory therapies that were studied in patients with type 2 diabetes (29).

Metabolic Effects of Anti-inflammatory Drugs

Targeted anti-inflammatory therapy has been suggested for both prevention and treatment of diabetes [28].

Anti–TNF-a

TNF-a was the first pro-inflammatory cytokine implicated in the pathogenesis of insulin resistance and type 2 diabetes; this has been confirmed in preclinical studies in various animal models. However, to date, TNF-a antagonism has not demonstrated any clear benefit in type 2 diabetes in men (30).

Anti–IL-1b

Since the discovery of the central role of IL-1b in the pathogenesis of type 2 diabetes, numerous studies have investigated the role of IL-1b blockade on insulin resistance and type 2 diabetes. To date, eight independent clinical studies conducted with an IL-1 receptor antagonist (anakinra) or IL-1b–specific antibody (gevokizumab, canakinumab, and LY21891020) have demonstrated beneficial effects on metabolic parameters including decreased HbA1c and enhanced insulin sensitivity and b-cell secretory function, with concomitant improvement in inflammatory markers.

Salsalate

Salsalate, a prodrug of salicylate, with fewer adverse reactions than aspirin and sodium salicylate, has demonstrated beneficial effects on glycemia and insulin sensitivity, probably through inhibition of the NF-kB pathway (28). A drug currently used in the treatment of arthritis, diacerein decreases levels of IL-1b, although its mechanism of action is unknown. In drug-na¨ıve patients with type 2 diabetes, diacerein treatment improved insulin secretion and HbA1c levels, while reducing IL-1b and TNF-a levels.

Antimalarials

such as hydroxychloroquine (HCQ) is commonly used to treat autoimmune rheumatic diseases, including rheumatoid arthritis and lupus. The precise anti-inflammatory mechanism of HCQ is not known and is probably related to the alkalinization of endosomal organelles in immune cells. HCQ has been shown to reduce the incidence of diabetes among patients with rheumatoid arthritis and lupus and to improve glycemia in patients with rheumatic disorders and diabetes (31).

Conclusion

The association between hyperglycemia, inflammation and vascular complications in diabetes is now well established. Different antidiabetes drugs, such as TZDs, DPP-4 inhibitors, GLP-1 RAs, and insulin, have bonafide anti-inflammatory effects. Since metabolic dysregulation itself induces inflammation, effective anti-diabetes treatments may alleviate inflammation under improving the metabolic

state. It is therefore difficult to differentiate the effects of the drugs on metabolism from their direct effects on the immune system. However, the anti-inflammatory effects of different medications are partial and inconsistent, probably due to incomplete normalization of metabolic dysregulation or because diabetes-associated inflammation is multifactorial; the mechanisms involved include, but are not limited to, hyperglycemia. However, it should be emphasized that the impact of such treatments on glycemia over long periods and more importantly on cardiovascular complications is still unknown. Preclinical studies in animal models are most helpful in this regard; however, it may be difficult to extrapolate from findings in animal models to the clinical setting. Finally, there are important questions as to the safety and cost of these treatments. Inflammation may have an important role in the development and progression of diabetes and its complications; however, the impact of experimental anti-inflammatory treatments on diabetes deterioration over time and cardiovascular outcomes is still elusive. It remains to be shown whether anti-inflammatory treatments administered alone or together with current anti-diabetes drugs can prevent the vascular complications of diabetes. Further studies are required to clarify the role of anti-inflammatory therapy in the management of type 2 diabetes. A better understanding of the inflammatory basis for diabetes may provide for improved modalities for diabetes prevention and treatment, using novel targeted approaches in conjunction with current pharmacologic and lifestyle interventions.

Conflict of Interest

All authors declare that no conflict of interest.

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