Revista MedEs
Revista Científica Estudiantil de Matanzas
MedEst. 2024: Vol.4 No.1 ISSN: 2789-7567 RNPS: 2524

REVIEW ARTICLE

The enzyme mieloperoxidasa like important biomarcador in the medical services of health

La enzima mieloperoxidasa como importante biomarcador en los servicios médicos de salud

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Received: 01/09/2023

Accepted: 23/11/2023

How to cite this article: Ruiz Reyes D, Enríquez Pérez E, Herrero Díaz A. The enzyme mieloperoxidasa like important biomarcador in the medical services of health. Med. Es. [Internet]. 2024 [cited access date]; 4(1). Available in: https://revmedest.sld.cu/index.php/medest/article/view/195

ABSTRACT

Introduction: the technological advances in the environment of the microscopic medicine have allowed going into in the molecular operation of the cellular processes, where they play a fundamental paper the enzymatic proteins. The mieloperoxidasa is a hemoprotein that is stored mainly in the granules azurofilos of the neutrophils human polimorfonucleares, monocytes and macrophages.

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ISSN: 2789-7567 RNPS: 2524

Objective: to characterize the enzyme mieloperoxidasa like important biomarcador for the diagnosis of illnesses in the medical services of health.

Methodological design: he/she was carried out a bibliographical revision understood in the period of July to August of the 2023, where original articles, case reports and systematic revisions of access were consulted opened up in academic publications revised for even, of the last 5 years. The databases of SciELO were revised, Regmed, Dialnet, Mayoclinic, among others.

Development: the activity of the MPO is used, a while ago, as a marker that indicates the presence of inflammatory processes. It plays a preponderant list in the fisiopatologia of the COVID-19. High levels are in several illnesses, among those that he/she is distinguished the cancer. The MPO, it could contribute to the defense mechanism against infectious agents, as well as to favor the pathogenesis from the illness when causing damage to the adjacent fabrics.

Conclusions: the activity of the enzyme mieloperoxidasa was significant as marker of cardiovascular risk, cancer, inflammatory processes and he/she has activity predictor with regard to the vascular damage. Also it has served as reference as marker presage of graveness of the COVID-19.

Keywords: Benefits, Enzyme, Mieloperoxidasa, Services Of Health

RESUMEN

Introducción: los avances tecnológicos en el ámbito de la medicina microscópica han permitido adentrarse en el funcionamiento molecular de los procesos celulares, donde juegan un papel fundamental las proteínas enzimáticas. La mieloperoxidasa es una hemoproteína que se encuentra almacenada principalmente en los gránulos azurófilos de los neutrófilos polimorfonucleares humanos, monocitos y macrófagos.

Objetivo: caracterizar la enzima mieloperoxidasa como importante biomarcador para el diagnóstico de enfermedades en los servicios médicos de salud.

Diseño Metodológico: se realizó una revisión bibliográfica comprendida en el período de julio a agosto del 2023, donde se consultaron artículos originales, reportes de caso y revisiones sistemáticas de acceso abierto en publicaciones académicas revisadas por pares, de los últimos 5 años. Se revisaron las bases de datos de SciELO, Regmed, Dialnet, Mayoclinic, entre otras.

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Desarrollo: la actividad de la MPO se emplea, hace tiempo, como un marcador que indica la presencia de procesos inflamatorios. Juega un rol preponderante en la fisiopatología de la COVID-19. Elevados niveles se encuentran en varias enfermedades, entre las que se distingue el cáncer. La MPO, podría contribuir al mecanismo de defensa contra agentes infecciosos, como también favorecer la patogénesis de la enfermedad al provocar daño a los tejidos adyacentes.

Conclusiones: la actividad de la enzima mieloperoxidasa resultó significativa como marcador de riesgo cardiovascular, cáncer, procesos inflamatorios y tiene actividad predictora con respecto al daño vascular. Asimismo ha servido de referencia como marcador pronóstico de gravedad de la COVID-19.

