International Journal of Technical Research and Applications e-ISSN: 2320-8163,
www.ijtra.com Volume 2, Issue 4 (July-Aug 2014), PP. 19-25

OXIDATIVE STRESS AND NITRIC OXIDE: A SIGNIFICANT MARKER IN CORONARY ARTERY DISEASE

Arpit Srivastava, Dr. Aditi Singh
Amity Institute of Biotechnology,
Amity University Uttar Pradesh,
Lucknow Campus, Lucknow (U.P.) –
India 226010

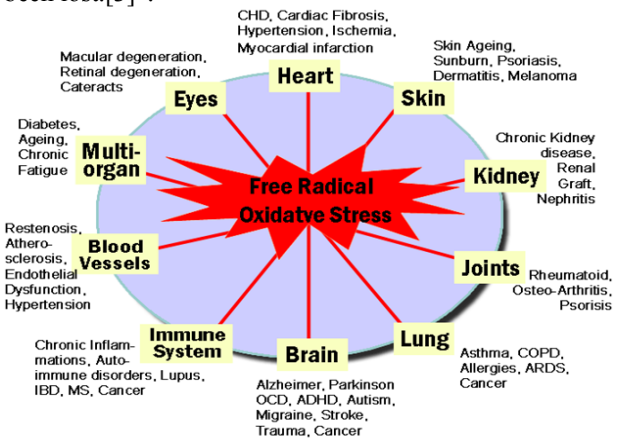
***Abstract*— Oxidative stress is well known to be involved in the pathogenesis of lifestyle-related diseases, including, hypertension, diabetes mellitus, coronary artery diseases, and malignancies. However, oxidative stress also has a useful role in physiologic adaptation and in the regulation of intracellular signal transduction. Therefore, a significant description of oxidative stress may be "a condition where oxidative forces go beyond the antioxidant systems due to loss of the equilibrium between them". Significant Nitric Oxide (NO) confirmed as a envoy of vasodilatation, derivative from the endothelium. Coronary artery disease also defined as atherosclerotic heart diseases are the outcome of the growth of antheromatous plaques (made up of fats, cholesterol etc) within the walls of the coronary arteries that provide the myocardium with oxygen and nutrients. The evidence of the plaque in the lumen (free space in the artery for the flow of nutrients, oxygen etc.) of an artery causes tapering of lumen of the artery by declining its diameter. NO levels show a significant relation with higher BMI and hypertension in coronary artery disease. Many research have shown that adipose tissue contains NO synthetase enzyme, and is thus an impending NO source. Biological activity of Nitric Oxide provides clinicians with additional therapeutic options in the treatment of cardiovascular disease which will subordinate oxidative stress, a process which is becoming gradually more standard as critical in the pathophysiology of vascular disease.**

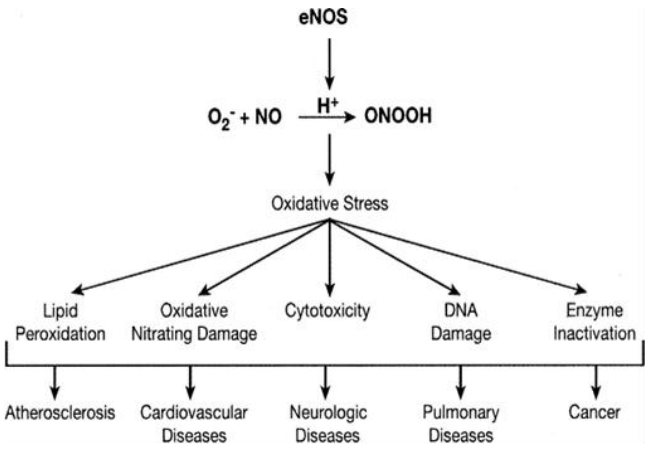
***Key words*— Oxidative stress, vasodilatation, myocardium, pathophysiology**

I. INTRODUCTION

Oxidative Stress

An imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage reflects Oxidative stress. Normal redox state of cells get disturbed which can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA. Further, some reactive oxidative species act as cellular messengers in redox signaling. Thus, disruptions in normal mechanisms of cellular signaling can cause by Oxidative Stress. The close relationship between oxidative stress and lifestyle-related diseases has become well known. Oxidative stress is defined as a "condition in which oxidation exceeds the antioxidant systems of the body secondary to a loss of the balance between them." It not only causes catastrophic events such as peroxidation of lipids and oxidative DNA damage, but also affects the physiologic adaptation phenomena and regulation of intracellular signal transduction. From a clinical point of view, if biomarkers that reflect the extent of oxidative stress were available, such markers would be useful for physicians to gain an insight into the pathological features of various diseases and assess the efficacy of drugs [3]. Oxidative stress play important role in some instances, For example, to prepare the birth canal for delivery oxidative stress induces apoptosis. Also, during appropriate physical exercise and ischemia- biological defense mechanisms are strengthened by oxidative stress. Therefore, a more useful definition of oxidative stress may be a "condition where oxidation exceeds the antioxidant systems because the balance between them has been lost.[3]".





