Correlation between the lipid and cytokine profiles in patients with coronary heart disease (CHD) (Review article)

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Abstract: Many population-based studies consistently demonstrate some significant correlation between plasma levels of TG, LDL cholesterol, HDL cholesterol, different inflammatory cytokines and the prevalence of coronary heart disease (CHD). This article aimed to analyze the correlation between the occurrences of CHD with profile of lipid and cytokines.This is a meta-analysis study evaluating all pubmed, web of sciences, science direct, Scopus and Google scholar articles about the CHD and lipid and/or cytokine profiles from 2010 to 2012 using analytical statistical nalysis. Data were collected and the related information extracted and put in statistical package and analyzed.According to the analysis of many studies healthy individuals have higher levels of HDL lipoprotein than those with CHD so that An estimated of 1 mg/dl higher HDL-C is associated with a 2% lower risk of CHD for men and a 3% lower for the women. The plasma levels of Interleukin-6, CRP, TNFα, IL-18, IL-15, complement C3, colony stimulating factor (M-CSF), ICAM-1, CD54) on CD14+ CD16+ all are increased among CHD patients and therefore considered as risk markers of MI-coronary death. Profiles of lipid and cytokines are good predictors for CHD particularly if they to be evaluated and analyzed simultaneously and management of both groups can change the severity of the disease.

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1. Introduction

Evidences now indicate that inflammation contributes considerably to the initiation and progression of atherosclerosis, (1, 2). and histopathological and immunochemical observations suggest that active inflammatory processes may trigger plaque rupture and enhance the risk of coronary thrombosis leading to a clinical ischemic event (3) . Inflammation is characterized by a local reaction that may be followed by the activation of an acute phase reaction (4). Some systemic inflammatory markers can indicate the severity of inflammation, and their levels have actually been associated with coronary disease for example the fibrinogen, which was previously recognized as an independent coronary heart disease (CHD) risk factor,(5-6) is now considered an inflammatory marker and not only a coagulation component (7). On the other hand, prospective epidemiological studies have shown a strong and consistent association between the clinical manifestations of atherothrombotic disease and systemic markers of inflammation, including white blood cell count (8) and various hemostatic proteins that are also acute phase reactants such as fibrinogen (9) plasminogen-activator inhibitor type-1, and von Willebrand factor (10-11). Evidences now indicate that inflammation contributes considerably to the initiation and progression of atherosclerosisand histopathological and immunochemical observations suggest that active inflammatory processes may trigger plaque rupture and enhance the risk of coronary thrombosis leading to a clinical ischemic event (12,13). The measurement of acute phase proteins in blood provides a measure of inflammation activity (14). Numerous plasma proteins have an acute phase response including proteins involved in coagulation(e.g., fibrinogen and factor VIII) and plasminogen, complement proteins and transport proteins (e.g., ceruloplasmin, ferritin), and other proteins such as C-reactive protein, serum amyloid A protein, A Acid Glycoprotein (AAG), and albumin (15). Some changes are positive (e.g., fibrinogen) and some are negative (e.g., albumin). The changes in acute phase proteins are related to their hepatic production in response to inflammatory mediators such as cytokines. The changes in the levels of acute phase proteins may provide an indirect measure of inflammation or injury to the arterial wall and the associated increases in cytokine production, especially by the macrophages (1).

It has been proposed that inflammation of arteries results in an increased production of cytokines, especially IL-6, and activation of clotting factors, increased platelet aggregation, and smooth muscle cell proliferation. Interleukin 6 (IL-6) is the

major initiator of acute phase response by hepatocytes and a primary determinant of hepatic CRP production as suggested by IL-6–deficient animals showing impaired acute phase reaction (16,17, 18). Experimental studies indicate that vascular endothelial and smooth muscle cells produce IL-6 and that IL-6 gene transcripts are expressed in human atherosclerotic lesions (19, 20, and 21). Given the role of IL-6 in CRP regulation and the hypothesis that atherosclerosis fundamentally represents a chronic inflammatory disorder (22, 23), the predictive value of IL-6 for cardiovascular ischemic events can has been evaluated showing an association of it with increased risk of future myocardial infarction (MI) in healthy middle-aged men (24) . Also it is to say that IL-6 and TNF-α as the inflammatory cytokines are the main inducers of the secretion of C-reactive protein in the liver (25). C-reactive protein is a marker of low grade inflammation, and recent studies suggest that this protein has a role in the pathogenesis of atherosclerotic lesions in humans (26, 27).