Palabras clave: Biomedicina; Enzima; Mieloperoxidasa; Salud

INTRODUCTION

Technological advances in the field of microscopic medicine have allowed the scientific community to delve into the molecular functioning of cellular processes, where enzymatic proteins play a fundamental role. (1)

Enzymes are complex proteins that produce a specific chemical change in living organisms thanks to their function as catalysts, which allows them to accelerate the speed of the chemical reaction by decreasing the activation energy. (1)

In their globular structure, they have an active site or center, a place to which the substrate binds to be transformed into a product, while the enzyme does not undergo any change. This catalytic activity is affected by: changes in temperature, denaturation due to changes in pH, substrate concentration, enzyme concentration and the presence of inhibitors (competitive or not). (1)

Peroxidases are a type of enzymes widely distributed throughout the phylogenetic scale. They catalyze bisubstrate reactions of a redox nature, using peroxide as an oxidant, and a second substrate with reducing characteristics that is oxidized by the peroxide. (1)

Members of the Chordata peroxidase protein subfamily include: myeloperoxidase (MPO), eosinophil peroxidase (EPO), lactoperoxidase (LPO), and thyroid peroxidase (TPO). Each catalyzes physiologically important reactions and shares critical structural features but is expressed differently, both with respect to intracellular and tissue location. (2)

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Myeloperoxidase is a hemoprotein that is stored mainly in the azurophilic granules of human polymorphonuclear neutrophils, monocytes and macrophages. Catalyzes the conversion of hydrogen peroxide and chloride to hypochlorous acid. It is capable of damaging lipids and lipoproteins, promoting thermogenesis and vascular damage. The decrease in vasodilators such as nitric oxide is also related. (2)

The molecular weight of the enzyme is estimated between 130-150 kDa. The heavy subunits are linked through a simple disulfide bond and a heme prosthetic group is covalently attached to each of them. These subunits are the only ones glycosylated and contain between 2-4 % carbohydrates. The amino acid content is characterized by approximately 1150 residues, which correspond to 573 amino acids in each homodimer. Of them, 466 form the heavy subunit and 107 the light subunit. It is reported that this protein is strongly cationic with an isoelectric point greater than 10 and its optimal pH is 5. (3)

MPO is a lysosomal enzyme that is released in phagocytic vacuoles during cell activation and its degree of activity is directly related to the concentration of neutrophils in the inflamed tissue; forming reactive radicals that cause oxidative damage at the sites of inflammation. Subsequently, MPO is released into the extracellular fluid and the general circulation, so the measurement of this enzymatic activity has been considered a sensitive quantitative marker of chemotaxis and neutrophil infiltration in the inflammatory process, it is also considered as an indication of oxidative stress. (4,5)

Plasma and leukocyte myeloperoxidase activity is related to ischemic heart disease, demonstrated angiographically, and this increase is independent of other risk factors. The incidence of death and myocardial infarction (MI) increased markedly in patients with MPO values >350µg/l, even if they had undetectable levels of troponin T and normal C-reactive protein. MPO can be considered a marker of plaque instability and a good early predictor of risk, as well as the subsequent incidence of cardiovascular processes in patients with Acute Coronary Syndrome (ACS), even in those without evidence of cardiac necrosis. (6)

Since 1968, the action of peroxidases in different immune processes has been known. However, international research focused on these enzymes, especially MPO, has gained momentum since the 1980s. The most notable, complete and informative studies were those by Tobler A and Hinter AN, who delved into the possible implications of oxidative processes in different circumstances. In Latin America, most authors followed the line of research of MPO associated with vascular processes. Such is the case of Correa JG. (8)

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In Cuba, the most recent studies of MPO collect its activity within the framework of the cardiovascular and immune systems. The article written by González Fanjul et al., [6] published in the journal Acta Médica del Centro, indicated that MPO, according to the biological and demographic variables, does not project significant results as a vascular marker.

The same author published an article where, following the line of research of MPO in the cardiovascular system, she established the relationship between said enzyme and the variables overweight, hyperglycemia and male sex in a group of workers. [7]

More recently, a study developed at the Villa Clara University of Medical Sciences determined the activity of said enzyme during COVID-19 infections through a spectrophotometric method as part of a validation method. [8]

Despite the biological importance of all mammalian peroxidases in human physiology, recent studies have been largely limited to that of MPO, with some notable exceptions. Consequently, this review focuses on the known details of human MPO, in order to answer the scientific question: Is the enzyme myeloperoxidase a reliable biomarker for diagnosing diseases in medical health services?

The above is evidently justified in the scientific interest related to the enzyme in question, in addition to the little visibility that medical students give to articles related to such a topic, due to their density or difficulty of acquisition. Therefore, the objective of the present review is: to characterize the myeloperoxidase enzyme as an important biomarker for the diagnosis of diseases in medical health services.