In humans, oxidative stress is thought to be involved in the development of many diseases or may exacerbate their symptoms. These include cancer, Parkinson's disease, Alzheimer's disease, atherosclerosis, heart failure, myocardial infarction, Schizophrenia Bipolar disorder, fragile X syndrome, Sickle Cell Disease, lichen planus, vitiligo, autism, and chronic fatigue syndrome. However, reactive oxygen species can be beneficial, as they are used by the immune system as a way to attack and kill pathogens. Short-term oxidative stress may also

be important in prevention of aging by induction of a process named mitohormesis. Oxidative stress is thought to be linked to certain cardiovascular disease, since oxidation of LDL in the vascular endothelium is a precursor to plaque formation.

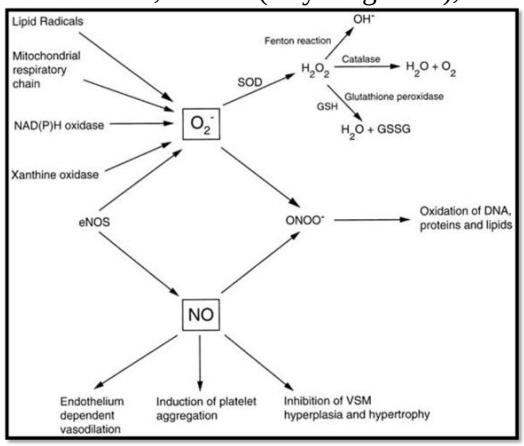
Oxidative Stress as a Biological Modulator and as a Signal

Oxidative stress not only has a cytotoxic effect, but also plays an important role in the modulation of messengers that regulate essential cell membrane functions, which are vital for survival. It affects the intracellular redox status, leading to the activation of protein kinases, including a series of receptor and non-receptor tyrosine kinases, protein kinase C, and the MAP kinase cascade, and hence induces various cellular responses. These protein kinases play an important role in cellular responses such as activation, proliferation, and differentiation, as well as various other functions. Accordingly, the protein kinases have attracted the most attention in the investigation of the association between oxidative stress and disease.

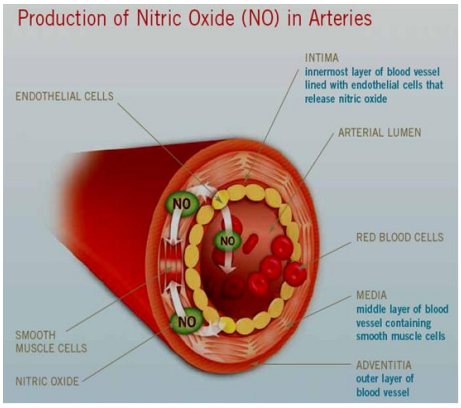
II. Nitric Oxide

Nitric oxide, or nitrogen oxide, [2] also known as nitrogen monoxide, is a molecule with chemical formula NO. It is a free radical [3] and is an important intermediate in the chemical industry. Nitric oxide is a by-product of combustion of substances in the air, as in automobile engines, fossil fuel power plants, and is produced naturally during the electrical discharges of lightning in thunderstorms. In mammals including humans, NO is an important cellular signaling molecule involved in many physiological and pathological processes.[4] It is a powerful vasodilator with a short half-life of a few seconds in the blood. Nitric oxide, known as the 'endothelium-derived relaxing factor', or 'EDRF', is biosynthesized endogenously from L-arginine, oxygen, and NADPH by various nitric oxide synthase (NOS) enzymes. Reduction of inorganic nitrate may also serve to make nitric oxide. The endothelium (inner lining) of blood vessels uses nitric oxide to signal the surrounding smooth muscle to relax, thus resulting in vasodilatation and increasing blood flow.

Dietary nitrate is also an important source of nitric oxide in mammals. Green, leafy vegetables, and some root vegetables (such as beetroot) have high concentrations of nitrate. When eaten and absorbed into the bloodstream nitrate is concentrated in saliva (about 10 fold) and is reduced to nitrite on the surface of the tongue by a biofilm of commensally facultative anaerobic bacteria. This nitrite is swallowed and reacts with acid and reducing substances in the stomach (such as ascorbate) to produce high concentrations of nitric oxide. The purpose of this mechanism to create NO is thought to be both sterilization of swallowed food, to prevent food poisoning and to maintain gastric mucosal blood flow. Nitric oxide also acts on cardiac muscle to decrease contractility and heart rate. NO contributes to the regulation of cardiac contractility. Emerging evidence suggests that coronary artery disease (CAD) is related to defects in generation or action of NO. Nitric Oxide is the natural performance booster that strengthens our heart, lungs, and nerves, along with every cell in our body. It also allows us to prolong your exercise, and prolonged exercise increases NO levels in our body.



