Role of C - reactive protein (CRP) as a Marker of an Acute Phase Response in Case Of Diabetes Mellitus: A Mini Review

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Abstract:

Diabetes Mellitus is one of the most common major public health problems having worldwide distribution. Depending on the etiology of diabetes mellitus, factors contributing to hyperglycemia may include; reduced insulin secretion, decreased glucose usage and increased glucose production. Recently, there in increasing evidence that an ongoing cytokine induced acute phase response which is sometimes called low grade inflammation, but part of a widespread activation of the innate immune system, is closely involved in the pathogenesis of type 2 diabetes mellitus and associated complications such as dyslipidemia and atherosclerosis. Elevated circulatory inflammatory markers such as C-reactive protein and interleukin-6 predict the development of type 2 Diabetes mellitus and several drugs with anti-inflammatory properties both lower both acute phase reactants and glycemia and possible decrease the risk of developing type 2 diabetes mellitus. In this mini review article, we aimed to systematically review the role of C-reactive protein (CRP) as inflammatory marker with increased risk of type 2 diabetes as well the relation with type 1 diabetes

Key Words: CRP, Inflammation, Diabetes Mellitus, Acute phase response.

Abbreviation: CRP:C-reactive protein; IL-1: Interleukin 1; IL-6: Interleukine-6; LEM: Leucoyctic Endogenous Mediator; IRS 1: Insulin Receptor Substrate-1; IRS 2: Insulin Receptor Substrate-2; SOCS: Suppressor of Cytokine Signaling; PRAR-γ: Peroxisome proliferator activated receptor gamma; TNF-α: Tumor necrosis factor alpha; IGT: Impaired glucose tolerance; BMI: Body mass Index

1. Introduction:

C-reactive protein (CRP) is a biochemical substance which produced from hepatocyte and level used to increases in serum due to inflammatory challenge in the body. An elevated C-reactive protein level is
identified with blood tests and is considered a non-specific “marker” for any type of inflammatory disease condition. CRP production is part of the nonspecific acute-phase response to most forms of inflammation, infection, and tissue damage and was therefore considered not to provide clinically useful information [1].

C-reactive protein (CRP) which used to consider as a marker of systemic inflammation, is emerging as an independent risk factor for cardiovascular disease [2][3]. It has also been determined that serum CRP levels are used to elevate in patients with impaired glucose tolerance (IGT) [4] or diabetes [5]. A few prospective studies have declared that increased CRP levels are an independent risk factor for diabetes mellitus in future prospective [6][7]. Although all these studies and findings indicate that CRP levels in peripheral blood are very much associated with glucose levels, it remains unclear whether a relationship exists between CRP levels and plasma glucose levels in the pre-diabetic range. The purpose of the present review study was to determine any positive association between CRP concentrations and plasma glucose levels in diabetic patient and what is the role of.

2. Acute phase response and circulating CRP:

During acute inflammatory states or secondary to certain type of tissue damage, the levels of certain proteins in plasma increased. These proteins are called acute phase protein or acute phase reactants and include C-reactive protein, (CRP), α-1 antitrypsin, ceruloplasmin, α-1 acid glycoprotein, haptoglobin and fibrinogen. The elevation of the levels of these proteins varies from as little as 50% to as much as 1000-fold as in case of CRP. In acute inflammatory state such as surgery, myocardial infarction, infection and tumor; concentration of these protein rises significantly [8]. These proteins are believed to play a role in body’s response to inflammation. For example, C-reactive protein can stimulate the classical complement pathway; α-1 antitrypsin can neutralize certain proteases released during acute inflammatory state. Interleukin-1 (IL-1), a polypeptide released from mononuclear phagocytic cells, is the principle but not the sole stimulator of the synthesis of the majority of acute phase reactants by hepatocytes. Additional molecules such as interleukin-6 (IL-6) are involved and as well as IL-1 appear to work at the level of gene transcription [9]. Acute phase reaction is a general reaction to inflammation, comparable to the increase in temperature or leukocyte count and is not specific for any given disease. A small protein known as LEM which is released from the site of injury probably triggers all these changes. Plasma levels of the individual acute phase proteins rise at different rates. First; the levels of C-reactive protein and α-1 antichymotrypsin rise, then within the first 12 hrs., α-1 acid glycoprotein followed by α-1 antitrypsin, haptoglobin, C4 and fibrinogen levels rise and finally there is a rise of C3 and ceruloplasmin levels. All levels reach their maximum within 2-5 days [8]. These changes which are caused by increased synthesis in the liver do not aid in the diagnosis of the cause of inflammation, but measurement of these proteins with the largest and earliest rises (e.g. CRP) can be used in monitoring the progress of inflammation or its response to treatment. Increase in synthesis of ARP is accompanied by the decrease in the synthesis of prealbumin, albumin and transferrin (so called negative acute phase reactants), so that only a slight rise in total plasma protein occurs. Therefore, the inflammation process causes nonspecific changes in level of individual proteins which may mask changes attributable to a specific disease [9]. The median concentration of CRP is 0.8 mg/l, the 90th centile is 3.0 mg/l, and the 99th centile is 10 mg/l in case of young healthy adult [10], but, following an acute-phase stimulus, values may increase as well as10, 000-folds of normal level. Plasma CRP is produced only by hepatocyte mainly influenced under transcriptional control by the cytokine IL-6, although other sites of local CRP synthesis and possibly secretion have been suggested. De novo hepatic synthesis starts very rapidly after a single stimulus, serum concentrations rising above 5 mg/l by about 6 hours and peaking around 48 hours. The plasma half-life of CRP is about 19 hours sand is constant under all conditions of health and disease,
so that the sole determinant of circulating CRP concentration is the synthesis rate, which thus directly reflects the intensity of the pathological process(es) stimulating CRP production [11]