METHODOLOGICAL DESIGN

A bibliographic review was carried out from July to August 2023, where original articles, case reports and open access systematic reviews in peer-reviewed academic publications from the last 5 years were consulted. The databases of SciELO, Regmed, Dialnet, Mayoclinic, among others, were reviewed. In this way, 26 articles were selected, where more than 75 % are from the last 5 years, and through an analysis of the publications, the information of interest was extracted. Search terms included benefits, enzyme, myeloperoxidase, health services, as well as their English translation.

DEVELOPMENT

Gen MPO

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The gene encoding human MPO contains twelve exons and is located on chromosome 17q22. MPO gene expression occurs between the late myeloblast and promyelocyte stages of normal myeloid development and is rapidly turned off as the cells differentiate. Consequently, MPO biosynthesis under normal conditions occurs only in myeloid precursors residing in the bone marrow and not in mature phagocytes in circulation or tissue. (9)

Only one of the three promoter regions identified in human MPO operates in vivo, while all three are operational in murine MPO expression. Many factors exert tight developmental and tissue control of MPO gene expression, both in normal myeloid precursors and in the context of acute leukemias. A comprehensive discussion of MPO gene regulation is beyond the scope of this review, but the importance of the -463GA polymorphism in the MPO promoter deserves mention. (9)

Reports from the Reynolds laboratory first described the existence of the -463G/A polymorphism in the Alu receptor response element in the promoter region of the primate MPO gene, with the -463G allele associated with increased gene expression. PPAR-γ agonists promote increased expression of the MPO gene in macrophages, a response that is blocked by estrogens and statins. (9)

The latest observations provide provocative links between increased MPO expression and macrophage biology in inflammatory diseases such as atherosclerosis, a disease already associated with MPO-dependent lipoprotein modifications and other critical elements in the development of atherosclerosis and neurological diseases. (9)

Additionally, many studies have examined the relationship between the -463GA polymorphism and the risk, either increased or decreased, of a broad spectrum of human diseases, including cystic fibrosis, hypertension, malignancies, inflammatory vasculitis, and neurodegenerative diseases, to name a few. Since many of the disorders of interest are polygenic in origin, the inability to identify clear associations with a polymorphism in a single gene such as MPO has been a challenge. (7,8)

MPO and cardiovascular alterations

MPO activity has long been used as a marker that indicates the presence of inflammatory processes in experimental animal models. There are techniques to determine it in rats and there are references in recent literature to determine it in humans.

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In a study carried out by Ventura et al. [9] it was shown that hypertension, dyslipidemia and acute coronary syndrome are associated with an increase in the activity of myeloperoxidase, which causes lipid peroxidation and contributes to the development of atherosclerosis, because they initiate an inflammatory process in the vascular endothelium.

Adolfo Rubinstein developed an analytical model based on Argentine mortality data and the prevalence of the main cardiovascular risk factors. Hypertension was the most influential factor in both men and women, because the pathogenesis of hypertension is the result of cardiac output and systemic vascular resistance. [10]

All this leads to changes in the thickness of the walls of blood vessels, which affects the increase in peripheral vascular resistance in hypertensive patients and causes ischemia, which is preceded by the accumulation and activation of degranulated neutrophils in the coronary circulation of patients, increasing blood pressure and enzyme levels. [11]

The association of chronic inflammation and insulin resistance states with greater MPO activity and greater oxidative stress (OS), endothelial dysfunction and cardiovascular risk has been described, which may explain the analogy with the results from the research of Galve et al., [12] and González Fanjul et al. [6]

What is the chemical mechanism behind this? Well, the hemoperoxidase family generates a battery of oxidants both for synthetic purposes and for innate immune defense against pathogens. Myeloperoxidase (MPO) is the most promiscuous member of the family and generates powerful oxidant species, including hypochlorous acid (HOCl). [9]

Although HOCl formation is important in the elimination of pathogens, this species is also implicated in host tissue damage and multiple inflammatory diseases. Significant oxidant formation and damage occurs extracellularly as a result of MPO release through phagolysosomal leak, cell lysis, and extracellular trap formation and inappropriate trafficking. [9]

