ejpmr, 2018,5(5), 593-599

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

MYELOPEROXIDASE AS A PREDICTIVE FACTOR FOR SYSTEMIC DISEASES: A MINI-REVIEW

Kwatra S Kanwaldeep[1], Sharma Puneet[2*] and Kumar Deepak[3]

[1]Senior Lecturer, Department of Pedodontics, Swami Devidyal Dental College, Barwala
[2]Senior Lecturer, Department of Periodontics, Jan Nayak Ch. Devi Lal Dental College, Sirsa.
[3]Senior Lecturer, Department of Pedodontics, Jan Nayak Ch. Devi Lal Dental College, Sirsa.

Corresponding Author: Dr. Sharma Puneet

Senior Lecturer, Department of Periodontics, Jan Nayak Ch. Devi Lal Dental College, Sirsa.

Article Received on 18/03/2018 **Article Revised on 09/04/2018** **Article Accepted on 30/04/2018**

ABSTRACT

Myeloperoxidase (MPO) is an enzyme stored in azurophilic granules of polymorphonuclear neutrophils and macrophages and released into extracellular fluid in the setting of inflammatory process. The observation that myeloperoxidase is involved in oxidative stress and inflammation has been a leading factor to study myeloperoxidase as a possible marker of plaque instability and a useful clinical tool in the evaluation of patients with coronary heart disease. The purpose of this review is to provide an overview of the pathophysiological, analytical, and clinical characteristics of MPO and to summarize the state of art about the possible clinical use of MPO as a marker for diagnosis and risk stratification of patients with acute coronary syndrome (ACS).

KEYWORDS: Myeloperoxidase(MPO), Atherosclerosis(ACS), biomarker.

INTRODUCTION

Myeloperoxidase (MPO) is the most abundant proinflammatory enzyme stored in the azurophilic granules of neutrophilic granulocytes, accounting for approximately 5% of their dry mass.[1] It catalyzes the formation of hypochlorous acid from hydrogen peroxide, generates other highly reactive molecules such as tyrosyl radicals, and cross-links proteins.[2] Recently, MPO has been found to be implicated in a multitude of diseases, including atherosclerosis[3], myocardial infarction[4,5], atrial fibrillation[6], multiple sclerosis[7], Alzheimer's disease[8], lung cancer[9], and transplant rejection.[10] Recently, myeloperoxidase has been proposed as a useful risk marker and diagnostic tool in acute coronary syndromes and in patients admitted to emergency room for chest pain.[11]

Synthesis of Myeloperoxidase

MPO is the product of a single gene, located on long arm of chromosome 17(17q23.1). Thus the mature enzyme is synthesized from a single polypeptide product spanning 14kb. It has 12 exons & 11 introns.[12] The MPO gene encodes for a primary translational product (MW 80 KDa), which following proteolytic removal of the 41 aminoacid signal peptide, undergoes N-linked glycosylation with the incorporation of mannose-rich side-chains to generate 90 KDa enzymatically inactive apo pro MPO. With the insertion of a heme, apo pro MPO is converted to the enzymatically active pro MPO. This conversion to pro MPO occurs in endoplasmic reticulum. The exact mechanism of conversion of Pro MPO to mature MPO is not clearly understood.[13] Mature MPO is covalently bound tetrameric complex of two glycosylated 467 amino acid heavy (alpha) chains (MW 59 64 KDa) and two glycosylated 112 amino acid light (beta) chains (MW 14 KDa) with total MW about 150 KDa.[14] MPO is a strongly basic protein with isoelectric point>10 and thus binds avidly to negatively charged complex. Myeloperoxidase synthesis occurs during myeloid differentiation in bone marrow and is completed within granulocytes prior to their entry into the circulation. The enzyme is stored within primary granules of neutrophils and monocytes and is not released until leukocyte activation and degranulation.[15]

Protective functions of MPO

Primary physiologic functions of MPO is to kill microorganisms in neutrophils and monocytes and to do this, it forms highly reactive HOCl in phagosomes for it to be responsible for killing. Other normal beneficial function of MPO is its protective role in infectious diseases by the detoxification of microbial toxins such as diphtheria or tetanous toxins. HOCl obtained from MPO also participates in activating neutrophil derived collagenase and gelatinase, both secreted as latent enzymes. At the same time, HOCl inactivates a α1–antitrypsin.

