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Role of oxidant-antioxidant enzymes in managing the cardiovascular risks in nephrotic syndrome patients

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ABSTRACT

Increased reactive oxygen species (ROS) in nephrotic syndrome (NS) are involved in the oxidation of membrane proteins, lipoproteins and several receptor molecules ultimately leading to their functional deficit. It is involved in the pathogenesis of dyslipidemia in NS and also increases the oxidation of LDL (oxLDL), which is an important risk factor in thrombus generation and atherosclerosis. Myeloperoxidase (MPO) is an early predictor of myocardial infarction and adverse cardiac events in patients with chest pain. MPO can also foresee the recurrent acute coronary syndrome (ACS) and myocardial infarction in patients. 'MPO oxidized LDL' also induces ROS production, lipid accumulation and reduces the antioxidant response in macrophages, however in an augmented way by using different pathways and might be more atherogenic. Paraoxonase 1 (PON1) prevents the oxidative modification of serum lipoproteins, which is one of the crucial steps in the initiation of atherogenesis. PON1 also contributes to the anti-atherogenic effect of HDL-c. Adult NS patients have increased lipid hydroxide levels and significantly decreased PON1 activity and total sulfhydryl levels when compared to healthy controls. While the increased risk of cardiovascular disease in NS patients is well documented, the exact etiology still remains controversial. This prevents the development of a specific treatment modality for the same. MPO as well as PON1 were found as important markers for the management of cardiovascular risk in NS patients. Estimation of these enzymes can therefore be performed in routine clinical practice as prognostic markers, owing to its ease of estimation and cost effectiveness.

Implication for health policy/practice/research/medical education:
Cardiovascular risk in NS is a serious matter of concern and preventive measures are to be taken from the initial stages of NS. In addition to dyslipidemia [with increased non-high density lipoprotein cholesterol and lipoprotein (a)] enhanced oxidative stress also should be considered as therapeutic targets. MPO as well as PON1 were found as important cardiac risk markers as well as prognostic markers to assess the severity of NS. Estimation of these enzymes can therefore be performed in routine clinical practice as prognostic markers, owing to its ease of estimation and cost effectiveness. Even after effective steroid therapy to normalize the symptoms of NS, dyslipidemia and oxidative stress persist in adult NS patients, which demands more attention to the impending cardiovascular risk in them.

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Introduction

Nephrotic syndrome (NS), a distinct combination of clinical and laboratory findings, is characterized by edema, hyperlipidemia, hypoalbuminemia and proteinuria. It accounts for significant morbidity which includes complications like infections, thrombotic events, hypertension, cardio-vascular diseases, side effects of corticosteroid therapy, low-quality of life and thereby early mortality. NS is further subdivided into discrete categories based on renal histopathology. Due to this, a

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considerable delay and uncertainty is present in deciding the prognostic and therapeutic means for these patients. Mostly, a generalized immunosuppressive therapy is provided without properly understanding the underlying pathogenesis. National Vital Statistics 2020 reports NS and associated kidney diseases as the tenth leading cause of deaths in the United States. Overt proteinuria, intermittent hyperlipidemia and cumulative steroid therapy resulted in thromboembolism in many patients which is therefore one of the major complications of NS. The incidence of thromboembolism is 25% in adults and 3% in children. This varies depending on the age, type of NS (primary or secondary) and the underlying renal histopathology of the patients (1). Even though venous thromboembolism is more common when compared to arterial thromboembolism, augmented atherogenesis is observed in a substantial number of NS patients.

Several studies have reported increased oxidative stress in NS. The normal homeostatic process in a cell includes the production of reactive oxygen species (ROS), however, excess generation of which causes cell damage. There are many enzymatic, non-enzymatic and dietary anti-oxidants which are involved in ROS scavenging. The value of the cumulative effect of endogenous and dietary antioxidants in the body is called total antioxidant status (TAS). Additionally, ROS are considered to be possible mediators of renal injury in experimental nephrosis. Reactive oxygen species are involved in the oxidation of membrane proteins, lipoproteins and several receptor molecules ultimately leading to their functional deficit. It is involved in the pathogenesis of dyslipidemia and increases the oxidation of LDL-c (oxLDL), which is an important risk factor in thrombus generation and atherosclerosis. Reactive oxygen species causes structural modifications of the transcription factors which alters the expression of key regulatory proteins of many metabolic pathways. The major parameters of oxidative stress studied in NS are vitamin C, vitamin E, superoxide dismutase (SOD), glutathione, glutathione peroxidase, and catalase, malondialdehyde (MDA) and also TAS. In this context, the role of myeloperoxidase (MPO) (a major oxidative enzyme) and PON (an anti-oxidative enzyme) will be discussed which is less researched in NS but established as cardiovascular risk factors.