MPO binds strongly to extracellular biomolecules, including polyanionic glycosaminoglycans, proteoglycans, proteins, and DNA. This localizes MPO and subsequent damage, at least in part, to specific sites and species, including extracellular matrix (ECM) components and plasma proteins/lipoproteins. [10]

Biopolymer-bound MPO retains or has enhanced catalytic activity, although evidence for non-catalytic effects is also available. These interactions,

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particularly at cell surfaces and with the ECM/glycocalyx, induce cellular dysfunction and altered gene expression. MPO binds with higher affinity to some damaged components of the ECM, rationalizing its accumulation at sites of inflammation. (11)

MPO-damaged biomolecules and fragments act as chemoattractants and cellular activators, and can modulate gene and protein expression in naïve cells, consistent with an increasing cycle of MPO adhesion, activity, damage, and altered cellular function at leukocyte sites without filtration and activation, with subsequent tissue damage and dysfunction. (11)

On the other hand, hypercholesterolemia as a cardiovascular risk factor did not show significant results with respect to enzymatic activity in the research by González Fanjul et al. (6) However, Galve et al., (12) confirmed that the main developments in lipids are framed in new findings of the control value of LDL cholesterol and non-HDL cholesterol (high-density lipoproteins), which are related to MPO levels.

Cardiovascular diseases (CVD) are the leading cause of death worldwide, and the majority of CVD deaths are related to coronary heart disease (CHD). It is characterized by chronic vascular stenosis and subsequent ischemic injury/target organ damage, mediated mainly by inflammatory remodeling of the arterial wall. (12)

Elevated MPO levels have been associated with increased cardiovascular risk in prediabetic patients. Furthermore, quantification of MPO levels could be especially useful for mortality risk assessment in the first hours after an acute myocardial infarction (AMI). (12)

Endothelial dysfunction is the preatherosclerotic manifestation associated with the invasion of immune cells into the vessel wall and the formation of reactive oxygen species (ROS). It is well documented that MPO is enriched in atherosclerotic plaques and that plasma MPO concentration is a predictor of cardiovascular mortality, after angiography in humans. (13)

The chlorination activity of MPO is thought to be particularly detrimental during CVD, as LDL and HDL are vulnerable to oxidation by HOCl and impair endothelial function through interference with nitric oxide production HOCl also induces endothelial apoptosis.

Pharmacological inhibition of MPO by 4-aminobenzoic acid hydrazide reduces plaque formation in the mouse apolipoprotein E knockout (ApoE -/-) model of atherosclerosis. (13)

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Recently, a new generation of small-molecule MPO inhibitors significantly reduced the size of necrotic nuclei of atherosclerotic lesions in Ldlr −/− mice fed a Western diet. Although the atherosclerotic plaque area remained similar, inhibition of MPO resulted in stabilization of the atherosclerotic plaque in this murine model. (12)

Contradictory to this study is that an increase in atherosclerosis was observed in MPO −/− mice. This may suggest that reactive intermediates generated by MPO could be protective in murine atherosclerosis or, alternatively, in microbial involvement after complete inactivation of MPO, a crucial antimicrobial enzyme. The latter possibility is supported by separate work showing the proatherogenic effects of Porphyromonas gingivalis in mice, rabbits, and pigs. (13)

High serum levels of thiocynate (SCN −) have been shown to improve long-term survival in patients after acute myocardial infarction. Ironically, smokers who are often at risk of developing early cardiovascular disease (CVD) have elevated blood levels of SCN −. Unlike hypochlorous acid, hypothiosian acid can be specifically degraded through thioredoxin reductase, reducing its oxidative capacity in vivo. (14)

In this way, HOSCN may bias the oxidative profile of MPO, thereby reducing oxidative injury of the arterial wall in atherosclerosis. This is consistent with observations in ApoE −/− mice fed a Western diet, which have reduced atherosclerotic plaque size after 8 weeks of NaSCN treatment. (15)

In this study, pro-inflammatory serum IL-6 levels decreased, while IL-10 levels increased with NaSCN treatment, although no effect was observed on monocyte or granulocyte infiltration in atherosclerotic plaque. (16)

Similarly, SCN − supplementation in atherosclerosis-prone Ldlr −/− mice transgenic for human MPO decreased total plaque area with no changes in serum MPO concentrations between SCN−-supplemented and control mice. Together, these studies highlight the therapeutic potential to modulate MPO oxidative activity toward HOSCN production in CHD. (16)

