



## Paraoxonase 1 in Type 2 Diabetes Mellitus - A Review

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### ABSTRACT

Paraoxonase 1 (PON 1) belongs to a family which consists of three members....PON1, PON2, PON3. PON 1 is the most studied enzyme of the three. Role of PON1 in preventing Ischemic heart disease has been proved by several studies. PON 1 exhibits antioxidant properties and thereby helps in combating the oxidative stress in Type 2 Diabetes Mellitus. The enzyme level goes down in Type 2 DM. This article discuss the chemistry, Functions, factors influencing in detail with special emphasis on PON1 role in Type 2 Diabetes Mellitus.

**Keywords:** Diabetes Millitus, LDL, Paraoxonase.

### INTRODUCTION

Studies across the globe show evidence of the prevention of LDL and HDL oxidation by Paraoxonase 1 (PON 1).<sup>1</sup> In fact, previous studies have shown that PON1 is able to hydrolyze preformed lipid hydroperoxides and to delay or inhibit the initiation of oxidation induced by metal ions on lipoproteins.<sup>2,3</sup>

Studies show that HDL reduces lipid peroxidation by an enzyme action and that antioxidant enzyme is PON 1.<sup>4</sup> Experiments have shown that PON 1 is closely associated with HDL subspecies that contains apo-A1 and clusterin. Upon centrifugation PON 1 remains with HDL. The serial reviews by Sara Deakin of Paraoxonase underline the importance of HDL for Paraoxonase -1 secretion, stability and activity.<sup>5</sup>

Liver is considered the principal site of PON1 synthesis. In fact there is a study which reviews that PON 1 could be a marker of Liver Function. This study showed that PON1 is completely associated with HDL.<sup>6</sup>

It is also hypothesized that release of PON 1 from the synthesizing cells involves a docking process whereby HDL transiently associate with the cell membrane and removes the peptide from the external membrane.<sup>7</sup>

Among the HDL population the HDL<sup>3</sup> sub fraction, having a major role in Reverse cholesterol transport, is reported to have the maximum PON 1 activity.<sup>8</sup> PON 1 has also been implicated in mediation of cholesterol efflux which is one of the key roles of HDL.<sup>9,10</sup> There is one study from Israel reporting the presence of PON1 in postprandial chylomicrons mediating the removal of atherogenic oxidized plaques.<sup>11</sup>

Further studies show that PON1 is more sequestered from apo A<sub>i</sub> in the interstitial fluid of the sub intimal space than in the serum which hints that PON 1 is active in the interstitial fluid than in the serum. In fact PON 1 is reported to be a more potent antioxidant and stimulant

of macrophage cholesterol efflux when associated with HDL than in lipoprotein deficient serum.<sup>12</sup>

### Biochemistry of Paraoxonase

The molecular mass of Human serum Paraoxonase enzyme is 43-45KD with three carbohydrate chains that constitute 15.8% of its weight.<sup>13</sup> There are two isoforms based on the oxidation states of PON 1, one with all the cysteine residues free and one with a disulfide bond. The highly purified active form is the one with the disulfide bond.<sup>14</sup> PON 1 gene is located in the long arm of chromosome 7.<sup>15</sup> The protein has 355 amino acid. Characterization of rabbit and human PON1 cDNA clones and protein sequence analysis indicated that the mature protein retain their hydrophobic signal sequences, with only the amino terminal methionine residue being removed. There is a high degree of similarity in the structural organization of mouse and human PON1 gene. This high degree of conservation suggests an important metabolic role for PON1 and a large constraint on its evolution.<sup>16,17</sup>

Calcium is required to retain the conformation of the active site. So EDTA sample should not be used in estimation of PON 1 activity.

### Functions of Paraoxonase

PON 1 has organophosphatase, arylesterase activity & Lactonase activities.