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is an emerging biomarker of CV risk that is pharmacologically modifiable and therefore well positioned to address novel mechanisms of atherosclerotic vascular disease (32). Although this enzyme has been referred to as platelet activating factor-acetyl hydrolase (PAF-AH), Lp-PLA2 exhibits much broader substrate specificity (33-34). In particular, Lp-PLA2 rapidly degrades polar phospholipids present in oxidized LDL-C, releasing downstream products such as lysophosphatidylcholine species and oxidized nonesterified fatty acids (35). These products of the Lp-PLA2 reaction exhibit a wide range of pro-inflammatory and pro-apoptotic effects in experimental settings (32). In this context, Lp-PLA2 could be proposed as the enzyme that links oxidized LDL-C with atherosclerosis progression and plaque vulnerability. Lowering the low density lipoprotein cholesterol (LDL-C) therapy for lipid modification in atherosclerosis treatment and prevention has increasingly been at the focus of many studies. Lipid-lowering treatment directed at LDL-C with standard doses of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (“statins”) has resulted in a relative risk reduction of one-third in major vascular events as compared with placebo (36). In patients at very high risk for vascular events, intensive lipid-lowering has been shown to be beneficial compared with standard therapy. The Framingham Heart Study in the 1980s demonstrated that the risk of coronary heart disease (CHD) was significantly lower among persons with higher levels of high-density lipoprotein cholesterol (HDL-C) (normal range 40 to 60 mg/dl). A number of studies have supported this inverse correlation between HDL-C and CHD (37, 38); hence, HDL-C has quickly evolved as one of the “traditional” risk factors used by clinicians to predict risk of incident CHD (39). As there some strong evidence about the relationship of cytokines and the biochemical risk factors among the patients suffering from heart disease the current review aimed to perform a systematic review to elucidate further aspects of such relationship.

2. Review process

A systematic review on relevant studies published in Web of Science, PubMed and Google scholar between 1976 and March 2012 reporting the associations between CHD risk and cytokine/biochemical risk factors was performed. The review was restricted to studies carried out on human subjects and written in the English language. Results were evaluated according to the date and subject and using the matrix model in which the analyze was based on both the chronologic theme and the subject and the report was written accordingly.

3. Body text

3.1. Cytokines and the CHD risk

Many immunological risk factors such as C-reactive protein, interleukin-6, fibrinogen, interleukin-8, interleukin-15, interleukin-18, plasma C3, FcγRIIIA, Lp-PLA2, TNF-α, NFKB1 and… for the prediction of coronary heart disease were evaluated .C-reactive protein is one of the most important immunological risk factors for the CHD prediction and majority of researchers believed that there was positive and direct relation between CRP and CHD. Some studies show that there was some associations between the CRP, interleukin-6 and fibrinogen some others have measured the hazard rate of CHD by the CRP that was 1.67. Evaluating the association between the CRP, IL6 and fibrinogen only interleukin-6 remained significantly associated with MI-coronary death when the 3 inflammatory markers were included in the model. Interleukin-6 appeared as a risk marker of MI and coronary death, and it improved the definition of CHD risk beyond the LDL cholesterol (41). In another Coronary Prevention Study 6447 men were evaluated to predict the CHD risk and also 5974 men to predict the incidence of the diabetes over the 4.9 years of follow-up. The mean LDL cholesterol was similar but the C-reactive protein was higher ($P<0.0001$) in the 26% of men with the syndrome compared with those without. Metabolic syndrome increased the risk for a CHD event {(HR) 1.76}). C-reactive protein enhanced prognostic information for both outcomes. Men with the syndrome had similar risk reduction for CHD as