Methods

This is a narrative review which non-systematically briefs about the selected articles on MPO or PON in NS. Article search was performed from data inception till July 2021, on platforms like Web of Science, PubMed, Scopus and Clinical Trial Registry, using the terms – "Myeloperoxidase AND nephrotic syndrome", "Paraoxonase AND nephrotic syndrome", "Oxidative stress AND nephrotic syndrome", "Cardiovascular risk AND nephrotic syndrome" and "Dyslipidemia AND nephrotic syndrome".

Results and Discussion

MPO and cardiovascular risk in NS

MPO, the intense green iron-containing enzyme contributing to innate host defence, is secreted predominantly from the azurophilic granules of leukocytes and some subtypes of macrophages and monocytes. Synthesis of MPO begins at the promyelocyte stage and ends at the myelocyte stage of neutrophil development. MPO gene is located on the long arm of chromosome number 17. The initial translation product of the MPO gene is proteolytically cleaved and glycosylated at the amino terminal to form apopro-MPO. Insertion of a haem moiety and removal of 125 amino acids from the N-terminal and further conformational changes and dimerization leads to the formation of 150 kD protein of MPO.

Mechanism of innate host defence by MPO; during phagocytosis, neutrophils get activated and MPO is released from their azurophilic granules, which in turn gets incorporated into the phagosome. Further assembly of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex produces unstable superoxide radicals converting into hydrogen peroxide due to the action of SOD. MPO along with its co-substrate hydrogen peroxide forms potent oxidants which exert its action by chlorinating [via generation of hypochlorite (HOCl)] and nitrating the phenolic compounds (e.g., conversion of free and protein bound tyrosine to 3-chlorotyrosine and 3-nitrotyrosine) and the final product possesses immense bactericidal and virucidal activities.

Mechanism of harmful oxidation by MPO; during chronic inflammatory conditions, continuous activation of neutrophils releases MPO into the tissue spaces, causing tissue damage through its oxidant by-products (2). Since MPO is a highly cationic glycoprotein with an iso-electric point 11, it easily binds to the electronegative surfaces of endothelium, lipoproteins, and proteoglycans. The following are the mechanisms of release of MPO subsequently resulting in the formation of reactive species 1. Inflammation inducing recruitment and activation of WBCs (MPO in circulation) 2. LDL-c particles in intima initiate the influx of monocytes which further mature into macrophage expressing MPO (in intima) 3. Neutrophils are attracted to bind with damaged endothelium and transcytosis to sub-endothelial matrix which again releases MPO (in sub-endothelial space).

MPO in cardiovascular diseases

MPO, an oxidative enzyme, the peroxidase activity of which forms a major first line of defence against

pathogens. However, accumulating evidence reports the role of MPO in the development of atherosclerosis. Association between MPO and cardiovascular diseases have been reported by many epidemiological studies conducted in population with established atherosclerosis and others with acute presentation of chest pain. Most of them have reported an increased baseline concentration of MPO when compared to controls and it correlated well with the extent and severity of atherosclerosis. However, few studies could not find an independent association between MPO and cardiovascular disease.

MPO in healthy subjects; various clinical studies have reported that, even in healthy elderly individuals with high level of high-density lipoprotein cholesterol (HDL-c) and low levels of low-density lipoprotein cholesterol (LDL-c) and C-reactive protein, increased MPO independently associated with the development of heart failure (HF). Best examples available are the EPIC-Norfolk (European Prospective Investigation into Cancer-Norfolk) study and another study by Tang et al (3) wherein they proved the increased cardiovascular risk in healthy people in the highest quartile of MPO, even after adjusting the conventional risk factors. Furthermore, MPO deficiency protected the patients from cardiovascular risk, but there was an increased risk of severe infections and chronic inflammations.

MPO in stable coronary artery disease
MPO levels were found to be significantly higher in stable coronary artery disease (CAD) patients and this predicted the risk of progression to MI and cardiovascular mortality. Reduced MPO expression due to a promoter polymorphism in the MPO gene was associated with a drop in the incidence of clinical events in CAD patients (4). Another study even predicted a threshold value of MPO, above which there was a significant risk of death or recurrent ischemic events in 30 days [odds ratio, 1.7 (95% confidence interval, 1.2–2.3); $P = 0.003$] (5).

