The Role of Malondialdehyde (MDA) and Ferric Reducing Antioxidant Power (FRAP) in Patients with Hypertension

Roshan Alam¹, Haseeb Ahsan², Saba Khan¹

¹Department of Biochemistry, Integral Institute of Medical Sciences and Research, Integral University, Lucknow, India
²Department of Biochemistry, Faculty of Dentistry, Jamia Millia Islamia, New Delhi, India

Oxidative stress contributes to the pathogenesis of hypertension and studies have shown that hypertension is associated with an increase in oxidative stress. Reactive oxygen species (ROS) lead to hypertension and antioxidants may be beneficial for its prevention. The main cause of oxidative stress in hypertension is endothelial dysfunction due to the malfunctions in the vasodilator systems, specifically the molecular mechanism of ROS and nitric oxide (NO). The level of malondialdehyde (MDA), a biomarker of lipid peroxidation and oxidative stress, is found to be higher in hypertension patients. Total antioxidant capacity (TAC), which has a strong relationship with blood pressure, is determined through the ferric reducing antioxidant power (FRAP). The aim of the review article is to elucidate the role of MDA and FRAP in hypertension.

Keywords: oxidative stress, hypertension, blood pressure, oxidative damage, malondialdehyde, FRAP

Introduction

A chronic medical condition, known as hypertension or arterial hypertension, causes high blood pressure in the arteries. The systolic and diastolic blood pressure, which corresponds to the maximum and minimum readings of the two measurements, are used to express blood pressure. The left ventricle is constricted at the systolic pressure, and most relaxed just before the next contraction during the diastolic pressure. Based on the Eighth Joint National Committee (JNC 8) recommendations, hypertension in adults is defined as the blood pressure that is higher than 140/90 mmHg.¹ Meanwhile, based on the Seventh Joint National Committee (JNC 7), blood pressure of 120/80 mmHg is considered normal. In addition, JNC 7 classifies hypertension to prehypertension, primary (essential) hypertension and secondary hypertension (Table 1).² Primary hypertension accounts for 90-95% of high blood pressure without an underlying cause.³ The other 5-10% classified as secondary hypertension, which is hypertension with a known cause, such as aortic or kidney artery constriction, chronic renal disease, or an endocrine disorder due to catecholamines, aldosterone, or cortisol.

Genetic and environmental factors are responsible for hypertension.⁴⁵ Similarly, other factors such as depression,
stress, lack of exercise, and obesity can all contribute to high blood pressure. It is less obvious how other variables, such as caffeine (coffee) intake and vitamin D deficiency may affect the mean arterial pressure.

Insulin resistance and obesity (metabolic syndrome) are also known to cause hypertension. Hypertension is rarely symptomatic and is typically discovered during screening or treatment for other unrelated diseases. Apart from the usual mild symptoms, some people with high blood pressure also experience headaches, especially at the back of the head in the morning, which may or may not be directly linked to high blood pressure.

Secondary hypertension, or hypertension with a known cause, may be indicated with certain specified additional signs and symptoms. Endocrine disorders such as Conn's syndrome, Cushing's syndrome, hypothyroidism, hyperthyroidism, acromegaly, or pheochromocytoma, hyperparathyroidism, and hyperaldosteronism cause secondary hypertension. Other factors that contribute to secondary hypertension are kidney disorders, obesity, sleep apnea, pregnancy, excessive alcohol intake, and a few prescription drugs, herbal treatments, and illicit substances. A low blood pressure in the extremities of the arms and a delayed/missing femoral arterial pulse are the common side effects of aortic coarctation. Pheochromocytoma can result in sudden ("paroxysmal") episodes of hypertension that are accompanied by palpitations, excessive sweating, headache, and a pale complexion. A "hypertensive crisis" is characterized by extremely high blood pressure (systolic 180 mmHg or diastolic readings of 110 mmHg, referred to as malignant or accelerated hypertension), leading to a significant risk of complications. Although people with extremely high blood pressure in this range may not experience any symptoms, they are more likely to experience headaches (22% cases) and dizziness compared to the general population. In addition to these symptoms, "hypertensive crisis" may also cause retinopathy-related vision loss, cardiovascular disease-related shortness of breath, or nephropathy-related sickness. High blood pressure is found in most patients experiencing a "hypertensive crisis", but there may be other factors that cause such emergences.