It's a virtuous cycle that can lead to improved athletic performance and better health. NO is a short-lived, gaseous molecule that is produced in your cells. Once released into the bloodstream, it signals the body to perform certain functions such as vasodilatation opening up the blood vessels and capillaries to increase blood flow and deliver oxygen and critical nutrients throughout your body at the time it needs them most. Do you ever wonder why people suffering from chest pain are often prescribed and instructed to take nitroglycerine? It's because the body uses nitroglycerine to produce high levels of NO quickly by opening the coronary arteries and increasing the flow of blood to the heart.



NO is primarily manufactured in the endothelium, which is the layer of cells lining the interior surface of the blood vessels. The endothelial tissue, which separates the blood from the smooth muscles of the vessel walls, is extremely thin and fragile. It's easy to see what occurs when such a vast, crucial network gets what it needs to function at its biological peak. When your endothelium is well nourished, it produces NO at optimal levels. The NO then rapidly spreads through the cell membranes to the underlying muscle cells, causing the arteries to dilate and blood to flow unimpeded to the heart and other organs.

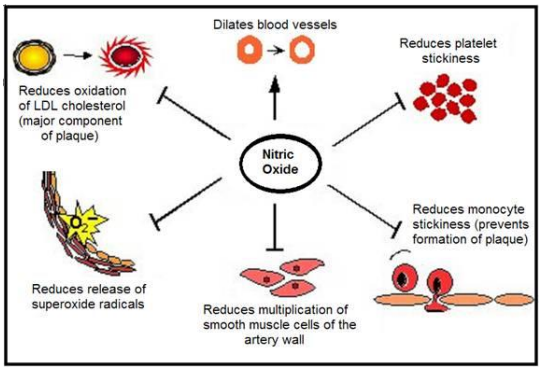
Because NO functions on a localized basis, it is released by billions of cells throughout the body, enhancing overall functioning. The longer NO circulates in the body, the greater benefit it provides to your cells, cardiovascular system, lungs, nervous system, and organs and the more optimal their functionality will be. The more efficiently each of your cells functions, the more you will be able to produce peak speed, strength, and endurance as part of your athletic endeavors.

Also, the desirable effects of NO aren't limited to athletes. On the contrary, this molecule is quickly becoming regarded as a critical component of a pro-wellness lifestyle for all people, ranging from athletes to the sedentary.

A. Benefits of Nitric Oxide

Some of the benefits of sufficient levels of NO include:

A. Helping to increase cardiovascular capacity and circulation and enhancing oxygen and nutrient delivery to cells.
B. Helping cells get rid of waste products.
C. Regulating the muscle tone of blood vessels and having a major impact in controlling blood pressure.
D. Stopping blood platelets from forming clots, this helps in preventing arterial blockages and heart attacks.
E. Transmitting messages between nerve cells, a process known as neurotransmission.

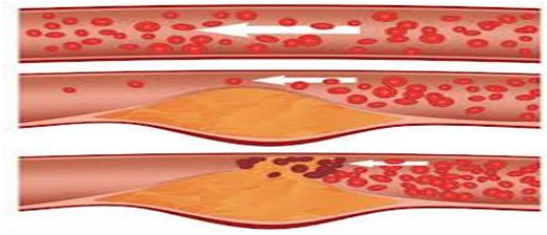


NO helps slow the accumulation of atherosclerotic plaque in the blood vessels. This artery hardening build up of cholesterol and fats that narrow or block the arteries is a major precursor to coronary heart disease, leading to heart attack and stroke. Our research strongly suggests that NO's ability to combat this plaque helps produce healthy levels of cholesterol by working in concert with medications commonly prescribed for people with high cholesterol.

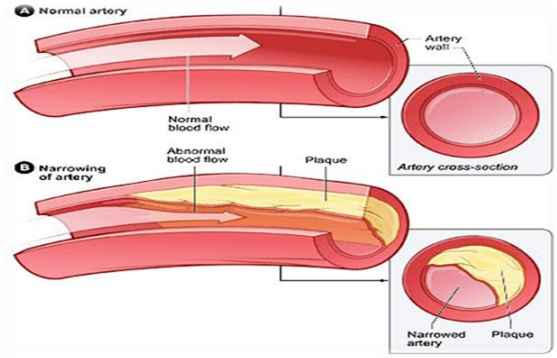
III.Coronary Artery Diseases (CAD)

Coronary artery disease (CAD; also atherosclerotic heart disease) is the most common type of heart disease and cause of heart attacks.[1] The disease is caused by plaque building up along the inner walls of the arteries of the heart, which narrows the arteries and restricts blood flow to the heart. It is the leading cause of death worldwide. While the symptoms and signs of coronary artery disease are noted in the advanced state of disease, most individuals with coronary artery disease show no evidence of disease for decades as the disease progresses before the first onset of symptoms, often a "sudden" heart attack, finally arises. After decades of progression, some of these atheromatous plaques may rupture and (along with the activation of the blood clotting system) start limiting blood flow to the heart muscle. The disease is the most common cause of sudden death, and is also the most common reason for death of men and women over 20 years of age.