MPO in acute coronary syndrome (ACS): MPO is an early predictor of MI and adverse cardiac events in patients with chest pain. MPO can also foresee the recurrent ACS and MI in patients after one episode of ACS, independent of troponin T levels (6). MPO showed an independent pattern in blood levels by peaking early (far before the rise of troponin T) and decreasing over time after an acute MI. Moreover, it did not correlate with troponin or neutrophil count. Brennan et al (7) reported a correlation between MPO and troponin T and suggested that MPO levels were predictive of acute MI. Patients in the highest MPO quartile experienced a 3.9-fold higher risk of having an MI. Baldus et al (6) proposed that patients with increased MPO (>350 μg/L) are at a greater risk of reporting a cardiac event in the subsequent 30 days with an adjusted

hazard ratio of 1.8 ($P = 0.013$) or in six months with an adjusted hazard ratio of 2.1 ($P = 0.006$). Thus, increased MPO could be a predictor of future cardiac events.

MPO in heart failure
Chronic systolic HF patients demonstrated elevated MPO levels which correlated with B-type natriuretic peptide levels independent of ischemic burden. It was proposed that the cytotoxic products generated by MPO are involved in ventricular remodelling and endothelial dysfunction. Since the plasma levels of MPO are predictive of long-term clinical outcomes in HF patients, it can be included in the HF screening profile to increase the specificity (8).

Pathogenesis of cardiovascular risk of MPO
Lipid oxidation by MPO
MPO is involved in the oxidation and modification of LDL-c into a more atherogenic form since it has a strong affinity to the Apo B100 moiety of LDL-c when compared to other lipoproteins. Hazen et al (9) reported a six-fold increase in 3-chlorotyrosine level in atherosclerotic lesion when compared to the normal aortic tissue thus confirming the presence of MPO in the lesions. LDL-c is oxidized in the circulation and in the subendothelial space after its migration from the plasma. Similar to oxLDL, 'MPO oxidized LDL-c' also induces ROS production, lipid accumulation and reduces the antioxidant response in macrophages, but in an augmented way by using different pathways and might be more atherogenic. MPO oxidized LDL-c can activate both monocytes and endothelial cells which secrete tumour necrosis factor α and interleukin (IL)-8 respectively. Interleukin 8 activates endothelial cells and monocytes/macrophages leading to ROS production, MPO release and thus the synthesis of new MPO oxidized LDL-c. Fibrinolysis is also disturbed by MPO oxidized LDL-c by a pathway different from plasminogen activator inhibitor and tissue plasminogen (2). LDL-c is converted into a high uptake form after being exposed to MPO-generated activated monocytes followed by lipid peroxidation and protein nitration. This is avidly taken up by macrophages via the macrophage scavenger receptor CD36.

Lipid carbamylation by MPO
Uremia and MPO independently induce carbamylation of lipoproteins (a post-translational modification) leading to its structural and functional change. Uremia, secondary to chronic renal disease, creates an optimum environment to initiate protein carbamylation. Carbamylated lipoproteins are more atherogenic and it was found that carbamylated LDL (cLDL) can induce monocyte adhesion to the endothelium through vascular cell adhesion molecule (VCAM) or intercellular adhesion molecule, and it forms

a ligand for scavenger receptor SRA-1. Thiocyanate ($SCN-$) and H_2O_2 serves as physiological co-substrates for protein carbamylation via MPO. Numerous findings support the role of carbamylation in atherosclerosis, like;

- Co-localization of cLDL antibody and MPO in human atheroma
- Conversion of LDL-c into a high-uptake form for SRA-1 by MPO even at low levels of carbamylation
- Systemic levels of carbamylated proteins independently predict the cardiovascular risk
- Marked elevation in atherosclerosis and aortic tissue content of protein bound homo citrulline (carbamoyl-lysine) in MPO-transgenic mice (10).

Impairment of HDL-c function by MPO: MPO oxidizes the apo A1 of HDL-c which prevents HDL-c maturation thereby generating dysfunctional HDL-c. Oxidized apo A1 impairs the cellular cholesterol efflux by ATP binding cassette A1 and furthermore, it was unable to activate lecithin cholesterol acyl transferase which rapidly converts free cholesterol to cholesteryl ester. There was a 16-fold increase in cardiovascular risk for individuals in the highest tertile of apo A-I 3-chlorotyrosine content when compared to those in the lowest tertile (11). MPO-dependent modification of HDL-c increases the affinity of HDL-c for MPO and also protects MPO from cellular uptake and therefore maintains the enzymatic activity. MPO also oxidizes Apo A2 and SRB-1 receptors.