Many people with established primary or essential hypertension experience elevated blood pressure with normal cardiac output due to total peripheral resistance, which is an increase in blood flow resistance. Some young individuals with borderline hypertension or prehypertension also have a rapid cardiac output and an increased heart rate, which is known as hyperkinetic borderline hypertension. With advancing age, they develop the usual symptoms of established essential hypertension when their peripheral resistance increases and cardiac output decreases. However, it is contentious whether the same pattern applies to everyone who eventually develops hypertension. The narrowing of arteries and arterioles is responsible for the increased peripheral resistance in established hypertension, while a decrease in the number or density of capillaries may be a contributing factor. These findings are based on the JNC 8 report on prevention, detection, evaluation and treatment of high blood pressure (Table 2).

Hypertension develops in 8-10% of pregnancies, although most pregnant women with hypertension also have preexisting primary hypertension. The presence of pregnancy-related hypertension is determined by two blood pressure readings taken more than six hours apart and greater than 140/90 mmHg. Preeclampsia, a serious medical condition during the second trimester of pregnancy, and puerperium which is due to high blood pressure, occur in 5% of pregnancies and are responsible for 16% of maternal fatalities worldwide. Moreover, preeclampsia...
also doubles the chances of perinatal death.\textsuperscript{12} Preeclampsia typically does not have any symptoms, but it is detected through normal screening. The most common symptoms of preeclampsia include headache, vomiting, epigastric pain, edema, and visual impairment (referred to as "flashing lights"). Furthermore, eclampsia, a hypertensive emergency with multiple complications, such as seizures or convulsions, vision loss, disseminated intravascular coagulation (a blood clotting disorder), pulmonary edema, kidney failure, and brain swelling, may occasionally develop from preeclampsia.\textsuperscript{23-27} In this review, we summarize the recent advances in oxidative stress and how it contributes to hypertension in humans.

**Oxidative Stress in Hypertension**

Oxidative stress is the imbalance between the generation of free radical species and the ability of cellular antioxidants to detoxify them or repair damaged biological molecules.\textsuperscript{9} Increased vascular oxidative stress, a significant risk factor for cardiovascular diseases, is linked to hypertension.\textsuperscript{28} Therefore, oxidative stress is linked to a decrease in the efficiency of antioxidant defenses or an increase in the generation of free radical species.\textsuperscript{29} Oxidative stress leads to proliferation, hypertrophy, and collagen deposition of vascular smooth muscle cells, which thickens and narrows the vascular lumen. Increased oxidative stress can also harm endothelium by impairing endothelium-dependent arterial relaxation and increasing vascular contractile activity, resulting in endothelial dysfunction. Generation of peroxides and free radicals has harmful effects on cellular constituents, such as proteins, lipids, and DNA.\textsuperscript{30} Oxidative stress promotes apoptosis and/or necrosis.\textsuperscript{31,32} An important harmful feature of oxidative stress is the generation of reactive oxygen species (ROS), including free radicals and peroxides \textit{e.g.} superoxide radical (O$_{2}^•-$), hydroxyl radical (•OH) and hydrogen peroxide (H$_2$O$_2$). Some free radical species are converted into more harmful intermediates that cause cellular damage by oxidoreduction reactions in the presence of transition metals or other redox cycling compounds, including quinones.\textsuperscript{33} Fenton reaction results in the generation of hydroxide ion (OH$^-$) and •OH through the reaction between iron (II) or ferrous (Fe$^{2+}$) ion and H$_2$O$_2$.\textsuperscript{34} Generation of ROS occurs with the reduction of metal ions, such as ferric (Fe$^{3+}$) to ferrous (Fe$^{2+}$) ion by superoxide anion (Fenton reaction), which leads to the breakdown of H$_2$O$_2$ to •OH and OH$^-$ (Haber-Weiss reaction).\textsuperscript{35,36}

