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Serum concentration and gene polymorphisms of IL-6 and TNF-α in cardiovascular disease

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Abstract
Interleukin-6 and Tumor Necrosis Factor-α has the major role in the cardiovascular diseases. The role of IL-6 in causing cardiovascular disease, ageing related problems, congenital heart problems in children and elderly are now the major target in research for finding solution to cardiovascular problems. The increased levels of IL-6 causes all these problems which are mainly due to polymorphism in gene coding for IL-6. The tumor necrosis factor-α is also found to be associated with the cardiovascular problems. The increased TNF-α levels cause nutritive stress thereby damaging the endothelial function. The increase in TNF-α level is also found to be associated with gene polymorphisms, leading to increased risk of heart failures. In some case it acts as a biomarker, especially in elderly heart failure patients, and the gene polymorphisms of TNF-α were correlated with coronary artery disease. Concisely, some SNP may increase the risk of Cardiovascular diseases.

Keywords: Gene Polymorphisms, IL-6, TNF-α and Cardiovascular diseases

1. Introduction

Interleukin-6 (IL-6) was first named as B-Cell Differentiation Factor, because it's promotes B-cell differentiation and survival [1] IL-6 is one of the members in the IL-6–type family. it's also comprise ciliary neurotrophic factor, leukemia inhibitor factor, and oncostatin-M it's having the different functions, like the directive of hematopoiesis, immune responses, acute-phase responses, inflammation, also called pleiotropic cytokine [2]. l-6 receptor contains a receptor, IL-6–binding chain (IL-6Ra) and gp130,called the signal-inducing component. IL-6R having the two forms, membrane-bound and soluble respectively [3]. From the different stimuli responses IL-6 produced by different cells, like endothelial cells, monocytes, fibroblasts, macrophages [2]. The T cells, B cells, hepatocytes, hemopoietic cells, leukocytes are the main targets of the IL-6 [4] in this IL-6 receptors binds and leads to the different signal transduction pathways, like *PI3K, JAK/STAT, ERK* [5] T-cell proliferation, plasma-cell production, B-cell differentiation and survival, promoted by the IL-6 [6]. The cytogenetic location of the IL-6 gene is 7p21 [7] with 7 exons which have approximate genomic DNA in 12.8 kb [8].

In 1975, an endotoxin induced serum factor which responsible for the necrosis of tumours discovered by carswell *et al*., after called Tumour necrosis factor alpha (TNF-α) [9]. It's a proinflammatory and pleiotropic cytokine [10] contains 157 aminoacids, polypeptide in nature [11]. TNF alpha has 2 receptors, respectively a high affinity receptor in 55kDa, and low affinity receptor in 75kDa [12, 13] and regulated in different pathophysiological conditions [14] Activated macrophages are the main resource of the Tumour necrosis factor alpha, also have the two type of molecule membrane bound and cell associated forms [15] TNF alpha produced by the fibroblasts, lymphocytes, neutrophils, mast cells and smooth muscle cells. It's rapidly produced but not in stored state [16] The TNF-alpha gene located chromosome 6, near to this location genes involved in many functions [17]

In past studies the variable TNF alpha production were seen in healthy peoples [18] because too much TNF alpha levels in blood circulation leads to the cardiac effects and reduce the vascular confrontation [19] clinical appearances of heart failure [20], left ventricular dysfunction [21], cardiomyopathy [22]. The role of the IL-6 and TNF-α in cardiovascular diseases is discussed below.

2. Interleukin 6 (IL-6) levels and gene polymorphisms in cardiovascular diseases

Like a sword it's has two inflammatory characters pro and anti-inflammatory. The reason why people seeking IL6 levels and it's polymorphism is because, there are 2 reasons, it's not only produced by immune cells, but some other cells like vascular smooth muscle cells, cardiovascular components, monocytes and macrophages also involve in the production of the Interleukin 6, participates the cardiac metabolism in the cardiovascular diseases [23-26] Past studies showed that IL-6 increased levels associated with the coronary heart disease, with the activation of the sympathetic nervous system. [27-28] associates with development of heart failure, cardiac function loss, dysfunction of left ventriculars [29].

The Women's Health and Aging study (WHAS) demonstrated that women with CVD, those with elevated serum IL-6 levels had a high risk of death in women, but the study did not find this relationship among those without CVD [30] some more research indicates IL-6 as well as TNFα, shows a representative markers of cardiovascular disease in woman [31].

Also in children with IL-6 were analyzed in congenital heart disease, in progression and development of the congenital heart disease. And this study opens in a new way, IL-6 levels positively correlated with the congenital heart disease. In future it will lead to the different kind of results [32]. In contrast, Tuomisto *et al.* (2006) [33] study showed that CRP and TNF-α, not important predictor among men. However, Scharnagl *et al.* (2010) [34] found IL-6 to be more strongly related with all-cause of cardiovascular diseases. Other recent studies had revealed that increased serum IL-6 will give important information for the risk of all-cause mortality in cardiovascular diseases [35, 36].