MPO reduces the bioavailability of nitric oxide

Nitric oxide (NO) as a powerful vasodilator has a critical role in regulating the vascular tone. It prevents binding of cells in the circulation to the vascular endothelium and also inhibits the proliferation of smooth muscle cells. MPO reduces the bioavailability of NO by the following mechanisms.

1. MPO serving as a catalytic sink for NO;
2. Scavenging of NO by MPO-derived reactive substances;
3. HOCl converts arginine to chlorinated arginine which inhibits all forms of NO synthase;
4. HOCl induces uncoupling of endothelial NOS, thereby converting it into a superoxide-producing enzyme.

MPO and plaque vulnerability

MPO activates metalloproteinases and weakens the fibrous cap of the plaque. MPO activity was rich in ruptured plaques when compared to the macrophages in fatty streaks. Thus, MPO might be responsible for turning late stage atherosclerosis into acute cardiovascular events.

MPO in nephrotic syndrome

Proteinuria, hypoalbuminemia and hyperlipidemia are the cardinal manifestations of NS. Chronic inflammation is also reported by the overexpression of pro-inflammatory cytokines during the acute stages of NS. IL-18, IL-13, IL-2 and IL-4 were found elevated during the relapse stage when compared to remission in different studies. Studies have shown that elevated MPO oxidised LDL-c can induce cytokine production, which in turn can convert monocyte to macrophages resulting in MPO release (2). The pathogenic mechanism underlying the presence of dyslipidemia in NS involves; 1) metabolic changes of key regulatory enzymes involved in lipid metabolism 2) structural change of receptor proteins 3) varied expression of cytokines and 4) proteinuria. The elevated LDL-c owing to dyslipidemia, is oxidised in the presence of MPO converting it into a highly atherogenic molecule. Apart from collecting cholesterol from peripheral tissues via ABC A1 mediated pathway, HDL-c acquires a significant amount of cholesterol from albumin which is also involved in free cholesterol transport from peripheral tissues to HDL-c. Hypoalbuminemia in NS causes a diminished enrichment of cholesterol in HDL-c (12). It was found that hyperlipidemia is more dependent on albumin excretion rather than hepatic synthesis of albumin. It was also claimed that reduced oncotic pressure triggers lipoprotein synthesis in NS. All these mechanisms ultimately result in a dyslipidemia picture. The action of MPO oxidizes the LDL-c and makes HDL-c dysfunctional, which adds to the atherogenic effect.

MPO in NS is a lesser researched topic, even though, studies have been conducted on Henoch-Schonlein purpura (a disease condition related to IgA nephropathy and most often presented with NS) and systemic lupus erythematosus. The only one article found during literature search reported that NS patients had increased MPO activity and oxidative stress when compared with healthy subjects. Furthermore, in patients with NS there was a positive correlation between the levels of proteinuria, serum MDA and MPO activity (13).

Figure 1 depicts a summary of the role of MPO in increasing the cardiovascular risk in NS patients.

Paraoxonase and cardiovascular risk in NS

PON [EC 3.1.8.1] is a group of antioxidant enzymes existing in three forms (PON1, PON2 and PON3) and the whole gene family is located on the long arm of chromosome 7. They are a conservative group of enzymes with high substrate specificity. Their enzymatic actions include various types of hydrolytic activities like lactonase activity, arylesterase activity and organophosphate activity. The PON1 exhibits all three aforesaid activities while PON2 and PON3 display only lactonase activity.