PATHOPHYSIOLOGICAL ROLE OF MYELOPEROXIDASE IN CARDIOVASCULAR DISEASES

Association between MPO and atherosclerosis

MPO, a member of the heme peroxidase superfamily, generates reactive oxygen species and diffuse radical species. It performs a physiological role as a part of the innate system. However, MPO also can apparently exert a deleterious impact on the anterior wall. Immuno-histochemical studies demonstrate the presence of MPO, its oxidant products, and their colonization with macrophages, in human atheroma. Genetic studies support a protective role of MPO deficiency. MPO-deficient individuals have less coronary artery diseases (CAD). In addition, a functional polymorphism in the promoter of the gene, resulting in decreased enzyme expression, was associated with a decreased risk of CAD. Furthermore, systemic levels of MPO and its oxidant products are associated with the prevalence of atherosclerotic disease. Systemic levels of MPO predict the presence and extent of angiographic disease.[3] Moreover, levels predict the risk of clinical events in both subjects presenting with chest pain[5] or acute coronary syndromes.

MPO promotes Atherogenesis via a range of mechanisms

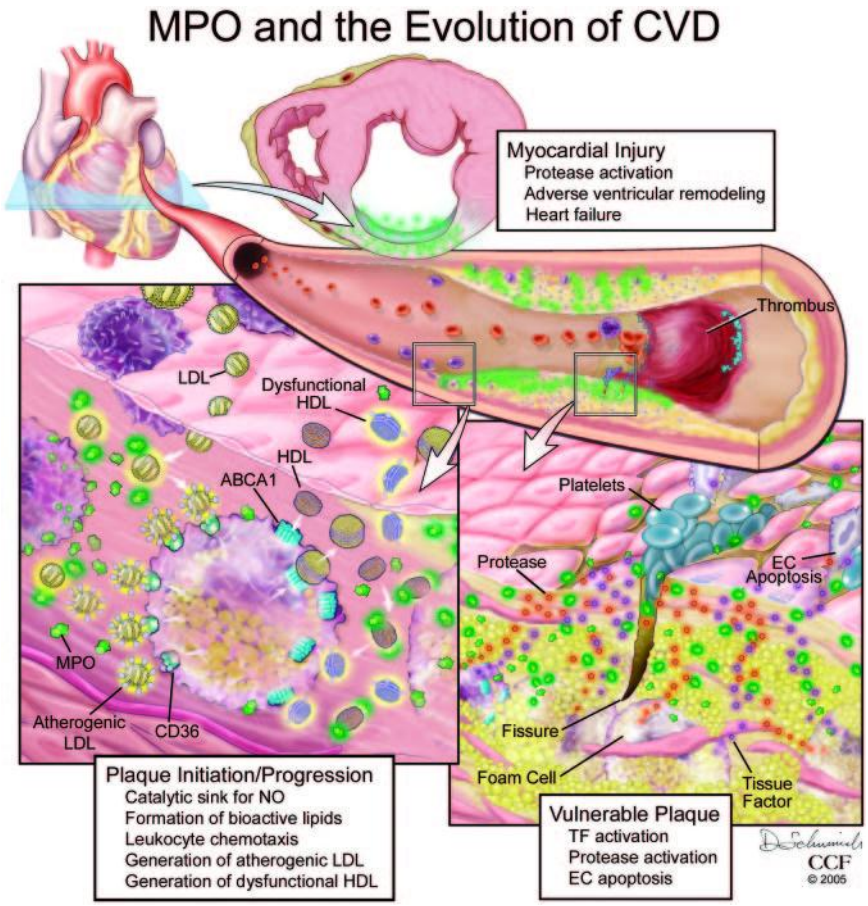
It appears that MPO, through the generation of nitric oxide (NO) derived oxidants, promotes numerous pathological events in the atherogenic cascade. In addition to generating potentially pro-atherogenic species, MPO utilizes the atheroprotective NO as a substrate. These factors have been implicated in the development of endothelial dysfunction, accumulation of foam cells in the arterial wall and the promotion of plaque vulnerability.[16] In particular, substantial evidence suggests that MPO derived oxidants influence the net flux of cellular cholesterol, via both an increase in its cellular uptake and a reduction in its removal.