3. Inflammation and activated innate immunity related to diabetes mellitus

There is increasing evidence that an ongoing cytokine induced acute phase response which is sometimes called low grade inflammation, but part of a widespread activation of the innate immune system, is closely involved in the pathogenesis of type 2 diabetes mellitus and associated complications such as dyslipidemia and atherosclerosis. Elevated circulating inflammatory markers such as C-reactive protein and interleukin-6 (IL-6) predict the development of type 2 diabetes and several drugs with anti-inflammatory properties such as aspirin and thiazolidinediones lower both acute phase reactants and glycemia and possibly decreased the development of type 2 diabetes. Among the risk factors for type 2 diabetes, which is also known to be associated with active innate immunity, are age, inactivity, certain dietary components, smoking, psychological stress and low birth weight. Other features of type 2 diabetes such as fatigue, sleep disturbance and depression are likely to be at least partly due to hypercytokinemia and activated innate immunity [12]. The exact effect of inflammatory cytokines on glucose metabolism in humans is still unclear. The followings are the possibly mechanisms of activated innate immunity in type 2 diabetes mellitus.

3.1. Insulin resistance

Innate immunity may give rise to the features of type 2 diabetes, including cytokine induced insulin resistance and impaired insulin secretion, increased capillary permeability and microalbuminuria, dyslipidemia, hypercortisolema, hypertension, central obesity and a hypercoagulation state. Cytokines such as TNFα can cause insulin resistance by activation of the prototype stress induced kinase, in which serine phosphorylates many signaling proteins including IRS-1 and IRS-2. This leads to inhibition of insulin signaling and stimulation of expression of SOCS proteins, which binds IRS-1 and IRS-2 and mediates their degradation [13]. Inflammatory cytokines such as TNF-α, IL-1β and IL-6 also down regulate PRAR-γ expression [14]. Interestingly, insulin is itself an inhibitor of acute phase protein synthesis [15] and in a model of diabetes, the acute phase response is increased by insulin deficiency [16]. This indicates that there could be a positive feedback in type 2 diabetes whereby cytokine induced insulin resistance further augments the acute phase response. The relative normal levels of acute phase reactants in type 1 diabetes [17] suggests that insulin replacement and much lesser degree of hepatic insulin resistance in this type of diabetes is enough to restrain acute phase protein production.

3.2. Fetal and neonatal programming

In the short term, innate immunity has survival value and restores homeostasis after an environmental stress, but in type 2 diabetes and IGT, it may be that prolonged lifestyle or environmental stimulants cause maladaptation to the normal psychological response to stress, causing disease instead of repair. A genetic or inborn propensity to a hyper responsive innate immune system might exist in certain individuals. This notion is supported by recent evidence that disproportionate size at birth is associated elevated levels of acute phase reactants such as cortisol and fibrinogen in adult life [18].

3.2. Genetic and race

Insulin sensitivity or resistance are associated with specific polymorphisms in the TNF-α gene promoter [19], TNF-α receptor gene [20] and IL-6 gene [21] Nondiabetic subjects with family history of type 2 diabetes have higher circulating CRP levels than age and BMI matched control subjects without a family history [22].

3.3. Nutrition

Activation of innate immunity in the genetically and metabolically programmed individual, including the effects of fat and the n3: n6 fatty acid ratio on
cytokine production may contributed by many dietary factors. Adipose tissue IL-6 production is increased by some five folds after milk intake when measured by subcutaneous micro perfusion, this offering a mechanism by which repeated dietary excess might favor hypercytokinemia. Vlassara et al.[23] shown that administration of high advanced glycation end products (AGEs) diet to type 1 and type2 diabetic subjects caused plasma CRP and mononuclear cell TNF-α to increase whereas a low AGEs diet caused CRP and TNF-α to decreased[24][25].

