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PARAOXONASE 1 COULD REVERSE THE OXIDATIVE CHANGES INDUCED BY TRIGLYCERIDE-RICH LIPOPROTEINS IN DIABETES

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In diabetes mellitus the higher morbidity and mortality from atherosclerosis is related to abnormalities in serum lipids, in particular the persistence of elevated triglyceride-rich lipoproteins (TRL) in the postprandial state. Paraoxonase1 (PON1) located on high-density lipoprotein (HDL) have been reported to possess antioxidant properties and may exhibit antiatherosclerotic capacities as well. In this review we summarize the existing literatures linking PON1 activity and TRL to the atherosclerotic process in diabetes.

Key words: paraoxonase-1, triglyceride-rich lipoprotein, diabetes mellitus.

INTRODUCTION

Diabetes mellitus is a frequent and incurable disease characterized by chronic hyperglycaemia. In recent years, oxidative stress has received growing attention as the unifying mechanism leading to biomolecular damage and cellular dysfunction in the pathogenesis of diabetes. Moreover, diabetes mellitus is an important risk factor for atherosclerosis and both the incidence and mortality of cardiovascular disease are increased in diabetic patients[1]. The mechanisms underlying this increased risk may be in part attributed to the imbalance between pro-oxidants (free radicals) and antioxidants which results in increased oxidative stress and oxidative damage to biomolecules[2].

Diabetic dyslipidemia is characterized by elevated very-low density lipoprotein (VLDL), low HDL, increased apolipoprotein B and the presence of small dense low-density lipoprotein (LDL), evident in the fasting state. Its pro-atherogenic consequences are aggravated by the delayed clearance of postprandial lipoproteins[3]. Persistence of these TRL, together with hyperglycemia, leads to an increase in oxidative stress[4] which is intricately linked to alterations in monocyte/ macrophage function[5]. This interest is based on the finding that atheroma plaques from diabetic patients contain higher amounts of lipids, macrophages and thrombus than those of non-diabetic subjects[6]. For instance, release of free radicals by the respiratory burst of monocytes is stronger in diabetes and is proportional to the degree of elevation of glucose and triglycerides[7-9]. This increases peroxidation of lipoproteins and as a consequence, enhances lipid uptake into macrophages and foam cell formation[10].

By this time is well know that paraoxonases are enzymes with three (paraoxonase, arylesterase and lactonase) activities which are inversely related to the atherosclerotic process. There have been many studies investigating the association between PONs gene polymorphisms and coronary heart disease (CHD) with mixed results and therefore the therapeutic possibilities of PONs in reducing the risk of CHD still need to be examined.

THE PARAOXONASE FAMILY: GENES, SUBSTRAT SPECIFICITY AND POLYMORPHISMS

The paraoxonase gene family has three known members, PON1, PON2 and PON3, located on the long arm of chromosome 7 between q21.3 and q22.1 in humans. The three genes are well conserved in mammals, sharing 79-95% identity at the amino acid level and 81-95% identity at the nucleotide level between different species[11]. This high degree of conservation suggests that the family has important physiological function(s), however even at this moment has been demonstrated the antiatherogenic capacities of the PONs the other functions as well as PONs´natural substrates have yet to be established. Next to the cluster of PON genes is a gene that codes for one of the pyruvate dehydrogenase kinases[12] and may explain the linkage of PON genotypes with diabetic glycemic control in some studies[13].

From an evolutionary standpoint, PON2 appears to be the oldest member, followed by PON3 and then PON1. By far the most studied member of the family is the serum PON1 (E.C 3.1.8.1), a 45kDa protein, a calcium-dependent esterase/lactonase whose primary physiological role is to protect LDL from oxidative modifications[14]. This enzymes is known to catalyse hydrolysis of organophosphates and its name derives from one of its most commonly used in vitro substrates, paraoxon (O,O-diethyl-O-p-nitrophenylphosphate) which is the toxic metabolite of the insecticide parathion[15]. In addition to paraoxon, PON1 has been shown to hydrolyze metabolites of a number of other insecticides such as diazinon, chlorpyriphos even with 10 and 20 times higher catalytic efficiencies than with paraoxon[16] and also to detoxify various nerve agents and a variety of aromatic and aliphatic lactones[17-18]. Recent investigations have suggested that the hydrolytic activity towards lactones (cyclic esters) is the native activity of PON1: structure-activity studies show that lactones are PON1's preferred substrate for hydrolysis[19].

Human PON1 is predominantly synthesized in the liver from where is secreted into the blood and associated with HDL[13,20]. The proposed mechanism by which PON1 would be released has been suggested to involve scavenger receptor class B type I (SR-BI), because this HDL receptor allows the transient association of HDL with the hepatocyte membrane without internalization or destruction of these lipoproteins[21]. Once in the blood, apoA-I and apoJ stabilize PON1 function and its association with HDL[22].

