SAS Journal of Medicine ISSN 2454-5112
SAS J. Med., Volume-1; Issue-2 (Jul-Aug, 2015); p-45-53
Available online at http://sassociety.com/sasjm/

Review Article

Correlation of inflammatory and metabolic biomarkers with cardiovascular risk in obesity: A review

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Abstract: Obesity is a substantial public-health crisis in the developed world and the prevalence is increasing rapidly in numerous developing nations worldwide. This growing rate represents a pandemic that needs urgent attention if its potential morbidity, mortality, and economic tolls are to be avoided. Adipose tissue is an active endocrine and paracrine organ that releases a large number of cytokines and bioactive mediators, such as leptin, adiponectin, interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), that influence not only body weight homeostasis but also insulin resistance, diabetes, lipid levels, tension, coagulation, fibrinolysis, inflammation and atherosclerosis.
Keywords: Obesity, interleukin-6 (IL-6) , tumour necrosis factor-α (TNF-α), lipid levels, inflammation

INTRODUCTION

Cardiovascular diseases are known to be one of the leading causes of morbidity and mortality among obese individuals, and the pathogenesis of cardiovascular complications in obese patients is far more complex than in the general population. Obesity has been associated with a number of atherogenic conditions such as hypertension, insulin resistance, glucose intolerance, hyper triglyceridemia, low serum high density lipoprotein (HDL) and elevated small dense low density lipoprotein (LDL).

In addition to adverse metabolic consequences of visceral fat, it also has a distinct role as an endocrine organ. Adipocytes are active endocrine organs secreting leptin, interleukin-6 (IL-6), tumour necrosis factor alpha (TNF-α) and angiotensinogen. Increased synthesis of cytokines such as IL-6 and TNF-α may contribute to insulin resistance, dyslipidemia and cardiovascular abnormalities.

Adipose tissue is an active endocrine and paracrine organ that releases a large number of cytokines and bioactive mediators, such as leptin, adiponectin, IL-6 and TNF-α, that influence not only body weight homeostasis but also insulin resistance, diabetes, lipid levels, tension, coagulation, fibrinolysis, inflammation and atherosclerosis [1].

Inflammation characterizes all phases of atherosclerosis. Formation of fatty streak, the earliest phase of atherogenesis, involves recruitment of leukocytes due to expression of leukocyte adhesion molecules on endothelial cells in turn triggered by primary cytokines. Finally, the thrombotic complications of plaques often involve physical disruption, usually, associated with signs of inflammation. Thus the inflammatory response participates in every stage of atherothrombosis.

The role of inflammation in atherogenesis has recently attained increased recognition and attention has focused on several key mediators and novel markers of the inflammatory process, including acute phase reactants like C-reactive protein (CRP) and TNF-α.

Obesity predisposes to atherosclerosis which is the underlying cause of major cardiovascular events. The process of obesity itself is an inflammatory state, therefore, various inflammatory markers can predict future cardiovascular events. These markers will help identify high risk patients, monitor disease activity and provide therapeutic guide to reduce inflammatory components of the disease.

CRP is a reliable and sensitive marker of inflammation. Elevation of baseline levels of CRP among apparently healthy individuals is associated with a higher long term risk for future cardiovascular events. CRP is one of the strongest markers of metabolic risk and, in addition, may participate directly in the arterial cell wall mechanisms leading to atherosclerotic lesions and cardiac events [2].

Considerable evidence suggests that overproduction or inappropriate production of TNF-α

may play a role in various inflammatory conditions. Produced largely by macrophages in response to inflammatory stimuli, TNF-α binds to its receptors present on virtually all cells throughout the body, and circulating TNF-α concentration rises with increasing degree of obesity and correlates with the level of hyperinsulinemia [3,4].

Predictive values of CRP and TNF-α are significantly higher than other traditional biochemical cardiovascular risk markers like total cholesterol, HDL and LDL. Thus risk prediction will be better when lipid values will be incorporated with CRP and TNF-α.

Until now these relationships between metabolic and inflammatory markers and cardiovascular risks have been found to be weak and the correlation between different metabolic abnormalities clustering with obesity and acute phase reactants like CRP and pro-inflammatory markers like TNF-α has not been studied in our population set up. This review article aims to provide an extensive insight into this dilemma.