PON1 is a 45 kD glycoprotein containing a total of 355 amino acids, in which there are three cysteine residues.
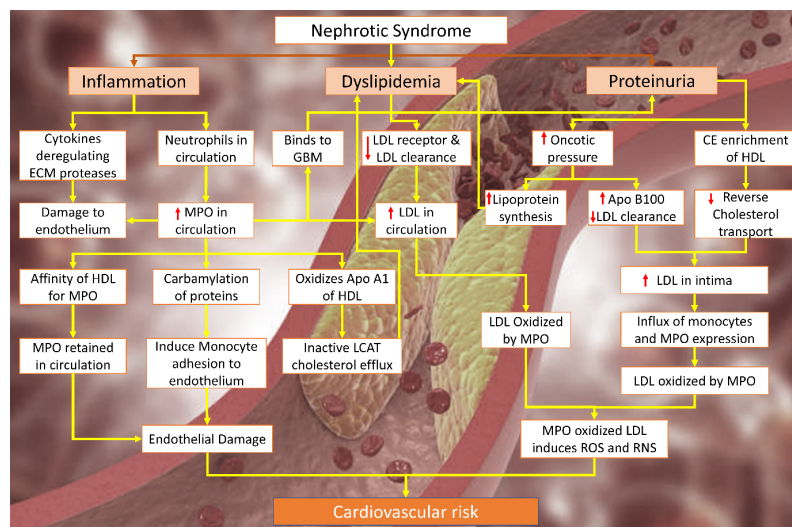
Figure 1. Inflammation, Dyslipidemia and Proteinuria are the important clinical features of NS. Inflammation releases cytokines which deregulate ECM proteases leading to damage of endothelium. Inflammation increases neutrophils in circulation which results in elevation of MPO in circulation. MPO can oxidise and damage the endothelium and also it oxidises the dyslipidemia driven excess LDL-c in the circulation. MPO increases affinity of HDL-c for MPO thereby persisting in the circulation and causes carbamylation of proteins leading to further endothelial damage. MPO also oxidises Apo A1 of HDL-c thereby inactivating lecithin cholesterol acyl transferase and contributes to dyslipidemia. MPO can also bind to glomerular basement membrane and damages it to cause proteinuria. Proteinuria increases lipoprotein synthesis and elevates LDL-c cholesterol in intima which again causes the influx of MPO. Thus, ROS and reactive nitrogen species produced by MPO oxidized LDL-c and endothelial damage caused by MPO can lead to the development of cardiovascular risk in nephrotic syndrome patients.

The residue at position 284 has a free sulfhydryl group, which is responsible for the anti-oxidant property of the enzyme. Human PON1 is synthesized in the liver and secreted into the circulation where it associates with the HDL-c cholesterol. Apo-A1 of HDL-c helps in stabilizing PON1 and enhancing the lactonase activity of the enzyme.

Paraoxonase 1 and cardiovascular risk
The main physiological functions of PON1 are listed as follows:
- It prevents the oxidation of LDL-c
- It hydrolyses the oxidized phospholipids and hydroxides of cholesteryl linoleate present in ox-LDL molecules.
- It prevents the accumulation of ox-LDL, reduces the conversion of monocytes into macrophages and increases the cholesterol efflux from macrophages through HDL-c thus decreasing the formation of atherosclerotic plaques.
- It protects the phospholipids in HDL-c from oxidation.

PON1 prevents the oxidative modification of serum lipoproteins, which is one of the crucial steps in the initiation of atherogenesis, and thus it certainly has an unavoidable role in the prevention of atherosclerosis. Deakin et al (14) confirmed the protective properties of PON1 in preventing oxidation by adding PON1 forms to VLDL-c and the final transformer molecules were more resistant to copper-induced oxidation. Gocmen et al (15) found the decreased PON1 activity and increased lipid peroxidation in patients with CAD in Turkey. They suggested that overproduction of lipid peroxidation by-products might be responsible for the inactivation of PON1. PON1 also contributes to the anti-atherogenic effect of HDL-c. Under certain pathological conditions, PON1 was found separated from HDL-c in the circulation. This results in:
- Existence of PON1 as a free glycoprotein which is less biologically active
- Decreased anti-atherogenic effect of HDL-cholesterol

This explains the greater probability of cardiovascular diseases in such conditions. Mansour et al (16) showed that hyperlipidemia with diminished anti-oxidant potential due to reduced PON1 in newly diagnosed Nephrotic syndrome patients predisposes the possibility of atherosclerosis. Mackness et al (17) have demonstrated that PON1 hydrolyse the platelet activating factor, which is otherwise involved in the transformation of monocytes to macrophages. PON1 knockout mouse, after a period of three months, showed a 50% increase in fatty streaks of the blood vessels when compared to controls. HDL-c from PON1 knockout mice was unable to prevent LDL-c oxidation in a co-culture model (in mice liver cells and HepG2 Human Hepatoma cell lines) simulating the

artery wall. Through a meta-analysis study, Wheeler et al (18) reported a weak association between PON1 polymorphism and CAD. Mackness et al (19) showed that the activity of PON1 enzyme is a more important factor in CAD than its genotype and suggested to measure the enzyme activity rather than the genetic polymorphisms. Gur et al (20) demonstrated that both PON and arylesterase activities significantly decreased with increase in the extent of stenosis in CAD patients. There are many studies supporting this finding. Gocmen et al (15) found a higher level of PON activity of PON1 in females than males with CAD. Research indicates that PON1 activity in the blood is inversely proportional to the risk of atherosclerosis and other related diseases.