Two common polymorphisms in the coding region of human PON1 have been studied extensively in the past decade: leucine (L)/methionine (M) at position 55 and glutamine (Q)/arginine (R) at position 192. More attention has been paid to the 192 polymorphism because the two allozymes differ considerably in their affinity for and catalytic activity with a number of substrates. Paraoxon is hydrolyzed 6 times faster by the PON1192R allozyme than by the PON1192Q allozyme, but some organophosphates and lactones are hydrolyzed faster by the latter[17-18]. In the 5´-regulatory region of human PON1 five polymorphisms have been identified: -108 (107) T/C, -126 G/C, -162 A/C, -832 (834) G/A and -909 (907) C/G[23,24]. The -108 (107) T/C polymorphism has been the most important genetic determinant of PON1 levels[23,25]. Serum levels of PON1 vary widely among individuals and polymorphisms of the PON1 gene are at least partly responsible for the interindividual differences in enzyme activities[17].

PON1, OXIDATIVE STRESS AND ATHEROSCLEROSIS

Oxidative stress is defined as the change in the pro-oxidant/antioxidant balance in favor of the former, potentially leading to biologic damage to macromolecules and cell dysfunction[2]. Oxidative stress is thought to play a key role in early artherogenesis and in macrophage foam cell formation which is the hallmark of early atherosclerotic lesion[26,27]. Oxidative stress is associated with lipid peroxidation in lipoproteins and in arterial cells, including macrophages[28]. These "oxidized macrophages" are characterized by increased peroxide levels, decreased glutathione content, and increased capability to oxidize LDL29. Serum PON1 was found to decrease macrophage oxidative stress[30] and to be decreased under oxidative stress in atherosclerotic process[31]. Hydrogen peroxide at millimolar concentrations was observed to partially inactivate PON1[32]. Under oxidative stress conditions, HDL constitute a target for oxidative modifications that may affect their antioxidant properties[33]. Nevertheless, there have been few attempts to define the in vivo conditions for oxidative inactivation of PON1 and the relationship between oxidative inactivation of

PON1 and its antioxidant capacity[34,35]. Moreover, has been sugested that rabbit serum PON3 is more efficient than rabbit PON1 in protecting LDL from copper-induced oxidation[13]. PON1 mRNA expression was significantly repressed during an acute-phase respons in rabbits whereas PON3 mRNA expression was not altered. Therefore PON1 and PON3 may play distinct roles in the prevention of atherosclerosis. PON3 may provide a basal constitutive atheroprotective function, while the protective effect of PON1 is more variable[20]. Further studies may determine whether PON3 activity is required in vivo for the prevention of atherosclerosis.

Obesity associated diabetes is a lifelong disorder with serious long-term health consequences and is itself an independent risk factor for athero-sclerotic cardiovascular disease. High dietary fat intake is one of the etiological factors of obesity[36]. Moreover, increased oxidative stress has been demonstrated in overweight patients, which could explain the enhanced atherosclerosis[37,38]. Several studies have demonstrated that moderate weight loss (5-10% of body weight) results in a decrease in blood presure and insulin resistance, and it also improves the atherogenic lipid profile[39,40].

Audikovszky M et al. found that 6-month treatment with 120mg orlistat three times daily reduced serum triglyceride levels by 15.3% and increased the serum HDL-C level by 12.4% and the antioxidant status was improved by increasing the serum PON1 activity and in this way contributing to the decrease in the cardiovascular risk of obese patients[41]. Obese subjects have significantly lower PON1 activity compared to healthy controls and plasma levels of leptin correlated negatively with PON1 activity[42].

PON1 AND THE TRL IN DIABETES MELLITUS

It became apparent, that the atherogenic role of triglycerides might be different from that of cholesterol. While “more is worse” with plasma cholesterol, more is not always worse with plasma triglycerides in terms of coronary artery disease (CAD) risk, and while the cholesterol level does not undergo postprandial changes, triglyceride levels do[43]. Since triglycerides are associated with free and esterified cholesterol, apoproteins and phospholipids as lipoprotein particles, research now focuses on TRL that include chylomicron (CM) and VLDL as well as remnants of CM and VLDL. Lipoprotein levels are generally measured in the fasting state, despite the fact that most of the day is spent in the postprandial period. CM remnants are TRL that are derived from the lipolytic processing of intestinal chylomicrons, and a delay in remnant lipoprotein clearance is also associated with an increased risk of cardiovascular disease[43,44].