As the degree of coronary artery disease progresses, there may be near-complete obstruction of the lumen of the coronary artery, severely restricting the flow of oxygen-carrying blood to the myocardium. Individuals with this degree of coronary artery disease typically have suffered from one or more myocardial infarctions (heart attacks), and may have signs and symptoms of chronic coronary ischemia, including symptoms of angina at rest and flash pulmonary edema. A distinction should be made between myocardial ischemia and myocardial infarction. Ischemia means that the amount of blood supplied to the tissue is inadequate to supply the needs of the tissue. When the myocardium becomes ischemic, it does not function optimally. When a large area of the myocardium becomes ischemic, there can be impairment in the relaxation and contraction of the myocardium. If the blood flow to the tissue is improved, myocardial ischemia can be reversed. Infarction means that the tissue has undergone irreversible death due to lack of sufficient oxygen-rich blood.



An individual may develop a rupture of an atheromatous plaque at any stage of the spectrum of coronary artery disease. The acute rupture of a plaque may lead to an acute myocardial infarction (heart attack). Typically, coronary artery disease occurs when part of the smooth, elastic lining inside a coronary artery (the arteries that supply blood to the heart muscle) develops atherosclerosis. With atherosclerosis, the artery's lining becomes hardened, stiffened, and swollen with all sorts of "grunge" - including calcium deposits, fatty deposits, and abnormal inflammatory cells - to form a plaque. Deposits of calcium phosphates (hydroxyapatites) in the muscular layer of the blood vessels appear to play not only a significant role in stiffening arteries but also for the induction of an early phase of coronary arteriosclerosis.



Risk factors for the Coronary Artery Diseases-

The following are confirmed independent risk factors (IRF) for the development of CAD:

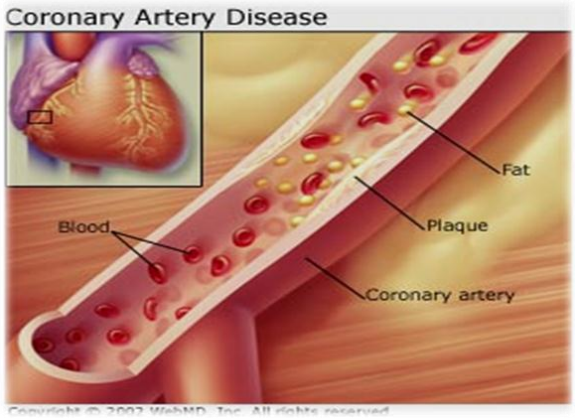
1. Hypercholesterolemia (specifically, serum LDL concentrations)
2. Smoking
3. Hypertension (high systolic pressure seems to be most significant in this regard)[9]
4. Hyperglycemia (due to diabetes mellitus or otherwise)[citation needed]
5. Hemostatic Factors High levels of fibrinogen and coagulation factor VII are associated with an increased risk of CAD. Factor VII levels are higher in individuals with a high intake of dietary fat. Decreased fibrinolytic activity has been reported in patients with coronary atherosclerosis.
6. Hereditary differences/genetic polymorphisms in such diverse aspects as lipoprotein structure and that of their associated receptors, enzymes of lipoprotein metabolism such as cholesteryl ester transfer protein

(CETP) and hepatic lipase (HL), homocysteine processing/metabolism, etc.

7. High levels of Lipoprotein, a compound formed when LDL cholesterol combines with a substance known as Apoliprotein.

Significant, but indirect risk factors include:

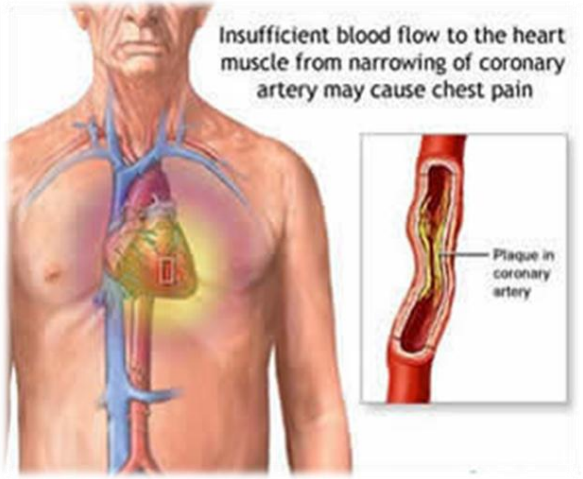
- Lack of exercise
- Consumption of alcohol
- Stress
- Diet rich in saturated fats[citation needed]
- Diet low in antioxidants
- Obesity
- Men over 60; Women over 65
- Low hemoglobin