A number of cellular antioxidants, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GRx), protect the body against ROS. Nitric oxide (NO) and ROS interact three times more quickly than SOD, forming the highly reactive compound known as peroxynitrite, which is produced by the vascular walls. NO dilates the arteries through an increase in the intracellular cyclic guanosine monophosphate (eGMP) content of vascular smooth muscle cells. The inhibition of platelet aggregation or white blood cell adherence to endothelial cells is caused by NO on the arteries that result in the decreased excretion of cell proliferative or migratory stimulatory substances from these blood cells. NO directly prevents the oxidation of low-density lipoprotein (LDL) or the growth of new cells. Therefore, vasoconstriction will occur when NO production declines, leading to the development of atherosclerosis.\textsuperscript{37-41}

**Malondialdehyde (MDA)**

Lipids are one of the primary targets of ROS. ROS causes lipid oxidation or peroxidation (\textit{i.e.}, as degradation products of fats). It has been reported that certain free radicals known as peroxyl radicals, formed by the reaction of molecular oxygen with carbon radicals, remove hydrogen from lipids, producing hydroperoxides (ROOH) that lead to a chain reaction pathway. ROOH reacts with transition metal ions, such as iron or copper to form stable aldehydes that lead to membrane damage.\textsuperscript{42} Lipid peroxidation leads to the generation of highly reactive products such as malondialdehyde (MDA), acrolein (2-propanal), 4-hydroxynonenal (HNE), 4-oxononenal (ONE), \textit{etc.}\textsuperscript{43} Malondialdehyde (MDA) is one of the most common and important markers of free radical-mediated lipid damage and oxidative stress.\textsuperscript{44-46} However, other lipid oxidation product biomarkers, including lipid hydroperoxide (LOOH), N-epsilon-hexanoyl-lysine (HEL), are isoprostanes (IsoPs).

Since ROS have extremely short half-lives and are difficult to detect, they can be measured by using the byproducts of oxidative damage, such as thiobarbituric acid reactive substances (TBARS). MDA is formed through decomposition of some primary and secondary lipid peroxidation products and is estimated in plasma using the colorimetric assay based on the reaction between MDA and thiobarbituric acid (TBA).\textsuperscript{46,47} TBARS, which are detected through the TBA assay, is used as an indicator of oxidative stress in various disease models. In diabetic rat models
induced by streptozotocin (STZ), the TBARS plasma concentration is elevated.⁵⁸–⁵⁹ TBARS concentration is reduced with several antioxidants, such as aminoguanidine and α-lipoic acid.⁴⁹,⁵₀ Several studies support the possible role of lipid peroxidation in predicting the progression of metabolic disorders and response to therapy.⁵¹ The role of oxidative damage to cellular components has been recognized in cardiovascular diseases (CVD)⁵²–⁵⁴ since the proposal of the oxidative theory of atherogenesis.⁵₂,⁵₃ Lipids are potential targets of oxidative damage due to their molecular structure containing long chain hydrocarbons and electron rich benzene rings.⁵₄ Hypertension is associated with increased generation of free radicals, leading to increase in lipid peroxidation products, such as MDA. An increase in generation of O₂⁻ or a decrease in production of NO may facilitate the development of functional arterial spasms.⁵₅

Ferric Reducing Antioxidant Power (FRAP)

An antioxidant may reduce oxidative damage through different mechanisms such as blocking/inhibiting reactions that produce free radicals, scavenging/quenching free radicals, converting them into harmless species. Antioxidants must be present in the vicinity of the radical species and/or have higher reactivity and concentration.⁵⁶ The endogenous enzymatic antioxidants and exogenous vitamins are usually measured to determine the antioxidant status in blood.⁵⁷,⁵₈ The foods of plant origin not only provide antioxidant vitamins but also other phytonutrients with antioxidant capacity. Some phytochemicals also provide nutrients and antioxidants for protection against oxidative stress⁵⁹–⁶⁶, which reduce the risk of diabetes and cardiovascular complications.