Paraoxonase 1 in nephrotic syndrome

Since NS is associated with increased risk of CAD and being PON1 as an increased risk factor for atherosclerosis, it is relevant to study PON1 in NS patients.

Idiopathic NS without histopathological evidence

Soyoral et al (21) reported that adult NS patients have increased lipid hydroxide levels and significantly decreased PON1 activity and total sulfhydryl levels when compared to healthy controls. In addition, a positive correlation between serum lipid hydroperoxide and proteinuria levels in NS patients was found. In accordance with the previous reports, there was no correlation between PON1 and HDL-c which infers that enhanced oxidative stress resulted in reduced activity of PON1 in NS patients. PON1 can destroy the active lipids in oxidized LDL-c of arterial wall thereby suppressing the induction of inflammation. The key antioxidant element of the plasma is the free sulfhydryl groups of proteins and they are associated with the degree of CAD. Reduced PON1 activity changes the redox status of free sulfhydryl groups, thus promoting ROS-induced inhibition of PON1. On reading together, reduced PON1 activity and sulfhydryl levels with increased lipid hydroperoxides levels play a significant role in atherosclerosis progression in NS. A decreased activity of serum and urinary PON1 was observed in patients treated for steroid sensitive nephrotic syndrome (22). According to Gullulu et al (22), arylesterase activity, the main component of the enzyme, was normal in glomerulonephritis patients while PON1 activity was decreased. This suggests an uninterrupted synthesis of PON1 enzyme but with a functional deficit which could be due to cytokines or lipid peroxidation. Low PON1 activity, initially suppresses the antioxidant system resulting in increased oxidation of apo-B-containing lipoproteins, thereby accelerating the CAD. Besides, it also causes renal damage and deterioration of renal function leading to increased morbidity and mortality in glomerulonephritis

patients. Patil et al reported that pediatric NS cases had atherosclerotic dyslipidemia and decreased PON1 activity. This may lead to increased oxidation of LDL-c thereby accelerating the process of atherosclerosis. They also reported that steroids cannot decrease the oxidative stress or lipid abnormalities in NS and therefore suggested a modification in the current treatment modality to prevent the formation of oxidized lipids. PON1 activity increased during remission after glucocorticoid therapy, but it was not as high as in the control group (23). Kniazewska et al (23) found that the PON1 activity in patients who were already treated for INS was comparable with the PON1 activity in the control group. Hashemi et al (16) also evaluated the PON1 activity in NS children and proposed that it can act as a biomarker to assess the efficiency of NS treatment. Several studies reported a reduced serum PON1 activity in pediatric NS patients (22,24,25).

Focal segmental glomerulosclerosis (FSGS)

The reduced PON1 activity in children caused by a PON1 gene polymorphism may promote FSGS. Frishberg et al (24) proved that L allele homozygosity of PON1 in Arab children is a risk factor for developing FSGS and it has the worst prognosis. In addition, they suggested that PON1 activity is entirely substrate dependent and the critical determinant is the ability of PON1 to hydrolyse lipid peroxides rather than its absolute level. L or B allele carriers have greater concentrations of PON1, but not activity, than M or A allele carriers.

Membranoproliferative glomerulonephritis (MPGN)

Bilge et al (25) proposed that homozygosity for the A allele of PON1 seems to be a risk factor for MPGN and it may also be associated to the poor prognosis of the disease. They also suggested Q192R polymorphism as a risk factor for developing MPGN.

All the aforementioned studies have invariably reported a decrease in PON1 activity, or PON1 protein or PON1 expression in various types of NS. Then again fewer studies are available regarding the association of PON1 with other established cardiovascular risk factors in NS patients.

Conclusion

While the increased risk of cardiovascular disease in NS patients is well documented, the exact etiology still remains controversial. This prevents the development of a specific treatment modality for the same. MPO as well as PON1 were found as important cardiac risk markers for the management of NS patients. Estimation of these enzymes can therefore be performed in routine clinical practice as prognostic markers, owing to its ease of estimation and cost effectiveness.

Authors' contribution

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