compared with those without (43). The plasma levels of C-reactive protein and serum amyloid A protein have showed a strong association (P<0.00001) while they were inversely related to the levels of serum albumin (P<0.00001). Also a significant associations of plasma CRP concentrations with cigarette smoking and obesity is reported (P<0.00001). Serum albumin levels raised a strong association with blood pressure (P<0.0001) and plasma lipids (P<0.001), while the serum amyloid A protein showed a strong correlation with obesity (P<0.0001). The strong associations of plasma levels of CRP with cigarette smoking and obesity indicate that this particular protein can mediate some of the effects of risk factors of coronary heart disease. CRP has been proposed as an independent risk factor for CHD (44). The significantly higher level of interleukin-8 in unstable coronary heart disease patients in comparison to the stable coronary heart disease patients (P ≤ 0•01) and the control group (P ≤ 0•02) indicated the effective role of this cytokine on CHD. These findings suggest that the soluble form of P-Selectin and interleukin-8 may be considered as some useful clinical predictors of unstable coronary heart disease (46). Cahide Gokkusua who is the first person that showed the relation between the IL-15 and the CHD, reported the influences of IL-15 gene variants and IL-15 levels on CHD. The results of this study showed that the serum levels of IL-15 were significantly higher in both acute and chronic patients than in controls. Also the genetic variants of IL-15 gene and IL-15 levels were associated with CHD. This study supports the hypothesis that genetic variation in IL-15 gene and IL-15 levels influence the risk of CHD (table-1) (47). IL-18 and TNFα were shown as the risk factors of CHD, as was reported that the baseline plasma levels of IL-18 and TNFα were significantly elevated in CHD cases versus the controls. Using univariable models IL-18 was associated with CHD risk (odds ratio [OR] upper third to lower third, 1.63; 95% CI 1.08, 2.46), but TNFα was not (OR 1.33; 95% CI 0.87, 2.02). After adjusting for major CHD risk factors and CRP, the association of IL-18 with CHD risk was attenuated (OR 1.69; 95% CI 0.94, 3.03). IL-18, but not TNFα, had a non-negligible association with CHD risk, although the association of IL-18 with risk was weak after full adjustment (48).

3.2.Complement components and CHD

The higher plasma levels of C3 were associated with a higher CHD prevalence, and there was a significant interaction with heavy smoking (p<0.01). In never & light smokers, the univariate OR for CHD per 1 smoking daily (0.33 g/L) increase in C3 was 1.09 [95% confidence interval (CI) 0.85–1.41] (p<0.505) whereas in heavy smokers it was 2.05 [1.43–2.93] (p< 0.001). Human plasma complement C3 was reported to be associated with prevalent CHD, but only in heavy smokers, and this association was independent of important metabolic cardiovascular risk factors (49).

3.3. Receptors involved in immunity to CHD

Ye Huang et al demonstrated a significant increase of FcγRIIIA at the mRNA level in leukocytes, and at the protein level for both soluble CD16 in sera and membrane CD16 on monocytes of CHD patients compared to the healthy control. Similar to the soluble CD14 (sCD14), the sera level of macrophage colony stimulating factor (M-CSF) was elevated in CHD patients than compared to the controls. Furthermore, the levels of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1), in sera and the mean fluorescent intensity of intercellular adhesion molecule 1 (ICAM-1, CD54) on CD14+ CD16+ monocytes were increased in CHD patients. The significant increase of CD14+ CD16+ monocytes in CHD patients therefore suggested that the increase of the FcγRIIIA level might be a sensitive marker for the CHD diagnosis (50). The NFKB1 promoter variant, previously shown to cause partial depletion of NF-κB p50, was associated with a higher risk of CHD in three independent prospective studies of generally healthy Caucasians (55). For every inherited copy of 358Ala the mean concentration of IL-6R was increased by 34.3% (95% CI 30.4–38.2) and of interleukin 6 by 14.6% (10.7–18.4), and mean concentration of C-reactive protein was reduced by 7.5% (5.9–9.1) and of fibrinogen by 1.0% (0.7–1.3). For every copy of 358Ala inherited, risk of coronary heart disease was reduced by 3.4% (1.8–5.0). Asp358Ala was not related to IL-6R mRNA levels or interleukin-6 production in monocytes. Large-scale human genetic and biomarker data are consistent with a causal association between IL-6R-related pathways and coronary heart disease (41).