A previous study established that serum IL-6 level is a good interprter of acute heart failure patients who's having long and short term progress of disease [37]. In two other prospective studies, long-term serum IL-6 levels were related with CHD (Danesh *et al.,* 2008). Haugen *et al.* (2008) [38] showed that an increased IL-6 concentration predicts mortality in elderly heart failure patients. Panichi *et al.* (2004) [39] reported plasma IL-6 to be a stronger predictor of total and cardiovascular mortality than CRP in patient's undergone haemodialysis. Recently, Dongfang *et al.* (2013)[40] confirmed these reports that the positive association to IL-6 level and following risk of mortality, resulting that serum IL-6 is a stronger interpreter of total and cardiovascular mortality than CRP, which supports the probable role of inflammation in the progression and prognosis of CHD. The possible functions by serum IL-6 participates to CHD pathogenesis, first, serum IL-6 is the major stimulator of hepatic acute-phase response, which is related with increased blood viscosity and elevated level of platelet number and its activity. Second, the paracrine and autocrine activation of monocytes in the vessel walls by IL-6 will leads to the deposition of fibrinogen [41]. Third, IL-6 reduces the activity of lipoprotein lipase, thus increasing the uptake of lipids by macrophages (Hardardottir *et al.,* 1994). Fourth, the circulating IL-6 also enhances the hypothalamic-pituitary-adrenal axis, the activation of which is related with hypertension, obesity and insulin resistance [42]. In a recent study from diet induced rats, the IL-6 levels were analyzed, and stated that IL-6 levels related to the risk of cardiovascular diseases [43].

Zheng *et al*., 2012 conducted meta-analysis using literature search. They took 27 research studies to prove which polymorphism in the IL-6 gene leads to the Coronary heart disease. Finally the Meta analysis shows that the 2174G/C polymorphism not contributed to elevated dangers of Coronary heart disease. on the other hand, the 2572G/C polymorphism associated with Coronary heart disease development [44]. A recent study indicates IL-6 G(-174)C polymorphism in cardiovascular disease in type 2 diabetes patients whose having the C allele [45] but it's not associated with the cardiovascular disease in old peoples [46] in same year a different study also conformed these results [47] Another study reports showed polymorphism in IL-6 gene 572 G/C region associated with coronary heart disease, also particularly they stated G allele in an significant genetic marker, because these polymorphisms elevated the levels of the lipoprotein and plasma lipid [48].

3. Role of TNF and Cardiovascular Diseases

In 1990 the first work had done in assessing the TNF alpha levels in the heart failure patients, and it's were elevated, at the end stage [49]. Continuous studies show that the TNF alpha levels were increased in heart failure patients [50] after that levels of tumour necrosis factor showed association in heart failure patients [51-52] Research in both animal models and humans provides convincing evidence identifying TNF-α as one of several regulators of vascular homoeostasis. The free radical of NO produced by NO synthase (NOS) with a help of terminal guanidino nitrogen of L-arginine, in the oxidation process.TNF-α controls the expression and activity of NOS which exerts direct effects on the production of NO [54] Further studies have also shown that TNF-α considerably decreased eNOS expression in ECs [55, 56] and consequently these contributes to nitrative stress and impair endothelial function. Several studies suggests that TNF-α damage NO-mediated vasodilation and endothelium-dependent in various vascular beds, for example, mouse coronary arterioles [57] rat coronary arterioles [58], cat carotid arteries [59] and bovine small coronary arteries [60].

Picchi *et al.* (2006) [58] suggested that endothelial dysfunction in diabetic, may have role in production of TNF-α effects. The contribution of TNF-α in ischaemia/reperfusion injury in TNF 1.6 mice, which over express TNF-α in cardiac tissue. Myocardial ischaemia/reperfusion increase in the expression of TNF-α, which induced activation of xanthine oxidase and the production of $O_2^{\bullet-}$, leading to coronary endothelial dysfunction [61]. Gao *et al.* (2007) [57] demonstrated that advanced glycation end-product/receptor for advanced glycation end-product and NF-κB signalling contribute a major role in elevating the levels and local vascular TNF-α production. The elevated TNF-α expression induces the production of ROS, leading to endothelial dysfunction in patients with type 2 diabetes. Endothelial dysfunction related with TNF-α in pathophysiological condition is linked to excess production of ROS and a decrease in NO bioavailability, which appears to affect several aspects of CVD.

In polymorphism studies, a recent study from Pakistani population showed pathogenesis of coronary heart disease in TNF alpha 863C/A, but not in 1031 T/C region [62]. Also there were no association proved in 308 G/A region in the TNF alpha gene [63]. Different polymorphisms in the TNF alpha gene were analyzed in this study, finally they found 5 polymorphisms associated with myocardial infarction, also the levels of the TNF alpha. it also suggested TNF alpha levels associated to the myocardial infarction, with a analyze of 1561 normal people and 1213 patient samples [64] Non-alcoholic Fatty Liver Disease people from Chinese Han population increased risk of Coronary Artery Disease whose having the TNF alpha 238 G/A polymorphism [65] on the other hand a meta-analysis from very recent study proved there was no association between 238 G/A polymorphism, Coronary Artery Disease risk [66].

4. Conclusion

The entire role of IL-6 and TNF-α in causing the cardiovascular disease has been discussed. There are many more unknown factors found to be associated with the progression of the cardiovascular diseases. In addition to the genetic polymorphism, certain environmental factors are also associated in causing cardiovascular disease. Treating the genetic polymorphism in cardiovascular disease is still under process. Until a proper and exact cure is obtained, exposure to pollutants which might cause cardiovascular disease can be avoided. Though the increased levels of IL-6 and TNF-α are found to be involved in cardiovascular disease, the complete analysis of how the increased levels exactly cause cardiovascular disease are yet to be determined as many other ailments of patients having cardiovascular disease might increase the levels of IL-6 and TNF-α.

5. References

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