OBESITY AND CARDIOVASCULAR RISK

Obesity is a fast growing problem that is reaching epidemic proportions worldwide [5] and is associated with an increased risk of premature death [6]. Obese individuals experience elevated cardiovascular morbidity and mortality, including stroke, congestive heart failure, myocardial infarction and cardiovascular death, and this is independent of the association between obesity and other cardiovascular risk factors [7,8]. Weight gain during adult life or even during childhood and adolescence [9] seems to have a great effect on diabetes and cardiovascular risk, even within the normal body mass index (BMI) range.

In addition to total body fatness, the accumulation of abdominal fat independently increases cardiovascular risk. The waist-to-hip ratio reflects abdominal fat in predicting type 2 diabetes, stroke, myocardial infarction and cardiovascular mortality in middle-aged individuals. The Nurses' Health Study confirmed these findings using the waist circumference [10]. Moreover, visceral fat correlates with cardiovascular risk factors [11]. There is an independent curvilinear association between visceral adiposity and mortality [12] suggesting that a large amount of visceral fat is required for an increased risk of mortality.

Epidemiological studies have reported a progressive increase in the incidence of chronic diseases such as hypertension, diabetes, and coronary heart disease with increasing body mass index [13].

DYSLIPIDEMIA IN OBESITY

Dyslipidemia in obesity is characterized by increased levels of very low-density lipoprotein (VLDL) cholesterol, triacylglycerols and total cholesterol, an increase in small dense LDL particles, and lower HDL cholesterol levels [14]. As to the effect of lipoproteins among conventional risk factors, there is little evidence that LDL cholesterol — known to be a major risk factor for CHD — is enhanced in obesity, among patients with visceral obesity in particular. Other lipoproteins, such as the apolipoprotein (Apo) B/A1 ratio [15] small dense LDL particles and low HDL cholesterol, are predictive for cardiovascular disease endpoints in people with visceral adiposity.

The serum levels of HDL cholesterol have been consistently shown to be inversely related to coronary artery disease (CAD) risk. In the Framingham Heart Study, patients initially free of clinically apparent cardiovascular disease and who had the highest HDL cholesterol values at study enrollment had the lowest risk of developing CAD during the next 35 years [16]. This inverse relationship between HDL cholesterol and CAD risk was noted at all levels of total cholesterol, including levels below the current desirable level of 200mg/dl [17]. Low serum levels of HDL cholesterol were associated with increased risk of myocardial infarction, restenosis after angioplasty, sudden death and stroke [18].

Obesity and the metabolic syndrome are often associated with an atherogenic dyslipidemia characterised by a lipid triad of low HDL cholesterol, high TG levels, and a preponderance of small, dense LDL cholesterol particles, secondary to metabolic changes induced by insulin resistance. Among patients with diabetes, in the United Kingdom Prospective Diabetes Study (UKPDS), CAD risk factors, in order of strength, included high LDL, low HDL, hyperglycemia, systolic hypertension and smoking [19].

It is not clear whether hypercholesterolemia further increases the risk of cardiovascular disease in obese individuals. But the insulin-resistant state of abdominal obesity adds substantially to the CHD risk of patients with familial hypercholesterolaemia [20]. Obesity also limits the beneficial effects of lipid-lowering strategies. However, aggressive reduction of lipids with the use of statins can have a beneficial effect on coronary plaque development in obese individuals [21].

Both increased adiposity and reduced physical activity are strong and independent predictors of CHD [22] and death[23]. In general, for each unit of BMI increment, the risk of CHD increases by 8% [22].

Besides an altered metabolic profile, a variety of adaptations/alterationsin cardiac structure and function occur in the individual as adipose tissue accumulates in excess amounts,[24] even in the absence of co-morbidities. Hence, obesity may affect the heart through its influence on known risk factors such as dyslipidemia, hypertension, glucose intolerance,

inflammatory markers, obstructive sleep apnea/hypoventilation, and the prothrombotic state, as well as through yet-unrecognized mechanisms. As a whole, overweight/obesity predisposes or is associated with numerous cardiac complications such as CHD, heart failure, and sudden death through its impact on the cardiovascular system.