Atherosclerosis is a process that can involve many of the body's blood vessels with a variety of presentations. When it involves the coronary arteries it results in coronary artery disease, the cerebral arteries; cerebrovascular disease (transient ischemic attack, stroke), the aorta; aortic aneurysms, the ileo-femoral and popliteal arteries; peripheral vascular disease, the mesenteric arteries; intestinal ischemia. Half of all deaths in the developed world and a quarter of deaths in the developing world are due to Cardiovascular Disease which are comprised of hypertension and the diseases caused by atherosclerosis.

A. The Pathogenesis of the Atherosclerotic Plaque:

Atherosclerosis is the main cause of coronary artery disease. The process begins as disruption of endothelial function due to the accumulation of lipoprotein droplets in the intima of the coronary vessels. Water insoluble lipids are carried in the bloodstream attached to water soluble apolipoproteins (lipoproteins). High concentrations of low density lipoprotein (LDL) can permeate an already disrupted or dysfunctional endothelium where it undergoes oxidation and, in diabetics, glycation. Modified LDL attracts leukocytes into the intima and can be scavenged by macrophages leading to the formation of foam cells. These cells replicate giving rise to one of the earliest pathological lesions; the fatty streak. The fatty streak is the earliest visualized lesion of atherosclerosis.



B. Pathophysiology of CAD

Limitation of blood flow to the heart causes ischemia (cell starvation secondary to a lack of oxygen) of the myocardial cells. Myocardial cells may die from lack of oxygen and this is called a myocardial infarction (commonly called a heart attack). It leads to heart muscle damage, heart muscle death and later myocardial scarring without heart muscle regrowth. Chronic high-grade stenosis of the coronary arteries can induce transient ischemia which leads to the induction of a ventricular arrhythmia, which may terminate into ventricular fibrillation leading to death. CAD is associated with smoking, diabetes, and hypertension. A number of recent studies have shown that family history of early CAD is an important predictor of CAD. Most of the familial association of coronary artery disease may be related to common dietary habits. Screening for CAD includes evaluating high-density and low-density lipoprotein (cholesterol) levels and triglyceride levels. Despite much press, most of the alternative risk factors including homocysteine, C-reactive protein (CRP), Lipoprotein, coronary calcium and more sophisticated lipid analysis have added little if any additional value to the conventional risk factors of smoking, diabetes and hypertension.

IV. Prevention of Coronary Artery Diseases

Coronary artery disease is the most common form of heart disease in the Western world. Prevention centers on the modifiable risk factors, which include decreasing cholesterol levels, addressing obesity and hypertension, avoiding a sedentary lifestyle, making healthy dietary choices, and stopping smoking. There is some evidence that lowering homocysteine levels may contribute to more heart attacks. In diabetes mellitus, there is little evidence that very tight blood sugar control actually improves cardiac risk although improved sugar control appears to decrease other undesirable problems like kidney failure and blindness. Some recommend a diet rich in omega-3 fatty acids and vitamin C. The World Health Organization (WHO) recommends "low to moderate alcohol intake" to reduce risk of coronary artery disease although this remains without scientific cause and effect proof.

A. Prevention by Diet and Exercise

It has been suggested that coronary artery disease is partially reversible using an intense dietary regimen coupled with regular cardio exercise. Vegetarian diet: Vegetarians have been shown to have a 24% reduced risk of dying of heart disease. The consumption of Trans fat (commonly found in

hydrogenated products such as margarine) has been shown to cause the development of endothelial dysfunction, a precursor to atherosclerosis. The consumption of trans fatty acids has been shown to increase the risk of coronary artery disease Foods containing fiber, potassium, nitric oxide (in green leafy vegetables), monounsaturated fat, polyunsaturated fat, saponins, or lecithin are said to lower cholesterol levels. Foods high in grease, salt, trans fat, or saturated fat are said to raise cholesterol levels. In addition to take supplements, it is important to maintain a healthy lifestyle by watching what you eat and being active.

- Do aerobic exercise for at least 20 minutes three days a week. This simulates endothelial cells to continuously produce nitric oxide, even on days that you don't exercise.
- Minimize intake of saturated fat. Saturated fat, found in such animal products as red meat, poultry, butter, and whole milk, contributes to the accumulation of arterial plaque and impairs nitric oxide production. Better: Olive oil, fish and flaxseed. The fats found in these foods help protect the endothelium by elevating levels of beneficial HDL cholesterol and lowering the harmful LDL form.
- Eat More Fiber. The dietary fiber in grains, fruits and vegetables lowers blood pressure and LDL cholesterol and raises HDL, thereby protecting endothelial cells.