A new concept is that atherosclerosis represents a state of heightened oxidative stress characterized by lipid and protein oxidation in the vascular wall. VLDL and chylomicrons as well as their remnants may be an important source of poly-unsaturated fatty acid containing phospholipids, and it is conceivable that their oxidation may generate substantial bioactivity[45]. Oxidized lipoproteins are cytotoxic for vascular endothelial and smooth muscle cells. These contribute to atherogenesis due to facilitated up-take by macrophage foam cells[46]. HDL composition/metabolism in the postprandial phase is in a dynamic state due to on-going catabolism of TRL[47]. The postprandial rise in TRL may compete with HDL for PON1 released from hepatocytes. PON1 associated with TRL is less stable, which may contribute to the reduced its specific activity and for this reason could be beneficial if we manage to limit postprandial rises in triglycerides to minimize their impact on PON1 and this could be a recommendation to lower coronary risk in diabetic subjects[48]. On the other hand diabetic HDL-C is know to be compositionally abnormal[49] and this may interact with the PON1 binding site to HDL-C. Furthermore, it has been reported that glycated HDL had a 65% reduction in PON1 enzymatic activity and also direct glycation of purified PON1 protein by incubation in 25mmol/L glucose caused a 40% reduction in enzymatic activity[50]. According to this results can be assumed that PON1 activity is reduced over time as a result of overconsumption due to increased oxidative stress and glycation of the enzyme itself in diabetes mellitus[51,52].

The disorder of plasma glucose predisposes to the development of a cluster of abnormalities, including an increase in plasma triglyceride, a decrease in HDL-C concentration, high blood pressure and smaller denser LDL particles, which are the risk factors of CHD. In diabetes, the postprandial phase is characerized by a rapid and large increased in blood glucose levels. Postprandial hyperglycemic episodes in diabetic patients are closely associated with increased

oxidative and nitrosative stress, and are the most important factor in the onset and progress of vascular complications, both in Type 1 and 2 diabetes mellitus[53,54]. Populations with insulin-dependent diabetes mellitus have been shown to have marked reductions in serum paraoxonase activity without having a significantly lower HDL-C concentration[55]. Moreover, has been found that young persons with type 1 diabetes and the L/L polymorphisms at position 54 of PON1 gene were more susceptible to retinal complications[56].

Recently, PON1 has been described to be associated with chylomicrons, a factor that may influence the determination of PON1 activity and mass in a postprandial state[57]. For instance, for 3 hours after cream intake and 1 hour after protein intake has been observed an increases generation of reactive oxygen species (ROS), cream intakes causes, in addition, a significant and prolonged increase in lipid peroxidation[58]. This is in agreement with in vitro studies in which PON1 was inactivated by oxidized lipoproteins[59]. Moreover the postprandial hypertriglyceridaemia was associated with changes to serum PON-1, and this were consistent with a reduced antioxidant potential of HDL[48].

Modifications to PON1 could contribute to increased risk of vascular disease associated with postprandial lipaemia, particularly in diabetic patients, who had increased oxidative stress, are already deficient in serum PON1[60] and this goes parallel to diabetes duration[52].

Type 2 diabetes is a major risk factor for the development of CAD and premature atherosclerosis[61] and in its many forms could truly be a disease that results from an interaction among diet, lifestyle and genetics background of the individual[62]. Delayed clearance of post-prandial triglyceride-rich lipoproteins and their remnants is an important characteristic of the diabetic dyslipidaemia and is linked to the generation of accelerated atherosclerosis. In fact, a recent report has demonstrated that high levels of TRL predict coronary events in patients with CAD, independent of traditional coronary risk factors[44]. The underlying mechanisms may involve increased generation of oxidative stress leading to endothelial dysfunction[63]. Small, dense LDL and remnant particles are especially susceptible to oxidative modification and those are frequently observed lipid abnormalities in type 2 diabetes. The post-prandial reductions in HDL-C and PON1 activity in patients with type 2 diabetes indicating a decrease in the protection of lipoproteins against oxidation. These potentially deleterious effects are partially reversed by the peroxisome proliferator-activated receptor (PPAR)-γ agonist rosiglitazone, which increased fasting PON1 activity, decreased fasting plasma peroxides and attenuated the post-prandial fall in PON1 activity[64]. Also, rosiglitazone improves insulin sensitivity and glycaemic control, stimulates reverse cholesterol transport and reduces inflammation in type 2 diabetes[65].

CONCLUSIONS AND FUTURE PROSPECTS

Currently available experimental studies have provided strong support for the association between delayed remnant removal and premature atherosclerosis. These seems to be especially applicable to patients with normal LDL levels but high triglycerides and insulin resistance. Also, have been demonstrated PON1 ability to protect against atherosclerosis by hydrolyzing specific derivatives of oxidized cholesterol and/or phospholipids in oxidized LDL and in atherosclerotic lesions. PON1 is sensitive to changes occurring during the postprandial phase and significant advances have been made in understanding the basic biochemical function of PON1 and the discovery of possible modulators of its activity.

Therefore, the regulation of plasma PON1, including transcriptional, translational, association with certain HDL particles, kinetics and metabolic fate of these plasma particles, may be complex and influenced by dietary components, age and gender[66].

More careful and extensive examinations will be required to fully elucidate the role of PONs in the progression of atherosclerotic process in diabetes mellitus.

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