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ASSOCIATION OF C-REACTIVE PROTEIN AND OTHER MARKERS OF INFLAMMATION WITH RISK OF COMPLICATIONS IN DIABETIC SUBJECTS.

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1.1 Abstract

The inflammatory process and factors that contribute to chronic low-grade inflammation have recently become a focus in cardiovascular disease, diabetes, peripheral vascular diseases, renal disease and hypertension.

The aim of this article was to discuss on the clinical utility of C-reactive protein and several other inflammatory molecules in diabetic patients.

Key words: diabetes mellitus, inflammatory markers, C-reactive protein, low- grade inflammation.

1.2 Introduction

The inflammatory process and factors that contribute to chronic low-grade inflammation have recently become a focus in cardiovascular disease (CVD) and diabetes research (1). It's now widely accepted that inflammation plays a major role in the pathogenesis and progression of atherosclerosis and that increased inflammation may be an explanation for accelerated atherosclerosis in the general population and in persons with type 2 diabetes mellitus (T2DM) (1).

Low-grade chronic inflammation is associated with insulin resistance, features of the metabolic syndrome and metabolic syndrome itself (2).

Many efforts have focused on the elucidation of common pathophysiological mechanisms among obesity, type 2 diabetes and atherosclerosis, underlining the role played by inflammatory condition (3). A feature of inflammatory activity is the increase in circulating plasma of acute- phase proteins produced by the liver such as C-reactive protein (CRP) and fibrinogen (4). These data have been confirmed by several studies reinforcing the association between diabetes and inflammation (3). Increased concentrations of various inflammatory markers such as: CRP, interleukin 6 (IL-6) and tumor necrosis factor a (TNF-a) have been reported in humans with insulin-resistance (5).

C-reactive protein, an acute-phase reactant, is synthesized in the liver largely in response to IL-6. Recent studies indicate that inflammation, as measured by CRP and IL-6, may predict not only cardiovascular events but also the development of diabetes (2).

Interest in CRP has grown rapidly during the last years, since it was shown that even a slightly increased production of CRP, within the normal range is associated with an increased risk of cardiovascular disease in diabetic patients (4).

Excess adiposity is the most important factor for the development of insulin resistance and type 2 diabetes. However, mechanisms by which body fat induces insulin resistance in distant tissues are not well understood. Recent studies indicate that obesity may be an inflammatory condition. It has been proposed that inflammatory cytokines secreted by adipocytes exert an endocrine effect conferring insulin resistance in liver, vascular endothelial tissue and skeletal muscles at last leading to the clinical expression of both type 2 diabetes and cardiovascular disease (6).

1.3 CRP

CRP is a member of the pentraxin protein family that possess five identical subunits (7). During an acute inflammation the concentration of CRP can increase several hundredfold (4). C-reactive protein is produced by hepatocytes in response to wide range of stimuli, mainly IL-6, IL-1 or TNF-? (8, 9, 10). Because of a long half-life, in average 19 hours, CRP levels correlate well to its synthesis induced by persistent inflammation (7,10). CRP activates complement, increases phagocytic activity of neutrophils, increases respiratory burst of neutrophils and induces expression of adhesion molecules, synthesis of tissue factor and cytokines from monocytes and platelet aggregation (10,11). It's a sensitive marker of systemic infection and is widely used in clinical settings circulating at low concentrations in healthy individuals (8, 9).

CRP has been used mostly in clinical settings to monitor disease status and treatment results (7,8, 9). About 90% of apparently healthy individuals have CRP concentrations <3 mg/l and 99% have concentrations <10 mg/l, if measured by high sensitivitmethod (hs-CRP). Lately, its use in predicting the risk of

of several studies now suggest that elevated CRP concentration may predict a higher risk for future cardiovascular disease (8, 9).

High sensitive-CRP (hs-CRP) is a novel biochemical marker for the prediction of first and recurrent coronary events (7). It's elevated in various conditions including: inflammation both acute and chronic, acute myocardial infarction, diabetes, peripheral vascular diseases, renal disease, hypertension. A positive association has been reported between CRP levels and age, smoking, body mass, total cholesterol, lipoprotein a [Lp(a)], fibrinogen and homocysteine (10,12,13).

1.4 Diabetes

Diabetes mellitus is estimated to affect >150 million adults worldwide, with an expected doubling number in the next 25 years, reaching 5,4% of the total adult population. At present diabetes affects close to 50 million people in Europe and this number is expected to increase to almost 60 millions by 2025 (14). In the US 15 million people are diabetics (95% with type 2 diabetes). Among them 5-6 millions are unaware of their condition and don't receive treatment (3).

Recent prospective study has shown that elevated levels of CRP may predict the development of type 2 diabetes among apparently healthy individuals (10).