Obesity produces an increment in total blood volume and cardiac output that is caused in part by the increased metabolic demand induced by excess body weight [25]. The increased cardiac output is attributable mostly to increased stroke volume because heart rate increases little if at all [26]. Also, in obesity, the Frank-Starling curve is shifted to the left because of incremental increases in left ventricular filling pressure and volume, which over time may produce chamber dilation. Ventricular chamber dilation may then lead to increased wall stress, which predisposes to an increase in myocardial mass and ultimately to left ventricular hypertrophy, characteristically of the eccentric type [27]. Left atrial enlargement may also occur in normotensive obese individuals but typically in the setting of increased left ventricular mass. Left atrial enlargement may not be mediated solely through left ventricular diastolic dysfunction impairment but may simply reflect a physiological adaptation to the expanded blood volume [28]. As a consequence, left atrial dilation may mediate the excess risk of atrial fibrillation associated with obesity [29]. However, left ventricular hypertrophy (LVH) in long-standing obesity and/or the effects of concomitant hypertension may also be contributing factors to left atrial enlargement.

Effects on Ventricular Function

Eccentric LVH, which is commonly present in morbidly obese patients (BMI >40 kg/m^2), is often associated with left ventricular diastolicdys function. Moreover, as with left ventricular mass, longer durations of obesity are associated with poorer left ventricular systolic function and greater impairment of left ventriculardiastolic function [30].

Hypertension

The majority of patients with high blood pressure are overweight. Hypertension is about 6 times more frequent in obese subjects than in lean men and women [31]. Not only is hypertension more frequent in obese subjects than in normal-weight control subjects, but also weight gain in young people is a potent risk factor for subsequent development of hypertension. A 10-kg higher bodyweight is associated with a 3.0-mm Hg higher systolic and a2.3-mm Hg higher diastolic blood pressure. This increase in blood pressure is greatest when the obesity is of abdominal distribution [32]. These factors include (1) direct effects of obesity on hemodynamics and (2) mechanisms linking obesity and an increase in peripheral vascular resistance: endothelial dysfunction, insulin resistance, sympathetic nervous system,substances released from adipocytes (IL-6, TNF-α, and so forth),and sleep apnea.

Obesity is characterized by chronic mild inflammation. The basis for this view is that the circulating level of several cytokines and acute phase proteins associated with inflammation is increased in the obese. A recent concept is that both obesity and diabetes are characterised by a state of chronic low-grade inflammation; and markers of inflammation such as pro-inflammatory cytokines and acute phase proteins are increased in the circulation. It is now thought that the inflammatory state may be causal in the development of insulin resistance and other disorders associated with obesity e.g. the metabolic syndrome and hyperlipidemia [33]. Recent research has focused on the origin of the inflammatory markers in obesity and the extent to which adipose tissue has a direct effect. Trayhurn and Wood [34] concluded that in certain circumstances, it seems probable that adipocytes contribute substantially to the raised circulating levels of particular pro-inflammatory cytokines and acute phase proteins in obesity, such as IL-6, plasminogen activator inhibitor (PAI-1) and haptoglobin.

It has been proposed by Trayhurn and Wood [34] that the secretion of inflammatory cytokines is the result of events within the adipose tissue itself. A possible suggestion from these researches is that as the fat mass increases in size, the system of blood vessels feeding the adipose tissue is insufficient to maintain a normal oxygen supply and localized hypoxia (or shortage of oxygen) occurs, triggering an inflammatory response, which in turn serves to trigger angiogenesis (development of the vasculature). Leptin and PAI-1, for example, are recognised angiogenesis signals.

ADIPOKINES

It is now recognised that white adipose tissue is highly dynamic, involved in a diverse range of physiological and metabolic processes [34]. In addition to deposition and release of fatty acids, fat cells secrete a number of hormones, such as leptin and adiponectin, along with many other signaling molecules known as adipokines.

LEPTIN

The key development that established white adipose tissue as an endocrine organ was the discovery of leptin in 1994, with its wide range of biological functions [34]). Leptin signals the status of energy stores and its secretion can reduce appetite and increase energy expenditure.