3.4. Age
Cytokines production from monocytes and macrophage [26] and circulating acute phase protein, IL-6 and TNF-α [27] increase with age, as of course does the propensity to develop type 2 diabetes. Indeed, it has been argued that a major characteristic of aging is a global reduction in the capacity to cope with a variety of stressors and a concomitant increase in proinflammatory status [28].

3.5. Smoking and inactivity
The risk factors for type 2 diabetes mellitus or smoking and lack of physical exercise are both associated with an increase in circulating acute phase reactants [29].

3.6. Stress and multiple ‘hits’
Stress might increase the like hood of developing type 2 diabetes by activation of the Hypothalamus Pituitary Adrenal (HPA) axis and the Locus Coeruleus Norepinephrine system (LC-NE system) with counter regulatory hormone release and cytokine induced insulin resistance [30] But two less obvious observation are of note. First, splanchnic blood flow is decreased by stress, increased intestinal permeability and results in increased absorption of lipopolysaccharide (LPS) from the gut. Elevated portal blood stream LPS levels stimulate Kupffer cell receptors and cytokine release. Presumably absorption of other intestinal activators of innate immunity might also be augmented stress, including AGEs present in food. Secondly, hippocampal damage can result by repeated stress with the repeated induction of corticosteroids, causing a failure in the down regulation of corticosteroid production by the feedback mechanism and thus persisting elevated circulating cortisol levels [31]. This encourage the idea that resetting the control point of innate immunity at a higher level of activation might be caused by multiple stimuli over time either a range of different stressors or repeated episodes of the same type.

4. The role of Hyperglycemia: The inflammatory response: Primary or Secondary.
A major uncertainty is whether hyperglycemia is a main determinant of the inflammation in type 2 diabetes mellitus- there is evidence for and against. Cross sectional studies of type 2 diabetes mellitus show that CRP and IL-6 are significantly correlated with blood glucose concentration or glycated hemoglobin percentage [32]. Lowering of blood glucose levels in type 2 diabetic patient are accompanied by reduced levels of inflammatory markers [33]. AGEs are known to have similar cytokine stimulating effect on macrophages [34]. Recent finding indicates that acute hyperglycemia in nondiabetic and IGT subjects elevate plasma IL-6 and TNF-α concentration higher and longer in an individual with IGT and when glucose was given as pulse [35]. By infusion of the antioxidant glutathione the effect was abolished, which suggests that hyperglycemia induced cytokine production is mediated by reactive oxygen species. Subcutaneous and intraabdominal adipose tissue is a major source of TNF-α and IL-6 production [36]. This raise the question of whether the acute phase reaction of type 2 diabetes is mainly secondary to obesity. In a recent study in which a case and control subjects were matched by BMI and waist circumference, neither CRP nor IL-6, predicted the development of type 2 diabetes, although lowered level of adiponectin did. Thus, a hypothesis was suggested that because inflammatory markers are associated with obesity, they only indirectly predict diabetes and act as surrogate markers of hypoadiponectinemia [37]. Atherosclerosis is another co segregate of type 2 diabetes which is strongly associated with acute
phase response in its own right [38]. Present evidence supports the notions that atherosclerosis develops in parallel with type 2 diabetes [39] with both conditions showing the common antecedent of activated innate immunity, but like hyperglycemia and possibly some other manifestation of type 2 diabetes such as obesity, microangiopathy once present, would presumably further enhance inflammation[40].

5. Conclusion:

For centuries we have known of the existence of two types of diabetes; the type 1, where the basic defect is an absolute deficiency of insulin due to an autoimmune destruction of the β cells and the type 2 diabetes, where the underlying pathology is decreased secretion of insulin or an increased resistance to the action of insulin by the insulin sensitive tissues. Then come the era of finding newer and newer mechanisms involved it the pathology. One that received wide acceptance and paved way for further research is the role of activated innate immunity in the development of type 2 and probably type 1 diabetes. Where there are studies on type 2 diabetes mellitus agreeing on the fact that acute phase proteins especially CRP, are increased, studies in type 1 patients remains contradictory. It was found that acute phase markers are not elevated in type 1 subjects who had the same degree and duration of hyperglycemia as type 2 subjects. At the same time, type 1 patients are at the same risk of developing atherosclerosis as the type 2 patient. Hence it was speculated that specifically diabetes related factors (possibly glucose) would need to be additionally sensitize the arteries to cytokines and other atherogenic factors such as hypercholesterolemia.

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