MPO as an inflammatory marker

The participation of MPO has been demonstrated in several lung diseases, including; acute respiratory failure syndrome, bronchopneumonia, asthma, idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease, in which their presence has been confirmed when analyzing markers of oxidant stress, which is the metabolic dysfunction caused by the imbalance between the generation of ROS that overcomes the body's antioxidant mechanisms,

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leading to predisposition to damage and alteration of intracellular homeostasis. MPO has been quantified in bronchoalveolar lavage and plasma, presenting a direct correlation with the presence of other oxidant stress markers. (17)

MPO deficiency is a disorder of oxidative metabolism and one of the most common inherited disorders of phagocytes, occurring with a frequency of 1 in 4000 subjects. MPO forms the basis of the green tint of pus that accumulates in areas of infection. There are studies that suggest that patients with cellular, phagocytic and other primary immunodeficiencies have greater susceptibility to fungal infections, mainly Candida and Aspergillus. (18)

MPO has been indirectly implicated in playing a role in carcinogenesis, through the activation of procarcinogens and genotoxic intermediates. (18,19)

MPO is used as an index of differentiation between lymphoblastic and myeloblastic leukemias, due to the increase in the enzyme in the latter. A significant increase in MPO inversely correlated with hemoglobin concentration was observed in patients with sickleemia, suggesting that polymorphonuclear cells and the complement system are involved in the pathophysiological mechanisms of the disease. (20,21)

Promising metallo-oxidereductases as cancer biomarkers

There is increasing evidence of a link between MPO, inflammation and cancer. It is one of the main components of the so-called neutrophil extracellular traps (NETs). NETs form during neutrophil-specific cell death, characterized by the release of DNA strands bound to histones and 20 other proteins. (22)

On the other hand, ceruloplasmin (CP) is a multifunctional enzyme: it helps transferrin bind to iron, which it oxidizes from Fe2+ to Fe3+, mediating its ferroxidase activity, complemented by other oxidase activity against many aromatic amines and phenols. High concentrations are found in several diseases, among which cancer is distinguished. (22)

Catalase (CAT) is the second most abundant enzymatic activity after superoxide dismutase (SOD) that degrades the levels of ROS associated with various pathological conditions such as cancer. (23)

Another metallo-oxidase is superoxide dismutase (SOD), a family of metallo-isoenzymes that contain copper, zinc, manganese or iron; they catalyze the conversion of the superoxide anion into H2O2 and O2, hence it is considered an antioxidant "sweeper" enzyme. (22,23)

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In addition to the enzymes mentioned above, there is another group of proteins that can mediate infection, inflammation and various other processes such as neoplasia. These include C-reactive protein, α-1 acid glycoprotein, albumin, transferrin, and ceruloplasmin itself, all of which are called acute phase reactants. (22)

Myeloperoxidase in periapical exudate from teeth with asymptomatic apical periodontitis (AAP) and acute apical abscess (AAA)

Several pathological processes have been related to increased MPO activity, which would be associated with an increased risk of oxidative stress, such as in the case of infectious diseases (general or local), inflammatory diseases and ischemia reperfusion. These pathologies include: familial hypercholesterolemia, acute coronary syndrome, atherosclerosis, liver cirrhosis, chronic hepatitis, cystic fibrosis, acute myeloid leukemia, degenerative neurological diseases, among others. (24)

It has been established that MPO activity is directly related to the number of PMNs infiltrated into tissues. For this reason, MPO activity is used in inflammation studies to determine the rate of leukocyte migration and therefore the level of oxidative stress. (24)

In periapical pathologies, an inflammatory process occurs that affects the periradicular tissues of the tooth. This process is regulated by the proteolytic activity of various mediators, including enzymes such as extracellular matrix metalloproteinases (MMPs) and the activity of tissue inhibitors. of metalloproteinases (TIMPs). An imbalance between these elements is related to tissue damage. (24)

MMPs correspond to a broad family of endopeptidases, dependent on zinc and calcium that act at neutral pH and that are expressed by various cell types that include keratinocytes, mesenchymal cells, endothelial cells and leukocytes. Together they are capable of degrading most basement membrane and ECM components. They are classified into 5 subgroups according to their substrate specificity and structure: collagenases (MMP-1, -8 and -13), gelatinases (MMP-2 and -9), stromelysins (MMP-3, -10 and -11), MMPs membrane-associated and other MMPs. (24)

HClO participates in the control of the interaction between TIMPs and MMPs. It produces the oxidative activation of both latent collagenases and gelatinases and the inactivation of TIMPs. This generates a change in the collagenase/anti-collagenase balance, which is considered a very important step in generating damage to the connective tissue. (24)

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The authors state that MPO, in both PAA and AAA, could contribute to the defense mechanism against infectious agents, as well as favor the pathogenesis of the disease by causing damage to adjacent tissues.