MPO promotes cellular accumulation of cholesterol

Oxidative modification of low density lipoprotein (LDL) is a key early event in the promotion of atherogenesis. Modification of LDL to a high uptake form allows for its internalization by macrophages, which undergo morphological changes to become foam cell, a major cellular component of the developing plaque. Evidence suggests that MPO-generated reactive nitrogen species convert LDL into high uptake foam, which is readily internalized by macrophages by a scavenger receptor mediated process. In addition to protein modification, MPO rapidly promotes the peroxidation of lipids. These modified lipids become attractive targets for uptake by macrophages and, in addition, promotes the elaboration of proinflammatory factors, including adhesion molecules and chemokines. Furthermore, MPO-generated nitrating species promotes the synthesis of cholesteryl esters and lipid loading of macrophages, resulting in the microscopic appearance of foam cells.

MPO impairs cholesterol efflux role density lipo-proteins

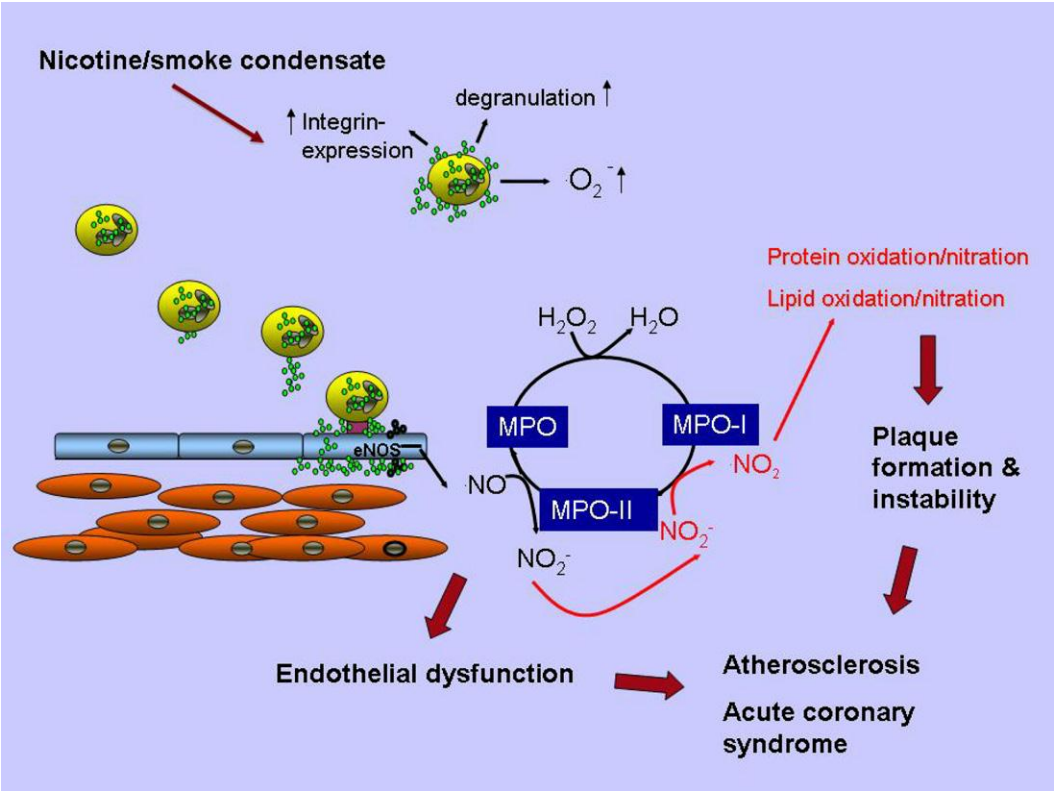
It also appears that MPO promotes the oxidative modification of high density lipoproteins (HDL), influencing its ability to promote cholesterol efflux. Apolipoprotein A-I (apo A-I) modified by MPO-generated HOCl in vitro is less effective at promoting cholesterol efflux and more readily degraded by macrophages.[17] It is possible that this chlorination impedes the interaction between apo A-I and the scavenger receptor SR-BI, which promotes cellular cholesterol flux.[18] It was recently identified apo A-I as a selective target for MPO catalyzed nitration and halogenation in vivo, with accompanying functional impairment in vivo. MPO facilitated modification of either HDL or apo A-I reduced their ability to promote ABCA1 dependent cholesterol efflux from cholesterol-laden macrophages. Serum Apo A-I demonstrated ~100-fold higher levels of nitrotyrosine and chlorotyrosine compared to total serum proteins, and apoA-I isolated from patients with CAD contained increased levels of nitrotyrosine and chlorotyrosine compared to healthy controls.[19] The greatest content of these species was found in apo A-I isolated from human atheroma, suggesting that this oxidative modification occurs preferentially in the arterial wall. In addition, MPO was found to directly associate with both intact HDL and apo A-I, with a specific contact site on the lipoprotein for interaction with MPO noted. These results provide a structural basis for the colocalization noted between epitopes specific for proteins exposed to HOCl and apo A-I within human atheroma.[20]