The Nitric Oxide Index

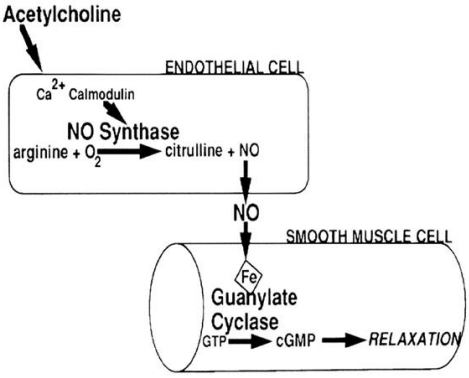
High		Medium		Low	
Kale	6825	Coleslaw	84	String Beans	9
Swiss Chard	2055	Asparagus	82	Sausage	8
Arugula	1452	Celery	80	Figs	7
Spinach	1123	Watercress	73	Prunes	6
Chicory	938	Artichoke	63	Sweet potato	5
Wild radish	814	Eggplant	39	Raspberries	5
Bok choy	775	Strawberry	34	Raisins	4
Beet	632	Potato	26	Banana	4
Chinese Cabbage	499	Garlic	19	Cherries	3
Beet (root) juice	482	Tomato	14	Onion	3
Lettuce	388	Vegetable juice	11	Red wine	3
Cabbage	312	Vegetable soup	10	Bean sprouts	2
Mustard greens	226	Cereal	10	Hot dog	1
Cauliflower, raw	167	Melon	10	Bacon	1
Parsley	150			Chickpeas	1
Kohlrabi	136				
Carrot	127				
Broccoli	122				

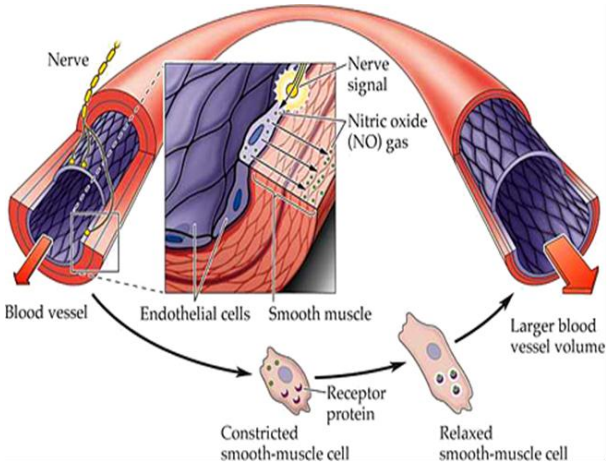
Many of the foods that contain fiber also are rich in antioxidants, which inhibit the cell damage that lowers nitric oxide. Eat at least 25 grams (g) of fiber daily – and drink at least eight-ounce glasses of water each day to make sure that the fiber moves through your system properly.

V. Nitric Oxide helping in Lowering Oxidative Stress

A. Preventing Coronary Artery Diseases

"Oxidative stress" is now a major concern for Cardiovascular researchers. When the body utilizes oxygen, it produces byproducts by the process of oxidation that can be either beneficial or catastrophic. Without oxidation, our cells would not be able to burn glucose, which provides us with energy. Studies have shown that adipose tissue contains NO synthetase enzyme, and is thus a potential source for "NO". The byproducts of oxidation in the body are called oxygen or "free" radicals. Free radicals can show harmful or toxic effects by neutralizing Nitric Oxide (NO), it contributes not only to cardiovascular disease but also to signs of the aging process from wrinkling of the skin to weakening bones. Free radicals can injure the endothelium. When LDL ("bad") cholesterol is oxidized, it is chemically altered in ways that allow it to infiltrate artery walls and do serious damage to the endothelial cells. Though the endothelial cells can repair themselves to some degree, constant oxidative stress can sabotage the opportunity for meaningful self-repair.





Nitric Oxide act against oxidative stress and can minimize the oxidative stress that will contributes to for the treatment of cardiovascular disease. When free radicals are present in high numbers, they try to overpower and disarm the NO produced in your body before it can take control of the situation. When your body is in a state of oxidative stress, you may have much less NO than normal. Antioxidants play an important role and can help as they act like "scavengers in the body". Antioxidant helps in neutralizing free radicals before they can cause much damage.

