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Paraoxonase: The boon against oxidative stress and lipid peroxidation

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Abstract

Coronary Artery disease (CAD) is estimated to be the number one cause of morbidity and mortality in the developing world. It is a multifactorial disease and diet plays an important role the development of CAD, and the risk further increases in the presence of dyslipidaemia. The lipoprotein profile is found to be deranged mostly in CAD. Low density lipoprotein cholesterol (LDL) is considered as the most important risk factor of CAD. However, a significant proportion of patients have a normal lipid profile. The oxidation of LDL is believed to have a central role in atherogenesis. The HDL associated paraoxonase (PON1) enzyme is known to have protective effects on lipid peroxidation. High density cholesterol associated PON which is known to have cardio protective properties have anti-atherogenic role and low PON1 activity could be an independent risk factor.

Apart from prevention of oxidation in circulating lipid molecules, it proves to be beneficial in various disorders related to imbalance in oxidants and antioxidants. Serum paraoxonase activity is also affected in cardiovascular diseases, cancer, diabetes, hypertension, renal failure, smokers and gastrointestinal disorders. The dietary factor which contributes to increase in paraoxonase activity in serum includes consumption of polyphenol-rich diets, wine and fruit juice consumption as it contains polyphenols.

Since we have long noted the advances and understanding the physiological benefits of PON based on extensive research. We look forward for further updates in researches based on PONs and wait for the anti-aging capsules of PON being marketed by pharmaceutical companies.

Key Words: Hyperlipidemia, Oxidized-LDL, Lipid Peroxidation, HDL-c, Paraoxonase.

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Since the incidence of Coronary Artery disease (CAD), is on the rise, it is estimated that it would become the number one cause of morbidity and mortality in the developing world by the year 2015[1]. People hailing from the Asian subcontinent have a higher probability of death due to CAD. It is a multifactorial disease, and some predisposing factors are heredity, hyperlipidaemia, obesity, hypertension, environmental factors and life style variables like stress, smoking, alcohol consumption, etc [2]. Diet, especially fat, plays an important role the development of CAD, and the risk further increases in the presence of dyslipidaemia [3]. The lipoprotein profile has been investigated extensively in recent years, which is found to be deranged in a large proportion of CAD patients; especially in Asians showing a mixed picture of dyslipidaemia. Low density lipoprotein cholesterol (LDL) is considered as the most important risk factor of CAD. However, a significant proportion of patients have a normal lipid profile [4]. The oxidation of LDL is believed to have a central role in atherogenesis [5].

Sub endothelial accumulation of foam cells plays a key role in the initiation of atherosclerosis [6].These foam cells, which may be generated by the uptake of oxidized LDL by macrophages via scavenger receptors, accumulate fatty streaks that evolve to more complex fibro fatty or atheromatous plaques [7]. Oxidized LDL may also be involved in atherogenesis by inducing smooth muscle cell proliferation [8] and generation

of foam cell. During oxidative stress, not only the LDL, but also other serum lipids are vulnerable to oxidation. High density lipoprotein (HDL) is one of the most important independent protective factors for arteriosclerosis, which underlies coronary heart disease (CHD) [9]. The HDL associated paraoxonase (PON1) enzyme is known to have protective effects on lipid peroxidation [10]. The human serum paraoxonase is a 43- to 45-kD protein. Its gene is located at q21 to q22 on the long arm of chromosome [11]. The amino acid sequence of paraoxonase is highly conserved among animal species, suggesting an important metabolic role for this enzyme [12]. The ability of paraoxonase to detoxify organophosphorous compounds has been known for years [13]. Its activity was determined earlier by the use of paraoxon, a widely used pesticide [14]. The physiological substrate of paraoxonase is yet to be unveiled. Paraoxonase , platelet activating factor acetyl hydrolase and lecithin: cholesterol acyl transferase which are the HDL associated enzymes that helps to retard/minimize the oxidation of LDL by preventing the generation of lipid peroxides [15] but among these, paraoxonase being the most extensively studied. High density cholesterol associated PON which is known to have cardio protective properties have anti-atherogenic role [16] which acts in number of ways. It decreases oxidative stress in serum, in lipoproteins, in macrophages, and also in atherosclerotic lesions [17]. It also minimizes oxLDL uptake by macrophages, inhibits macrophage cholesterol biosynthesis rate and stimulates HDL mediated cholesterol efflux from macrophages [18].

Numerous cohort studies and clinical trials have confirmed the association between a low HDL-cholesterol concentration and an increased risk of CHD [19]. Though many factors may play a role in its pathogenesis, low PON1 activity could be an independent risk factor [2]. Paraoxonase activity is inversely related to the risk of developing an atherosclerotic lesion, which contains cholesterol-loaded macrophage foam cells [20]. Although experimental studies have demonstrated the reduction in PON1 activity due to oxygen free radicals in ischemia and reperfusion [2], there are controversial data on correlation between PON1 HDL-C and the ischemia process.

Apart from prevention of oxidation in circulating lipid molecules, it proves to be beneficial in various disorders related to imbalance in oxidants and antioxidants. Serum paraoxonase activity is also affected in cardiovascular diseases, cancer, diabetes, hypertension, renal failure and gastrointestinal disorders [21]. It also provides microbial protection by hydrolyzing bacterial quorum lactone [22]. It is also affected in smokers [23]. Paraoxonase is much discussed and in limelight as it has an important role in various inflammatory diseases and also in preventing the organophosphorous insecticides and nerve agents, has made the debate quite interesting among clinicians as well as amongst researchers, also through conferences which took place in the last decade in five countries. As per the search results in PubMed, only few papers were published till 1980, but currently one can find more than 3000 papers are published which substantiates the vast interest among researchers regarding paraoxonase.

The PONs gene cluster contains three gene members, which shares high sequence, namely giving rise to PON1, 2, and 3 and beside their clear protective role against cardiovascular diseases. Paraoxonase plays an explicit role in lipid metabolism. PON1 favorably effects on macrophage cholesterol metabolism PON2 attenuates macrophage triglyceride accumulation and PON3 improvement of bile acid metabolism [24].

The dietary factor which contributes to increase in paraoxonase activity in serum includes consumption of polyphenol-rich diets, wine and fruit juice consumption as it contains polyphenols [25]. Research studies have shown that naringenin, flavones and quercetin increased PON1 mRNA about two folds in cell culture. Even oleic acid have reported to be an effective in an in-vitro study in protecting PON1 activity from oxidative stress [26]. Moderate alcohol consumption (40g/day in men and 30g/day in women) have shown to increase serum HDL-c by 6.5% and PON1 by 3.7%. Also daily consumption of pomegranate juice for 1 year by patients with carotid artery blockage induced an increase in serum PON1 activity and also decreased the amount of ox-LDL and progression of atherosclerosis (which is measured by the carotid intima-media thickness).

Since we have long noted the advances and understanding the physiological benefits of PON based on extensive research. We look forward for further updates in researches based on PONs and wait for the anti-aging capsules of PON being marketed by pharmaceutical companies.

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