Scheme illustrating multiple processes throughout the evolution of atherosclerosis in which MPO is implicated.MPO has been linked to events that participate in the initiation and progression of plaque formation including lipid peroxidation, generation of atherogenic lipoproteins and dysfunctional HDL, and catalytic consumption of nitric oxide (NO). MPO may thus contribute to endothelial dysfunction, leukocyte transmigration, and accumulation of foam cells. MPO may participate in ischemic complications of atherosclerosis via activation of protease cascades and promotion of endothelial cell (EC) apoptosis,leading to breakdown of the fibrous cap. Mechanistic links with activation of tissue factor (TF) and the coagulation cascade are also reported. Studies with MPO knockout mice and models of myocardial infarction have supported a role for the heme protein in progression of myocardial necrosis to adverse ventricular remodeling and heart failure via its ability to activate proteases and promote degradation of the extracellular matrix.

Association of Myeloperoxidase and Smoking-dependent Vascular Inflammation

It has also been shown that the levels of myeloperoxidase (MPO), a neutrophil-derived enzyme, are significantly elevated in smokers compared with nonsmokers.[21] Even previous smokers were indicative of higher circulating levels of MPO than never-smokers. Upon activation and degranulation, MPO is released into phagocytic vacuoles, into the extracellular space, and, in the case of PMN activation within the circulatory system, MPO can also be released into the blood stream. An important prerequisite for the effect of MPO on vascular inflammatory diseases is its ability to oxidize NO to nitrite, leading to a reduced vascular NO bioavailability. MPO, which is highly cationic, is able to interact with the anionic-charged heparansulfate-glycosaminoglycans of the surface of endothelial cells. Upon binding to endothelial cells, catalytically active MPO reaches the subendothelial layer by transcytosis, and sequestrates in the layer between endothelial cells and smooth muscle cells.[22] Considering the antiinflammatory properties of endothelial-derived NO, as evidenced by relaxation of smooth muscle cells, inhibition of smooth muscle cell proliferation, adhesion molecule expression, as well asplatelet aggregation, MPO likely affects homeostasis and antiinflammatory properties of the vessel wall.



Activation of Polymorphonuclear Neutrophils by Nicotine/Smoke condensate and its consequences in the vessel wall. MPO = myeloperoxidase; MPO-I = myeloperoxidase compound I; MPO-II = myeloperoxidase compound II; NO = nitric oxide; H_2O_2 = hydrogen peroxide; NO_2^- = nitrite; NO_2 = nitrogen dioxide; O_2^- = superoxide.