VI. Conclusion

In the pathogenesis of diseases Oxidative stress is well known to be involved. Hypertension, diabetes mellitus, coronary artery diseases, and malignancies are part of it, including the patients who are utilizing arsenic or any heavy metal contaminated water for their domestic or drinking purpose suffers from oxidative stress as these toxic water initiate the function of free radicals. However, in physiologic adaptation and in the regulation of intracellular signal transduction oxidative stress also plays an essential role. Therefore, a perfect definition of oxidative stress may be "a condition where oxidative forces exceed the antioxidant

systems due to loss of the balance between them". Nitric Oxide (NO) called a "Vasodilatator agent" which is derived from the endothelium show a significant relationship. Coronary artery disease is an atherosclerotic heart disease that occur due to the result of the accumulation of plaques (made up of fats, cholesterol etc) within the walls of the coronary arteries that supply the myocardium with oxygen and nutrients. Deposition of the plaque in the lumen of an artery causes narrowing of lumen of the artery by decreasing its diameter. NO levels showed a significant relation with higher BMI and hypertension in coronary artery disease. Adipose tissue contains NO synthetase enzyme, and is thus a potential NO source. Biological activity of Nitric Oxide provides researchers with additional therapeutic options in the field of cardiology. By lowering oxidative stress, a process which is becoming increasingly recognized as critical in the pathophysiology of vascular disease. The causes of diseases can be divided into three major categories, genetic, habitual, and environmental. Studies said that genes that are associated with biological oxidative stress have been identified for that in-silico studies are also going on with the genes for NO synthetase (NOS) and being considered for such diseases.