Leptin is a 16-kD protein produced predominantly in white adipose tissue and, to a lesser extent, in the placenta, skeletal muscle, and stomach. The major role of leptin in body-weight regulation is to signal satiety to the hypothalamus and thus, reduce dietary intake and fat storage while modulating energy

expenditure and carbohydrate metabolism to prevent further weight gain.Althoughidentified as a classic peptide hormone, the four α-helix domainsin the folded structure make leptin most similar to cytokinessuch as IL-2. Although the role of leptin in controlling energy homeostasisis increasingly well defined, it remains unclear whetherleptin plays a role in the inflammatory syndrome caused by abdominalobesity. Clearly, serum leptin concentrations rise in proportionto body adiposity [35]; therefore, obese individuals with themetabolic syndrome generally have higher circulating leptinconcentrations. However, obese individuals seem to be resistantto the hypothalamic effects of leptin; therefore, the catabolicpathways designed to reduce appetite and increase energy expenditureare not activated and excess body weight is maintained.

INTERLEUKIN – 6

Within adiposetissue, both adipocytes and macrophages secrete IL-6 [36], andstudies measuring arteriovenous increases of serum IL-6 concentrationhave clearly shown net secretion of IL-6 from adipose tissuedepots, suggesting that fat accounts for roughly 30% of circulatingIL-6 concentrations in humans [37]. Like leptin, productionof IL-6 by adipose tissue increases with increasing adiposity,and circulating IL-6 concentrations are highly correlated withpercentage of body fat [38] and with insulin resistance [39]. C-reactive protein (CRP) is oneof the strongest markers of metabolic risk and, in addition,may participate directly in the arterial cell wall mechanismsleading to atherosclerotic lesions and cardiac events [40].Because CRP production by the liver is governed by circulatingIL-6 and because, in industrialized countries, the single mostimportant determinant of serum IL-6 concentration is whole-bodyadiposity, it is likely, therefore, that this adipose tissuecytokine contributes significantly to the chronic systemic inflammatorydisorder associated with the metabolic syndrome. Although increasedCRP is the most recognized marker of IL-6 action, numerous otherIL-6-dependent factors may contribute to cardiovascular risk.Increases of fibrinogen, another acute-phase reactant, are mediatedby IL-6, as are increases in both platelet number and plateletactivity, all of which would contribute to the risk of clotformation [41].

TUMOUR NECROSIS FACTOR –ALPHA

TNF-α, previously known as lymphotoxin and cachetin, is believed to be involved in the wasting that occurs during acute and chronic illness and malignancy. In the basal state TNF-α is directly proportional to fat mass and has been shown to be involved in the development of insulin resistance [42]. In-vitro studies have demonstrated that TNF-α decreases the insulin receptor tyrosine phosphorylation, and down regulates several steps in the insulin signaling pathway [43]. Thus, TNF-αis not only aclassical cytokine but may be causal in the insulin resistance of the metabolic syndrome.

Within adipose tissue, macrophages account for nearly all TNF-α production and both TNF-α mRNA content and TNF-α production increase in adipose tissue of obese individuals [3].

In humans, elevated TNF-alpha expression in adipose and muscle tissue is positively correlated with the degree of obesity and the level of hyperinsulinemia, and negatively related to the adipose tissue lipoprotein lipase activity [3]. Several recent studies also show that circulating TNF-α levels [44] positively correlate with serum leptin concentrations, an adipocyte-derived protein of energy homeostasis. In addition to its direct actions on insulin-sensitive tissues, TNF-alpha regulates leptin secretion and free fatty acid (FFA) release from adipocytes [45].

Visceral fat in particular contributes to endothelial dysfunction through the direct effect of adipokines, mainly adiponectin and TNF-α, which are secreted by fat tissue after macrophage recruitment (through monocyte chemoattractant protein-1, MCP-1). Indirect effects of TNF-α and IL-6 might influence inflammation (CRP) and endothelial dysfunction. Insulin resistance induced by cytokines (IL-6, TNF-αand adiponectin), may induce oxidative stress and subsequent endothelial dysfunction (PAI-1 and ICAM-1). Fat accumulation, insulin resistance, liver-induced inflammation and dyslipidaemic features may all lead to the premature atherosclerotic process.