Association of Myeloperoxidase and Chaga's Disease

In vitro and in vivo studies with experimental models have shown that infection by Trypanosoma cruzi (T. cruzi) elicits both proinflammatory responses and reactive oxygen species (ROS) that appear essential for control of the parasite. Reactive oxidants are generated as a consequence of an "oxidative burst" of phagocytic cells (e.g., macrophages andneutrophils) activated by T. cruzi infection. NADPH oxidase, activated in all phagocytic cells, produces superoxide. Besides ROS, activated macrophages produce nitric oxide via the inflammatory activation of inducible nitric oxide synthase in response to T. cruzi infection. Nitric oxide produced in abundance by iNOS, directly reacts with O to form peroxynitrite and peroxynitrous acid, which have been shown to kill T. cruzi. The activated expression and activity of MPO is positively correlated with increased protein oxidation and nitration in seropositive subjects and MPO is the major cause of collateral damage through protein modification in humans with Chagas' disease.

Association of Myeloperoxidase and Carcinogenesis

A number of studies have implicated MPO in the development of malignancies. MPO system in stimulated neutrophils can catalyze the conversion of certain procarcinogens to carcinogenic form and in this way; it may contribute to the development of malignancies.[23]

Association of Myeloperoxidase and Alzheimer 's disease

MPO protein has been detected in microglia adjacent to senile plaques in the cerebral cortex of patients with Alzheimer's disease.[24] Apo E which colocalizes with amyloid B in senile plaques of the patients with Alzheimer's disease is highly susceptible to oxidation by the MPO system. In addition MPO is shown to be involved in pathogenesis of brain infarction and Parkinson's disease.

Association of Myeloperoxidase and Renal Injury

MPO has been implicated in the pathogenesis of renal disease. A role of MPO in the glomerular injury observed in rapidly progressive glomerulonephritis in humans was suggested by the presence of MPO in the glomeruli of most patients with this condition in association with an increase in the titer of MPO specific, antineutrophil cytoplasmic antibody (MPO –ANCA).[25]

Association of Myeloperoxidase and Multiple sclerosis

MPO has been detected in microglial macrophages in and around the lesions in multiple sclerosis suggesting its involvement in multiple sclerosis.[26]

Association of Myeloperoxidase and Other diseases

Myeloperoxidase activity in leukocytes is significantly reduced in NIDDM patients, systemic vasculitis like Wegener's granulomatosis, microscopic polyangitis, and

Churg Strauss syndrome inflammatory bowel disease, and MPO is also risk stratification of major adverse cardiovascular events (MACE) in patients with Peripheral arterial diseases.[27,28,29]

CLINICAL EVIDENCES FOR MPO AS A BIOMARKER OF CHRONIC INFLAMMATION IN VARIOUS SYSTEMIC DISEASES

A number of epidemiological studies have been reported that address the association of MPO with Cardio Vascular Diseases (CVD) and markers of atherosclerosis, chest pain in a wide range of patients populations.

Established Atherosclerosis

The first epidemiological report assessing the association between MPO and CVD was a case-control study published by Zhang and coworkers in 2001. Using an enzyme assay, Zhang et al showed that blood and leukocyte MPO activity were higher in patients with CAD than angiographically verified normal controls, and that this increased activity was significantly associated with presence of CAD (odds ratio, 11.9; 95% confidence interval (CI), 5.5–25.5).[3]

Meuwese et al in the EPIC- (European prospective investigation into cancer and nutrition-) Norfolk prospective population study, have evaluated the association of MPO levels with the risk of future CAD in apparently healthy individuals.[30] In a case-control study in 680 patients, 382 patients with stable CAD and 194 controls with normal coronary angiograms, MPO was higher in patients with CAD compared to controls.[31] Biasucci et al first observed that circulating neutrophils in patients with acute myocardial infarction (AMI) and unstable angina (UA) have a low MPO content, and therefore high MPO levels in the circulation, as compared with those with chronic stable angina and variant angina.[32] Stefanescu and coworkers found no independent association between MPO and all-cause mortality in 382 patients with stable CAD during 3.5 years of follow-up.[33] In contrast to the above-mentioned studies, all of which had reported significant associations between MPO and CVD, 1 case-control study in HIV patients showed no significant independent association of MPO with CVD events.[35]