Metabolizing Xenobiotics: PON1 hydrolyzes certain organophosphates especially paraoxon, which is the metabolite of the insecticide parathion and the enzyme, received its name from it.<sup>18</sup> PON1 is an esterase capable of hydrolyzing the O-P ester bond in paraoxon. A similar type of bond may exist in lipoprotein associated Phospholipid peroxides, and in cholesteryl ester peroxides. Such a chemical structure in oxidized lipoproteins may serve as a physiopathological substrate for HDL associated PON 1. The ability of PON1 to



hydrolyze toxic peroxides in oxidized lipids of both LDL and HDL can thus reverse potential atherogenic effects. PON1 is reported to efficiently act on not only the lipoprotein – associated peroxides, but also Hydrogen peroxide.<sup>19</sup>

Mackness et al. showed that human PON1 could inhibit LDL oxidation *in vitro*, (prevent formation of oxidized LDL) and protect phospholipids in HDL from oxidation by inactivating LDL-derived oxidized phospholipids:

These actions suggest that PON1 could prevent the accumulation of lipoperoxides in LDL and has a protective role against cardiovascular diseases and atherosclerosis. Hence low PON1 activity could be a detector of Coronary artery diseases. There are studies supporting that PON 1 activity is a better predictor of atherosclerosis risk than are genetic polymorphisms assays alone.<sup>20-23</sup>

PON 1 has unique antioxidant properties. The effect of HDL associated PON1 in decreasing the LDL lipid peroxidation is maintained for longer than that of antioxidant vitamins and could therefore be more protective.<sup>24</sup> PON 1 has a role in metabolism of pharmaceutical drugs also.<sup>25</sup> There are a wide range of serum concentrations and activities of PON1 in humans. It should be noted that in a given population, plasma PON1 activity can vary up to 40 fold, and PON protein levels up to 13 fold are also present within a single PON 1 genotype. It has been suggested that subjects with low PON1 activity may have a greater risk of developing diseases in which oxidative damage and lipid peroxidation are involved, compared to subjects with high PON1 activity.<sup>26</sup>

### Factors Influencing Paraoxonase Activity

#### Age

PON 1 protection effect towards LDL peroxidation has shown to be decreasing with age. This decline in PON1 activity could be related to development of oxidative stress conditions with aging. This decrease in activity is shown to be due also to diminished SH content in PON 1.<sup>27,28</sup>

#### Gender

A study from the National University of Singapore reports that the genetic heterogeneity in humans would obscure any gender effects on PON1 activity. Very few studies prove a marginal increase in PON 1 activity among females.<sup>29</sup>

#### Alcohol

Serum PON 1 activity was significantly decreased in alcoholic patients when compared with controls as per Judith Marsillach et al.<sup>30</sup>

#### Smoking

Smoking is also implicated in reduced PON1 activity due to modifications of the Free Thiol groups in the enzymes.

On quitting smoking it takes two –three months for the enzyme to get back to its normal activity.<sup>31-33</sup>

#### Diet

After intake of a fatty meal, by healthy men serum PON1 activity decreased by 27% for up to 8 hours but returned to normal values by 12 hours. Replacement of dietary saturated fat with trans fat was found to reduce PON1 activity by 6%.<sup>34,35</sup> PON 1 undergoes inactivation by oxidative stress and its activity is preserved by dietary antioxidants.<sup>36</sup> A Cholesterol rich diet decreases serum PON1 activity in wild type rabbits.<sup>37</sup> On the contrary consumption of pomegranate juice<sup>38,39</sup> as well as Vitamin C and E<sup>40</sup>, increased serum PON1 levels. Reduced serum PON1 Activity was observed in post prandial state after consumption of degraded cooking oil.<sup>41,42</sup>

#### Drugs

Oral Hypoglycemic drugs are found to have antioxidant effect. This could be one of the confounding factors in estimation of Total antioxidant status. Gemfibrozil is believed to have beneficial effect on PON1 activity.<sup>43</sup>

#### Paraoxonase 1 in Diabetes

Diabetes is associated with oxidative damage. The increased serum oxidative stress in DM could be the result of glycation and glycol-oxidation of LDL by glucose.<sup>44</sup> The higher levels of lipid peroxidation products in plasma of diabetic patients could be related to a higher susceptibility of their plasma lipoproteins to oxidation and/or to a decrease of plasma antioxidant defenses.<sup>45,46</sup> Paraoxonase, an antioxidant enzyme is being used up in balancing the oxidative stress in diabetes mellitus and hence a decrease of PON1 activity has been observed in diabetic patients .A study from Paris reports that PON1 activity decreased even in early stages of Diabetes Mellitus<sup>47</sup> Likewise a study in Pakistan also reports decreased PON1 activity in diabetics.<sup>48</sup> Further, in a study among North West Indian Punjabi diabetics also there was decreased PON 1 activity in comparison to healthy population.<sup>49</sup>