C – REACTIVE PROTEIN

CRP is a substance which appears in the blood in the course of a variety of disease processes. There is a widespread agreement that CRP is a very sensitive marker for acute phase response. However, the causes of tissue damage are many. Hence CRP estimation is not pathognomic and cannot be used as a diagnostic marker. So its application is limited. Nevertheless, CRP measurement in patients sera can provide useful information to the clinician.

CORRELATION BETWEEN INFLAMMATORY AND METABOLIC MARKERS AND CARDIOVASCULAR RISK

There is growing recognition that coronary heart disease (CHD) has an inflammatory component [46]. Prospective studies have shown that plasma CRP concentration, a marker of the acute-phase reaction, can predict CHD events in subjects with [47,48] or without [49] established cardiovascular disease beyond what can be estimated by traditional risk factors.

However, its exact role in the etiology of CHD remains obscure. CRP may be a marker of the inflammatory component of the atherosclerotic disease process. It may also be a marker of an as-yet-undefined

inflammatory process (eg, chronic infection),which may be favoring the development of atherosclerosis. Finally, CRP might be pathogenic in CHD. For example, it has the ability to induce monocytes to express tissue factors that may favor the occurrence of vascular atherosclerosis [50].Largely driven by the pioneering work of Ridker and colleagues [51]; results of epidemiological studies, of primary and secondary prevention studies as well as of trials conducted in patients with acute coronary syndromes, have revealed that the plasma concentration of a relatively simple marker of inflammation, CRP, could predict the risk of a first or a recurrent coronary event, beyond the contribution of classical risk factors [52].

Compared with other novel and traditional markers of CHD, CRP was shown to be the strongest predictor of future coronary events, and when combined with total cholesterol, HDL-cholesterol, and LDL-cholesterol, its ability to predict risk was improved further [51,52]. It is important to note that high-sensitivity (hs) methods are needed for the measurement of CRP for the purpose of assessing risk of cardiovascular disease in apparently healthy individuals. In addition, CRP was found to add to the ability to predict risk at any LDL-cholesterol concentration or Framingham Risk Score, indicating that this marker identifies a group of individuals at increased risk who are currently missed under traditional measures. CRP has been shown to have prognostic utility in patients with acute coronary syndromes [53] even in the absence of myocardial necrosis, suggesting that CRP may reflect plaquevulner ability and its likelihood to rupture [54]; on the basis of these findings, the Centre for Disease Control (CDC) and the American Heart Association (AHA) issued guidelines for the utility of this marker in the primary prevention setting and in patients with stable coronary disease or acute coronary syndromes [55]. The guidelines also included specific recommendations that pertain to the laboratory aspect of CRP and defined cut-points for clinical interpretation; CRP concentrations <1 mg/L are considered low, 1–3 mg/L average, and >3 mg/L high relative risk.

TREATMENTS CAN MODIFY METABOLIC AND INFLAMMATORY MARKERS

CRP represents a modifiable risk marker. In a randomized trial of low dose aspirin, the relative efficacy of this agent in decreasing coronary risk was greatest among those with evidence of low grade inflammation as determined with CRP level, but was sequentially smaller as levels of CRP declined, data that suggest potentially important anti-inflammatory effects for aspirin.

Similarly, in cholesterol and recurrent events [56], the attributable risk reduction associated with pravastatin was greater among individuals with a persistent inflammatory response as determined by CRP such that statin therapy attenuated almost completely the elevated risk associated with inflammation. Moreover, therapy with pravastatin in CARE trial reduced levels of CRP over a 5 year period this finding corroborates in humans experimental studies that suggest that lipid lowering attenuates inflammation and the use of statins reduces macrophage content and activity within atheromatous plaque.

This study suggests a role for statin therapy above and beyond the traditional concept that attributes all of the benefits of such interventions solely to modification of LDL-C.