ACUTE PRESENTATION WITH CHEST PAIN

In a cross-sectional study by Esporcatte et al., an MPO concentration higher than 100 pmol/L had a diagnostic sensitivity of 92% and specificity of 40% as a marker for identifying patients with an acute myocardial infarction (AMI) presenting with acute chest pain and non–ST elevation electrocardiogram findings. In this study, AMI was defined by troponin I concentration of >1.0 µg/L.[30] In contrast, a study by Apple et al. found no additional diagnostic value of MPO (99th percentile) compared to troponin I in patients with clinically diagnosed acute coronary syndrome (ACS).[36]

MPO Promotes Myocardial Dysfunction and Abnormal Ventricular Remodeling After Myocardial Infarction

Inflammation continues to play a central role in the pathological events that occur after rupture of the fibrous cap and luminal occlusion. Leukocyte migration to peri-necrotic zones and reperfusion of an occluded artery exposes the ischemic territory to further inflammatory and oxidative stresses. It remains to be determined whether the increase in MPO activity that accompanies models of ischemia reperfusion injury contributes to the resulting tissue damage and infarct extension. However, recent studies have demonstrated that MPO contributes to adverse ventricular remodeling after myocardial infarction.[31] Using a chronic coronary artery ligation model, MPO knockout mice demonstrated a marked reduction in leukocyte infiltration and left ventricular dilatation, associated with delayed myocardial rupture and preservation of systolic function. [37]This benefit was associated with reductions in the oxidative inactivation of plasminogen activator inhibitor-1 and subsequent tissue plasmin activity. By promoting the development of abnormal ventricular geometry, MPO may thus play a role in the susceptibility to and progression of heart failure after myocardial infarction.

Development of MPO-Targeted Therapeutic Interventions

The many links between MPO and proatherogenic activities that might participate in many stages of cardiovascular disease has stimulated considerable interest in the development of therapeutic strategies to inhibit MPO catalysis. One potential difficulty with development of an MPO inhibitor is the concern that such a drug might have adverse effects related to impairment in the role of enzymes in innate host defenses. It should be noted, however, that only subjects with profound (near total or complete) deficiencies in MPO appear to have a significant increase in risk for infections, and only in the setting of concomitant factors that predispose to immunosuppression, such as diabetes. Moreover, whereas levels of MPO per leukocyte appear relatively stable in a given subject over time, there appears to be a wide range of MPO levels per leukocyte within populations of normal subjects, and thus a large potential therapeutic range may exist while maintaining MPO levels still within a functional range for host defenses. Finally, MPO stores within leukocytes may be relatively protected from inhibition because the enzyme is stored in a crystalline form within granules and only released into the phagolysosome compartment and extracellular space upon leukocyte activation. As a result, through use of more polar inhibitors, it may be possible to target extracellular MPO, such as enzyme trapped within the subendothelial space, and not to significantly impede leukocyte killing of phagocytosed pathogens. The development of MPO inhibitors awaits further investigation.

CONCLUSION

MPO is a marker of inflammation and oxidative stress that has been consistently demonstrated to be elevated in patients with ACS. However, the data so far available are relatively few; therefore, more studies are requested to precisely define the role of MPO. In particular all studies involving MPO assessment have used different methods, thus a standardization effort is needed. Furthermore, increased MPO is not likely to be specific for cardiac diseases, as activation of neutrophils and macrophages can occur in any infectious, inflammatory, or infiltrative process, therefore, more studies should address and clarify these points.