REFERENCES

[1] Peter H. Proctor, Free Radicals and Human Disease, CRC Handbook of Free Radicals and Antioxidants, vol 1 (1989), p209-221.
[2] Proctor, Peter; Reynolds, Edward.S. (1984). "Free radicals and disease in man". Physiol. Chem. Phys. 16: 175–195
[3] Yoshikawa, T.: A Guide to Free Radicals. Part 2. Sentan Igaku , Tokyo,1998
[4] Yoshikawa, T.: Science of Free Radicals. Koudan Sha Saientifikku, Tokyo,97
[5] Ramond A, Godin-Ribuot D, Ribuot C, Totoson P, Koritchneva I, Cachot S, Levy P, Joyeux-Faure M. (December 2011). "Oxidative stress mediates cardiac infarction aggravation induced by intermittent hypoxia". Fundam Clin Pharmacol.
[6] Proctor,P, Electron-transfer Factors in Psychosis and dyskinesia,Physiol Chem.& Physics, 4 (1972)349-360
[7] Dean OM, van den Buuse M, Berk M, Copolov DL, Mavros C, Bush AI. (July 2011). "N-acetyl cysteine restores brain glutathione loss in combined 2-cyclohexene-1-one and D-amphetamine-treated rats: relevance to schizophrenia and bipolar disorder". Neurosci Lett. 499 (3): 149–53.
[8] de Diego-Otero Y, Romero-Zerbo Y, el Bekay R, Decara J, Sanchez L, Rodriguez-de Fonseca F, del Arco-Herrera I. (March 2009). "Alpha-tocopherol protects against oxidative stress in the fragile X knockout mouse: an experimental therapeutic approach for the Fmr1 deficiency."Neuropsychopharmacology 34 (4): 1011–26.
[9] Amer, J., Ghoti, H., Rachmilewitz, E., Koren, A., Levin, C. and Fibach, E. (January 2006). "Red blood cells, platelets and polymorphonuclear neutrophils of patients with sickle cell disease exhibit oxidative stress that can be ameliorated by antioxidants". British Journal of Haematology 132 (1).
[10] Aly, D. G.; Shahin, R. S. (2010). "Oxidative stress in lichen planus". Acta dermatovenerologica Alpina, Panonica, et Adriatica 19 (1): 3–11.
[11] Segal, AW (2005). "How neutrophils kill microbes". Annu Rev Immunol 9 ((5)): 197–223.
[12] Gems D, Partridge L (March 2008). "Stress-response hormesis and aging: "that which does not kill us makes us stronger"". Cell Metab. 7 (3): 200–3.
[13] "Nitric Oxide (CHEBI: 16480)". Chemical Entities of Biological Interest (ChEBI). UK: European Bioinformatics Institute.
[14] {New Oxford Dictionary for Scientific Writers and Editors}
[15] Derosa, Frank; Keefer, Larry K.; Hrabie, Joseph A. (2008). "Nitric Oxide Reacts with Methoxide". The Journal of Organic Chemistry 73 (3): 1139–42.
[16] Robert H. Crabtree: "The Organometallic Chemistry of the Transition Metals", John Wiley and Sons, 2005, ISBN 0-471-66256-9, p. 32.
[17] Robert H. Crabtree: "The Organometallic Chemistry of the Transition Metals", John Wiley and Sons, 2005, ISBN 0-471-66256-9, pp. 96–98.
[18] Elizabeth Culotta and Daniel E. Koshland Jr (1992). "NO news is good news. (nitric oxide; includes information about other significant advances & discoveries of 1992) (Molecule of the Year)". Science 258 (5090): 1862–1864.
[19] Traube, Wilhelm (1898). "Ueber Synthesen stickstoffhaltiger Verbindungen mit Hülfe des Stickoxyds". Justus Liebig's Annalen der Chemie 300: 81.
[20] Nagano, T; Yoshimura, T (2002). "Bioimaging of nitric oxide". Chemical reviews 102 (4): 1235–70.
[21] Ignarro L.J. (2001): Nitric Oxide. A Novel Signal Transduction Mechanism For Transcellular Communication; 16: 477- 483.
[22] Weller, Richard, Could the sun be good for your heart? TedxGlasgow March 2012, posted January 2013
[23] Davies, S.A., Stewart, E.J., Huesmaan, G.R and Skaer, N. J. (1997): Neuropeptide stimulation of the nitric oxide signalling pathway in Drosophila melanogaster Malpighian tubules. Am. J. Physiol.; 273, R823-827.
[24] Hou, Y.C.; Janczuk, A.; Wang, P.G. (1999). "Current trends in the development of nitric oxide donors". Curr. Pharm. Des. 5 (6): 417–471. PMID 10390607.
[25] Heart attack/coronary artery disease - Mount Sinai Hospital, New York
[26] Thomas AC, Knapman PA, Krikler DM, Davies MJ (December 1988). "Community study of the causes of "natural" sudden death". BMJ 297 (6661): 1453–6.
[27] American Heart Association: Heart Disease and Stroke Statistics-2007 Update. AHA, Dallas, Texas, 2007
[28] Rosamond W, Flegal K, Friday G (February 2007). "Heart disease and stroke statistics--2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee". Circulation 115 (5): e69–171.
[29] Lanza GA (February 2007). "Cardiac syndrome X: a critical overview and future perspectives". Heart 93 (2):.Kaski JC (February 2004). "Pathophysiology and management of patients with chest pain and normal coronary arteriograms (cardiac syndrome X)". Circulation 109 (5): 568–72.
[30] Stegmann, T.J.: New Vessels for the Heart. Angiogenesis as New Treatment for Coronary Heart Disease: The Story of its Discovery and Development. Henderson, Nevada 89012, USA, 2004. ISBN 0-9765583-0-0
[31] Stegmann, T.J.: Protein promise in heart disease. GCPj, March 2007, 21-24
[32] Underwood and Cross, James, (2009). General ans Systematic Pathology. London: Churchhill livingstone. pp. 279.
[33] Smith FB, Lee AJ, Fowkes FG, Price JF, Rumley A, Lowe GD (November 1997). "Hemostatic factors as predictors of ischemic heart disease and stroke in the Edinburgh Artery Study". Arterioscler Thromb Vasc Biol. 17 (11): 3321–5.
[34] Wallin R, Schurgers L, Wajih N (2008). "Effects of the Blood Coagulation Vitamin K as an Inhibitor of Arterial Calcification". Thromb. Res. 122 (3): 411–7.
[35] Swardfager W, Herrmann N, Cornish S, Mazereeuw G, Marzolini S, Sham L, Lanctôt KL (2012). "Exercise intervention and inflammatory markers in coronary artery disease: a meta-analysis". Am Heart J 163 (4): 666–676.
[36] Key TJ, Fraser GE, Thorogood M, Appleby PN, Beral V, Reeves G, Burr ML, Chang-Claude J, Frentzel-Beyme R, Kuzma JW, Mann J, McPherson K (1998). "Mortality in vegetarians and non-vegetarians: a collaborative analysis of

8300 deaths among 76,000 men and women in five prospective studies". Public Health Nutr 1 (1): 33–41.

[37] Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, Trichopoulos D. (1995). "Mediterranean diet pyramid: a cultural model for healthy eating". Am J Clin Nutr 61 (6 Suppl): 1402S–1406S.

[38] Perez-Llamas, F., et al., J Hum Nutr Diet, December 1996, 9:6:463-471

[39] Alberti-Fidanza A, Paolacci CA, Chiuchiu MP, Coli R, Fruttini D, Verducci G, Fidanza F. (1994). "Dietary studies on two rural Italian population groups of the Seven Countries Study. 1. Food and nutrient intake at the thirty-first year follow-up in 1991". Eur J Clin Nutr 48 (2): 85–91.

[40] Lopez-Garcia E, Schulze MB, Meigs JB, Manson JE, Rifai N, Stampfer MJ, Willett WC, Hu FB. (2005). "Consumption of trans fatty acids is related to plasma biomarkers of inflammation and endothelial dysfunction". J Nutr 135 (3): 562–6.

[41] Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC (April 2006). " Trans fatty acids and cardiovascular disease". N. Engl. J. Med. 354 (15): 1601–13. doi: 10.1056/NEJMra054035.