Deficiency of antioxidant vitamins in the diet is a major factor in the development of hypertension, since antioxidants lower blood pressure and restore endothelial function. Antioxidant vitamins reduce the damage caused by oxidative stress, such as endothelial dysfunction, lipid peroxidation, and tissue damage, but they may not be able to reverse the negative effects of hypertension on other factors e.g., nervous system activity, vascular smooth muscle cell function, or vascular remodeling. The effect of antioxidants on blood pressure varies due to antioxidant types, administration methods, timing and doses.⁶⁷ Several studies have shown a strong association between blood pressure and oxidative biomarkers and oxidative stress in the severity of hypertension.⁶₈ These findings suggest a strong association and role of oxidative stress in the pathophysiology of essential hypertension⁶⁹–⁷₁, which may contribute to the endothelial dysfunction in hypertension.⁷₂,⁷₃

Hypertension markedly reduces the total antioxidant level in patients. Decrease in total antioxidant capacity and increase in lipid peroxidation activate inflammatory immune responses, leading to hypertension and coronary heart diseases.⁶⁹ The markers of oxidative damage in plasma and kidney of rats with experimental hypertension induced by chronic inhibition of nitric oxide synthase (NOS) with N omega-nitro-L-arginine methyl ester (L-NAME) have been determined. This inhibition results in the elevation of systolic blood pressure, which is associated with an increase in thiol (-SH) groups concentration in renal cortex, while lipid peroxidation products and ferric reducing antioxidant power (FRAP) in plasma and renal medulla remain unchanged, resulting in the development of renal pathology.⁷₀

There are several methods to determine the total antioxidant capacity (TAC) in biological samples. FRAP assay uses the reduction of Fe²⁺-tripyridyltriazine (TPTZ) to produce a blue coloured intermediate Fe²⁺-TPTZ at low pH.⁷₄,⁷₅ This is the only assay that determines the TAC.⁷₆ FRAP assay⁷⁷–⁷₉ has gained importance due to simplicity, cost-effectiveness, processing time, and reproducibility.⁸₀

MDA and FRAP in Hypertension

Increased levels of oxidative stress have been associated with various pathological conditions. Higher levels of MDA in the serum are found in hypertensive patients compared to individuals with normal blood pressure.⁸₁ Moreover, pregnant women with hypertension have a decrease in catalase activity compared to normotensive individuals.⁸₂ In preeclampsia, the MDA concentration in cord blood plasma is lower than maternal plasma.⁸₃ Therefore, it is assumed that MDA is a significant biomarker for lipid peroxidation and FRAP is directly correlated with oxidative stress-related parameters and blood pressure. Due to the direct relationship between oxidative stress and hypertension, certain drugs with antioxidant potential may lower blood pressure.⁸₄ In addition, candesartan and valsartan have been shown to decrease oxidative stress in hypertensive patients.⁸₅,⁸₆ Hence, antioxidant compounds and vitamins have the potential as anti-hypertensive agents.⁸₇
Conclusion

The level of MDA is found to be notably higher and FRAP markedly decreases in hypertensive patients. The elevated MDA and decreased FRAP suggest that lipid peroxidation is a causative factor in hypertension. Oxidative stress in hypertension may lead to long term adverse effects, such as atherosclerosis and CVDs.

Authors Contribution

RA and SK were involved in the concepting and design of research. RA, HA, and SK performed the literature survey and collection. HA and SK drafted the manuscript and designed the tables. RA, HA, and SK were involved in analysis of data. HA and SK were involved in critical revision of the manuscript.

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