REFERENCES

1. Schultz J, Kaminker K. Myeloperoxidase of the leucocyte of normal human blood. I. Content and localization. Arch Biochem Biophys, 1962; 96: 465–467.
2. Heinecke JW. Mechanisms of oxidative damage by myeloperoxidase in atherosclerosis and other inflammatory disorders. J Lab Clin Med, 1999; 133: 321–325.
3. Zhang R, Brennan ML, Fu X, Aviles RJ, Pearce GL, et al. Association between myeloperoxidase levels and risk of coronary artery disease. JAMA, 2001; 286: 2136–2142.
4. Nahrendorf M, Sosnovik D, Chen JW, Panizzi P, Figueiredo JL, et al. Activatable magnetic resonance imaging agent reports myeloperoxidase activity in healing infarcts and noninvasively detects the antiinflammatory effects of atorvastatin on ischemia-reperfusion injury. Circulation, 2008; 117: 1153–1160.
5. Brennan ML, Penn MS, Van Lente F, Nambi V, Shishehbor MH, et al. Prognostic value of myeloperoxidase in patients with chest pain. N Engl J Med, 2003; 349: 1595–1604.
6. Rudolph V, Andrie RP, Rudolph TK, Friedrichs K, Klinke A, et al. Myeloperoxidase acts as a profibrotic mediator of atrial fibrillation. Nat Med, 2010; 16: 470–474.
7. Gray E, Thomas TL, Betmouni S, Scolding N, Love S. Elevated myeloperoxidase activity in white matter in multiple sclerosis. Neurosci Lett, 2008; 444: 195–198.
8. Reynolds WF, Rhees J, Maciejewski D, Paladino T, Sieburg H, et al. Myeloperoxidase polymorphism is associated with gender specific risk for Alzheimer's disease. Exp Neurol, 1999; 155: 31–41.
9. Feyler A, Voho A, Bouchardy C, Kuokkanen K, Dayer P, et al. Point: myeloperoxidase -463G –. A polymorphism and lung cancer risk. Cancer Epidemiol Biomarkers Prev, 2002; 11: 1550-1554.
10. Swirski FK, Wildgruber M, Ueno T, Figueiredo JL, Panizzi P, et al. Myeloperoxidase-rich Ly-6C+ myeloid cells infiltrate allografts and contribute to an imaging signature of organ rejection in mice. J Clin Invest, 2010; 120: 2627–2634.
11. Baldus S, Heeschen C, Meinertz T. Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. Circulation, 2003; 108: 1440-1445.
12. Chevner I, Tregouet DA, Castel MS, et al. Myeloperoxidase genetic polymorphism modulate human neutrophil enzyme activity: genetic determinant for atherosclerosis? Atherosclerosis, 2006; 188(1): 150 - 154.
13. Hansson M, Olsson I, Nauseef WM. Biosynthesis, processing & sorting of human myeloperoxidase. Arch Biochem Biophys, 2006; 445(2): 214-224.
14. Olsen RL, Little C. Studies on the subunits of human myeloperoxidase. Biochem J, 1984; 222(3): 701-709.
15. Soehnlein O, Zernecke A, Weber C. Neutrophils launch monocyte extravasation by release of granule proteins. Thromb Haemost, 2009; 102(2): 198-205.
16. Hazen SL. Myeloperoxidase and plaque vulnerability. Arterioscler Thronb Vasc Biol, 2004; 24: 1143-1146.
17. Panzenbocck U, Raitmayer S, Reicher H. Effects of reagent and enzymatically generated hypochlorite on physicochemical and metabolic properties of high density lipoproteins. J Biol Chem, 1997; 272: 29711-29720.
18. Marsche G, Hammer A, Oskolkova O. Hypochlorite-modified high density lipoprotein, a high affinity ligand to scavenger receptor class B, type I, impairs high density lipoprotein-dependent selective lipid uptake and reverse cholesterol transport. J Biol Chem, 2002; 277: 32172-32179.
19. Zheng L, Nukuna B, Brennan ML. Apolipoprotein A-I is a selective target for myeloperoxidase-catalysed oxidation and functional impairement in subjects with cardiovascular disease. J Clin Invest, 2004; 114: 529-541.
20. Bergt C, Pennathur S, Fu X. The myeloperoxidase product hypochlorous acid oxidizes HDL in the human artery walland impairs ABCA1- dependent cholesterol transport. Proc Natl Acad Sci USA, 2004; 101: 13032-13037.
21. Lavi S, Prasad A, Yang EH, Mathew V, Simari RD, Rihal CS et al. Smoking is associated with epicardial coronary endothelial dysfunction and elevated white blood cell count in patients with chest pain and early coronary artery disease. Circulation, 2007; 115: 2621–2627
22. Baldus S, Eiserich JP, Mani A, Castro L, Figueroa M, Chumley P et al. Endothelial transcytosis of myeloperoxidase confers specificity to vascular ECM proteins as targets of tyrosine nitration. J Clin Invest, 2001; 108: 1759–1770.
23. Suruta Y, Subrhamanyam VV, Marshall W, et al. Peroxidase mediated irreversible binding of arylamine carcinogens to DNA in intact polymorphonuclear leukocytes activated by a tumor promoter. Chem Biol Interact, 1985; 53(1-2): 25 -35.
24. Maki RA, Tyurin VA, Lyon RC, et al. Aberrant expression of myeloperoxidase in astrocytes