The [56] was a landmark study that demonstrated significant improvement in fatal and non-fatal myocardial infarction in secondary prevention despite normal baseline cholesterol levels. Subgroup analysis of CARE trial demonstrated reduction in stroke and improvement in diabetes, elderly patients and women.

In this retrospective analysis of CARE study [57], randomized post MI patients to receive pravastatin or placebo. CRP levels in blood samples taken 8 to 9 months after discharge were predictive of future events in this case-control study upto 5 years. The relative risk was 1.77 for patients in the top quintile versus those in the lowest one (CRP levels equal to 6.6 and 1.2 mg/L respectively). More importantly, the risk was attenuated and no longer significant in patients randomized to pravastatin.

In a subsequent study [58]; a significant reduction in CRP levels was demonstrated in patients randomized to pravastatin suggesting that this drug and probably all statins, might have an “anti-inflammatory effect” which does not seem to be associated with the extent of cholesterol reduction.

In another study by Nicholas P Jenkins, Nicholas H Brooks 2002 [59], patients prescribed beta-blockers had significantly lower C-reactive protein concentrations than did patients in whom these were not prescribed (by 1.2 mg/L or 40% difference in geometric mean concentration (<0.001). This association remained significant (P=0.03) after excluding patients with contraindications to the use of beta-blocker therapy and other clinical predictors of C-reactive protein concentration, including body mass index, high density lipoprotein cholesterol level, family history of coronary artery disease, and angiographic severity. Use of diltiazem and of nicorandil was associated with high plasma CRP.

Fragmin during instability in coronary artery disease [60], a study in which correlation between short term risk of death and blood levels of CRP and troponin-T was done. The rates of death from cardiac causes were 5.7% among the 314 patients with blood

CRP levels of less than 2 mg/L, 7.8% among the 294 with levels of 2-10 mg/L and 16.5% among the 304 with levels of more than 10 mg/L (P=0.29 and P=0.001 respectively).

Kaplan-Meier analysis [64] showed that patients with highest levels of CRP at enrolment (> 10 mg/L) had a significantly higher probability of death from cardiac causes during the entire follow-up period than did patients with levels of 2-10 mg/L of those with levels of less than 2mg/L.

Biasucci et al. [61] have shown that CRP remains elevated for at least three months after the index event in a large proportion of patients with unstable angina. Therefore, the prognostic value of elevated inflammatory markers in many patients with unstable coronary artery disease may be related mainly to low grade inflammation.

In Multiple Risk Factor Interaction Trial [62] significant association between available distribution of CRP and subsequent CHD mortality was seen. For smokers, at baseline, the risk of CHD deaths in quartile 4 of CRP as compared with quartile 1 was 4.3 (95% impedance interval 1.74 – 10.8). The association persisted where adjusted for characteristics related to smoking and smoking cessation during the trial and to pulmonary function. This was the first perspective study in 'healthy but high risk individuals" to document the relation between CRP and CHD mortality.

The European Concerned Action on Thrombosis of Disability [63], angina pectoris study group reported that at baseline, CRP in 2,640 patients was positively correlated with fibrinogen, factor VII C, Von-Willibrand factor, tissue plasminogen and WBC count suggestive of a low grade inflammatory process in patients with existing atherosclerosis [47].

Currently, we do not know whether the acute phase reaction is just a passive reflection of the inflammatory character of atherogenesis, or whether the inflammatory state alters the risk factor profile in a pro-atherogenic direction.

At the current state of our knowledge we cannot definitely tell which factor is driving and which is driven. We do not know, however, whether the cytokine-driven acute phase reaction in its turn drives atherogenesis (and thus is causally involved in coronary atherosclerosis and cardiovascular risks) or whether it is just a marker. In this relatively new field, time and more research are required to find out which interpretation is the correct one.

CONCLUSION

Our study showed that predictive values of CRP and TNF-α are significantly higher than other traditional biochemical cardiovascular risk markers like total cholesterol, HDL and LDL and these inflammatory markers can predict future cardiovascular events in obese subjects. Thus, these markers can be used to identify high risk patients, monitor disease activity and provide therapeutic guide to reduce inflammatory components of the disease. Therefore, risk prediction would be better when lipid values will be incorporated with CRP and TNF-α.

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