3.4. Lipid Profile and CHD

The Lp-PLA2 activity has been shown to be significantly associated with myocardial infarction. Levels of Lp-PLA2 activity were shown a significant association with incident of CHD among women. The Lp-PLA2 levels was positively correlated with age, body mass index, low-density lipoprotein, triglycerides, and C-reactive protein, and negatively correlated with high-density lipoprotein (52).

Among the biochemical risk factors for CHD, the LDL and HDL are important than the other biochemical risk factor. Jonathan C examined the effect of DNA-sequence variations that reduced the

plasma levels of LDL cholesterol on the incidence of coronary events in a large population and compared the incidence of CHD (myocardial infarction, fatal CHD, or coronary revascularization) over a 15-year interval in the Atherosclerosis Risk in Communities study according to the presence or absence of sequence variants in the proprotein convertase subtilisin/kexin type 9 serine protease gene (PCSK9) that were associated with the reduced plasma levels of LDL cholesterol. Of the 3363 black subjects examined, 2.6 percent had nonsense mutations in PCSK9;these mutations were associated with a 28 percent reduction in mean LDL cholesterol and an 88 percent reduction in the risk of CHD (P <0.008). Of the 9524white subjects examined, 3.2 percent had a sequence variation in PCSK9 that was associated with a 15 percent reduction in LDL cholesterol and a 47 percent reduction in the risk of CHD. These data indicate that moderate lifelong reduction in the plasma level of LDL\ cholesterol is associated with a substantial reduction in the incidence of coronary events, even in populations with a high prevalence of non–lipid-related cardiovascular risk factors (58).

4.Conclusion-

The association of different Immunological and biochemical risk factors for the CHD disease has been the focus of many studies but such analysis of these risk factors in a systemic review is a matter of necessity. Some findings have showed the association of the soluble form of P-Selectin and interleukin-8 with unstable coronary heart diseases and some other hypothesized that genetic variation in IL-15 gene and IL-15 levels can influence the risk of CHD. Still another cytokines levels such as IL-18 and TNFα were stablished as predictors of CHD. Human plasma complement C3 and prevalence of CHD is been reported too. There is also strong association reported for the increasing level of FcγRIIIA at the mRNA and at the protein level for both soluble CD16 in sera and membrane CD16 on monocytes of CHD patients. Sera level of CD14 and macrophage colony stimulating factor (M-CSF) was elevated in CHD patients as was seen for the inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) , interleukin-1 (IL-1) and intercellular adhesion molecule 1 (ICAM-1, CD54). Also the increase of the FcγRIIIA level has been considered as a sensitive marker for the CHD diagnosis. There has also been proven that the partial depletion of NF-κB p50, is associated with a higher risk of CHDis some population like the Caucasians. The relationship of lipids such as Lp-PLA2 levels was also been proved to be positively correlated with age, body mass index, low-density lipoprotein, triglycerides, and C-reactive protein, and negatively with high-density lipoprotein while moderate lifelong reduction in the plasma level of LDL\ cholesterol is associated with a substantial reduction in the incidence of coronary events. These data all together indicated that a rise in Immunological and lipid risk factors is proportional to high prevalence of cardiovascular diseases.

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