Myeloperoxidase as an indicator of oxidative stress in metabolic syndrome

Oxidative stress (OS) is currently proposed as a potential inducer of inflammation, with involvement in the development of chronic pathologies at a systemic level, such as metabolic syndrome (MS). The presence of EO implies an imbalance in redox metabolism resulting from the unrestrained production of reactive oxygen species (ROS) and nitrogen species (RNS). It is known that the overproduction of ROS and ERN at the level of the vascular wall generates endothelial dysfunction, a condition that would increase the risk of developing cardiovascular diseases (CVD). [25]

The prooxidative state triggered by EO can induce insulin resistance by causing the phosphorylation of insulin receptors and an increase in the levels of proinflammatory cytokines, both conditions that are expressed in MS. [3] It has also been postulated that the excessive formation of reactive species would directly impact insulin action, modifying antioxidant enzymatic mechanisms such as superoxide dismutase (SOD). The SOD enzyme catalyzes the decomposition of harmful oxidants, neutralizing their toxicity and preventing their concentrations from becoming pathological; in this way, EO would condition the dysfunction of the endothelium. [25]

In the continuous search for new pro-oxidant markers that allow identifying the determinants of MS, the enzyme myeloperoxidase (MPO) becomes important. Excessive MPO activity can cause tissue damage through the production of oxidants and thus generate reactive lipid and protein species. Recent studies have shown that exposure of low-density lipoproteins to activated leukocytes generates nitrogen and halogenated species through MPO, which facilitate lipid peroxidation, protein nitration, and conversion to proatherogenic forms of LDL in the vascular wall. Furthermore, MPO intervenes in the production of dysfunctional high-density lipoproteins (HDL), converting its anti-inflammatory properties into pro-inflammatory ones. [25]

Likewise, pro-inflammatory and pro-oxidative states have been related to myocardial damage and endothelial deterioration, which shows the importance of the implementation of oxidative biomarkers such as MPO in asymptomatic stages of MS. This enzyme could define cardiovascular risk and would be an indicative test for said pathology. [25]

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MPO and COVID-19

COVID-19 is a disease caused by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), declared a pandemic in March 2020, spreading rapidly throughout the world and easily spreading. It has had an unfavorable impact on people's health, causing serious respiratory illnesses, great associated distress and other complications. (26)

Neutrophil activation was correlated with 17 genes associated with neutrophil extracellular traps (NETs) in COVID-19 patients. If NETs are not properly regulated, they can spread inflammation and microvascular thrombosis even in the lungs of patients with acute respiratory distress syndrome. Elevated levels of two serum markers of neutrophil extracellular traps (NETs), myeloperoxidase DNA (MPO) and citrullinated histone, were found in the serum of COVID-19 patients. These NETs are responsible for the initiation and accretion of thrombotic events in arteries, veins and, particularly pertinent to COVID-19, the microvasculature, where thrombotic disease can occur. It also causes damage to the end organs of the lungs, heart, kidneys and other organs. (26)

As can be seen, myeloperoxidase plays a predominant role in the pathophysiology of COVID-19. Thus, in the Department of Biomedical Research of the University Of Medical Sciences Of Villa Clara, a spectrophotometric method is applied to determine the activity of myeloperoxidase; so that reliable results are guaranteed.

CONCLUSIONS

The activity of the myeloperoxidase enzyme was significant as a marker of cardiovascular risk, in neoplastic diseases, inflammatory processes and has predictive activity with respect to vascular damage. It has also served as a reference as a prognostic marker for the severity of COVID-19.

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STATEMENT OF AUTHORSHIP

DRR: Methodology, Visualization, Writing – original draft and Writing: review and editing.

ERP: Conceptualization, Research and Writing – original draft.

AHD: Research, Methodology and Resources.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

FINANCING

The authors did not receive funding for the development of this article.