1.5 Associations between inflammatory markers and diabetes.

Several data have been published on the association between C-reactive protein and diabetes, glucose, or insulin concentrations. C-reactive protein was shown to be higher in diabetic patients or patients with glucose intolerance than in normoglycemic subjects and was independently associated with diabetes (8,9). hsCRP was shown to increase gradually even in the normal fasting glucose range (15)

Higher concentrations of circulating CRP, increased oxidative stress, trombophilia (plasminogen activator inhibitor-1) and endothelial dysfunction are associated with an increased risk of the metabolic syndrome. Though the mechanism is questionable, some suggest that CRP is causally linked to the development of the metabolic syndrome. Potential mechanisms of action involve CRP eliciting pro-inflammatory responses through the mediation of cytokines, adhesion molecules, other signaling molecules, or endothelial nitric oxide (16).

Increased systemic inflammation with increased concentration of a related marker e.g. CRP, might be an indicator of pre-obese and obese states as a result of increased adiposity and consequent up-regulation of the cytokines: IL-6 and TNF as summarised on figure 1 (16).

Coppola et al. have shown increase of circulating acute phase proteins in type 2 diabetes (17). There are several possible mechanisms by which diabetes might induce inflammation state. In hyperglycaemic condition the concentration of advanced glycation end products is elevated that have been shown to activate macrophages, increase oxidative stress and upregulate the synthesis of IL-1, IL-6 and TNF, resulting in the production of CRP.

Another possibility is that increases in CRP concentrations are related to adipose tissue derived cytokines (17).

Figure 1. Associations between circulating CRP concentrations and metabolic syndrome (16).

Adiponectin, a new adipokine with anti-inflammatory properties Adiponectin, a new adipokine with anti-inflammatory properties derived from fat cells, is reported to be essentially associated with metabolic syndrome. Low concentration of adiponectin was found in the early stage of low-grade inflammation, obesity and subjects with insulin-resistance. Decreased adiponectin and elevated CRP concentrations were observed in subjects who met any criteria of metabolic syndrome (18). In the other study lowered adiponectin level observed in women with type 2 diabetes was found to be only partly related to insulin resistance and inflammation (19).

The associations of elevated levels of hs-CRP with increased risk for CVD and diabetes mellitus were discussed by Haffner (20) . Elevated hs-CRP levels may be predictive of development of the metabolic syndrome (20).

Streja et al., found that despite strong correlation between CRP and fibrinogen (FIB) in patients with type 2 diabetes these inflammatory markers reflect different parts of the picture of the disease (21). In this cross- sectional study, FIB was higher in patients with the complications of type 2 diabetes mellitus while CRP was not (4,21). In type 2 diabetic subjects fibrinogen compared with hsCRP might be closely associated with diabetic microangiopathy, however both markers might not correlate with intima media thickness a marker of macroangiopathy (22).

In another study Soinio et al. have reported that in subjects with type 2 diabetes CRP is a predictor for coronary heart disease deaths (23).

The associations of CRP and IL-6 concentrations in type 2 diabetic patients with and without coronary heart disease (CHD) were studied by Mojiminiyi et al (12). Concentrations of CRP but not IL-6 were elevated in diabetics with CHD when compared with age- and sex-matched subjects without CHD suggesting that CRP is a stronger discriminator for detection of CHD in diabetic patients (12).

It has been reported that markers of inflammation are strongly and independently associated with microvascular complications and cardiovascular disease also in type 1 diabetes (24).

In both, type 1 and type 2 diabetic patients correlations between CRP and markers of endothelial dysfunction have been shown recently. Inflammatory activity and endothelial dysfunction increased in the time course of the disease and these increases were strongly interrelated (4, 25).

In subjects with type 2 diabetes myocardial infarction may be one of essential complications of atherosclerosis. It seems that increased concentration

of some inflammatory markers like TNF-alpha may be related to endothelial dysfunction in such patients after cardiovascular incident (26).

Development of type 2 diabetes may even be preceded by endothelial dysfunction. Meigs et al suggested that elevated plasma levels of markers of endothelial dysfunction such as PAI-1 and von Willebrand factor increase risk of development of type 2 diabetes that is independent of other risk factors like obesity, insulin resistance and inflammation (27).

Complications in patients with T2DM such as peripheral arterial disease may be associated with IL-6 gene polymorphism influencing plasma levels of inflammatory markers. It was suggested that GG genotype may increase IL-6 release leading to elevated concentrations of inflammatory molecules : CRP and fibrinogen (28).

IIn the other study Saraheimo et al. have shown that levels of CRP and IL-6 were higher in normoalbuminuric diabetic patients than in healthy controls (29). Within the diabetic group, patients with micro- and macroalbuminuria had higher concentration of CRP than normoalbuminuric and IL-6 showed an increase in parallel with the renal dysfunction. Their studies provided evidence that low-grade inflammation is associated with diabetic nephropathy in type 1 diabetes (29). Some inflammatory markers are linked to renal insufficiency also in subjects with type 2 diabetes. Plasma levels of fibrinogen and vascular cell adhesion molecule-1 but not CRP were found to be increased when glomerular filtration rate was moderately decreased (30).

1.6 Conclusion

Inflammation seems to be strongly and independently associated with microvascular complications and cardiovascular disease in diabetes. Measurement of inflammatory biomarkers may be useful for assessment of the risk of complications in diabetic patients, however the ability of these markers to predict the future risk of diabetes is still to be proven.

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