promotes phospholipid oxidation and memory deficits in a mouse model of Alzheimer's disease. J Biol Chem, 2009; 284(5): 3158-3169.
25. Poh-Yi Gan, Steinmetz OM, Tan DSY, et al. Th17 Cells Promote Autoimmune AntiMyeloperoxidase Glomerulonephritis. JASN, 2010; 21(6): 925-931.
26. Gray E, Thomas TL, Betmouni S, Scolding N, Love S. Elevated myeloperoxidase activity in white matter in multiple sclerosis. Neurosci Lett, 2008; 444(2): 195-198.
27. Wanda F, Reynolds, Coen A, et al. G/A myeloperoxidase promoter polymorphism is associated with clinical manifestations and the course of disease in MPO-ANCAAssociated Vasculitis. Clinical Immunol 2002; 103(2): 154-160.
28. Hoskin, TS. Neutrophil activation in inflammatory bowel disease http://hdl.handle.net/10523/2060 accessed on date 07/03/2013.
29. Haslacher H, Helmuth, Perkmann T, et al. Plasma myeloperoxidase level and peripheral arterial disease. Eur J Clin Invest, 2012; 42(5): 463–469.
30. Meuwese MC, Stroes ESG, Hazen SL et al. Serum myeloperoxidase levels are associated with the future risk of coronary artery disease in apparently healthy individuals. The EPIC-Norfolk prospective population study. Journal of the American College of Cardiology, 2007; 50(2): 159–165.
31. Ndrepepa G, Braun S, Mehilli J, von Beckerath N, Schomig A, Kastrati A. Myeloperoxidase level in patients with stable coronary artery disease and acute coronary syndromes. Eur J Clin Invest, 2008; 38: 90–6.
32. Biasucci LM, D'Onofrio G, Liuzzo G. Intracellular neutrophil myeloperoxidase is reduced in unstable angina and acute myocardial infarction, but its reduction is not relatedtoischemia,Journal of the American College of Cardiology, 1996; 27(3): 611–616.
33. Stefanescu A, Braun S, Ndrepepa G, Koppara T, Pavaci H, Mehilli J et al. Prognostic value of plasma myeloperoxidase concentration in patients with stable coronary artery disease. Am Heart J, 2008; 155: 356–60.
34. El Bejjani D, Hazen SL, Mackay W, Glass NE, Hulgan T, Tungsiripat M et al. Higher plasma myeloperoxidase levels are not associated with an increased risk for cardiovascular events in HIV infected adults. HIV Clin Trials, 2008; 9: 207–11.
35. Esporcatte R, Rey HC, Rangel FO, Rocha RM, Mendonca Filho HT, Dohmann HF et al. Predictive value of myeloperoxidase to identify high risk patients admitted to the hospital with acute chest pain. Arq Bras Cardiol, 2007; 89: 377–84.
36. Askari AT, Brennan ML, Zhou X, Drinko J, Morehead A, Thomas JD, Topol EJ, Hazen SL, Penn MS. Myeloperoxidase and plasminogen activator inhibitor 1 play a central role in ventricular remodeling after myocardial infarction. J Exp Med, 2003; 197: 615– 624.