Glycation of PON1 impairs its enzyme activity.<sup>50</sup> Hedrick and coworkers have reported *in vitro*, direct glycation of purified Paraoxonase enzyme protein by incubation with 25mmol/l glucose caused a 40% decrease in enzymatic activity and they also documented a similar decrease in Type 2 Diabetic patients. The Glycated PON 1 could not inhibit monocyte adhesion to human aortic endothelial cells *in vitro*. They have also reported Coronary artery disease in these Type 2 diabetics compared to non diabetics. Moreover, previous studies have shown the susceptibility of HDL to atherogenic modifications induced *in vitro*, such as glycation and homocysteinylolation.<sup>51</sup> Reduced PON1 activity in type 2 diabetic patients was found to be associated with a significant increase in the risk of cardiovascular disease (CVD) which leads to the conclusion that PON1 activity could be a predictor of CVD in type 2 diabetes.<sup>52,53</sup> Ikeda



et al from Japan have shown low PON 1 activity in diabetes patients with macro vascular complications in comparison with those without any complication.<sup>54</sup> The decrease of PON1 activity in diabetic patients and the lowered HDL protective action against membrane peroxidation could contribute to acceleration of arteriosclerosis in type 1 & 2 diabetes mellitus.<sup>55</sup>

Several mechanisms have been postulated for this decrease in Activity: According to the study of Mira Rosenblat et al<sup>55</sup> this is due to the dissociation of PON1 from HDL as a free, unstable PON1. Another study gives an explanation at the secretory level. It appears that large sized HDL complexes favor PON1 secretion. In clinical syndromes like Diabetes the HDL size tends to diminish.<sup>56</sup> Further the fact that free cholesterol addition to reconstituted HDL influences its capacity to promote PON1 release may also have clinical implications.<sup>55</sup> Un esterified cholesterol partitions into the outer lipid layer in native lipoprotein complexes, and it can adversely affect the lipoprotein function if present in elevated concentrations. Pathological changes due to un esterified cholesterol have been reported for diabetic patients. These factors together set the stage for the progression of associated complications of Diabetes Mellitus.

Decrease in Paraoxonase activity creates susceptibility to diabetes complications as reported by a study from Hungary.<sup>56</sup> In a study at South Karnataka, Renuka Suvarna *et al* reports that the levels of HDL-C and PON 1 activity are decreased significantly in diabetic patients with complications in comparison to diabetics without complications.<sup>57</sup> Both Paraoxonase and arylesterase activities of PON1 were lower in diabetic foot patients from a Romanian study compared to healthy control subjects<sup>58</sup> Low Paraoxonase activity in type 2 diabetes mellitus complicated by retinopathy have also been reported.<sup>59</sup>

Bharti Mackness et al assayed PON1 activity as well as PON1 concentration in controls and type 2 diabetic patients and found that though the activity of the enzyme varied, the concentration remained the same.<sup>60</sup> Further the same groups have reported that Gene polymorphism had no relation to decrease of PON 1 activity among a South Wales population.<sup>61</sup>

The PON1 concentration was not different between the patients with diabetes and the controls, but their specific activity assayed showed difference as reported in a study from Japan.<sup>62</sup> Another study from Prague revealed that PON1 activity was decreased in type 1 and type 2 diabetic patients compared to non-diabetic control subjects although the concentration of serum PON 1 were not significantly different between the 2 groups.<sup>63</sup> Reports of a study from a South Chennai population also prove that PON1 decreases with progression of Type 2 Diabetes mellitus.<sup>64</sup>

## CONCLUSION

Paraoxonase 1 proves to be a miracle enzyme with all its functions. Natural methods to increase the levels of this antioxidant surely ought to be beneficial for maintaining the quality of lifestyle of Diabetic subjects.

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