Endothelial dysfunction and oxidative stress

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The various forms of athero-sclerosis, including coronary thrombosis, stroke and pe-ripheral arterial disease, continues to be the leading cause of death worldwide. Black Africans are to-day too suffering from an increased incidence of cardiovascular disease due to the adoption of a western lifestyle and diet.

The endothelium (the largest organ in the body) controls vascular smooth muscle tone by secreting relaxing and contracting fac-tors. There is a constant release of endothelium-derived relaxing factors (EDRFs), whose biologic activity is provided by nitric oxide (or similar molecules) and con-stantly counteracts vasoconstrictor substances such as noradrenaline, angiotensin II or endothelin I. The normal functioning endothelium is able to increase the release of EDRFs in response to physiological stimuli, such as the stress exerted by the circulating blood, or to humoral stimulation by vasoactive substances such as acetylcholine or bradykinin. The endothelium is in effect both a target and a modula-tor of blood pressure-related and hormonal influences.

Normal functions of endothelial cells include mediation of coagula-tion, platelet adhesion, immune function, control of volume and electrolyte content of the intravas-cular and extravascular spaces.

As we age, some of the special-ized functions of the endothelium become blunted. The self renewal process weakens, the endothelial barrier becomes leaky and signals to the middle wall smooth muscle cells that regulate their function become altered. The vascular aging process and atherosclerosis become intertwined as we age.

The arterial wall under attack (excerpt lef October 2005)

High blood pressure, elevated LDL and triglycerides, cigarette smok-ing, diabetes, obesity, and lack of exercise contribute to endothelial dysfunction and the subsequent de-velopment of atherosclerosis.[15-25]

Additional endothelial-damaging factors include excess levels of glu-cose, insulin, iron, homocysteine, fibrinogen, and C-reactive protein, as well as low HDL and free testo-sterone (in men).[3,9,10,24,26-28]

Homocysteine is particularly dan-gerous because it can induce the initial injury to the endothelium. Homocysteine then facilitates oxida-tion of the fat/LDL that accumulates beneath the damaged endothelium, and finally contributes to the abnor-mal accumulation of blood compo-nents around the atherosclerotic lesion.[29]

Fibrinogen is a clotting factor that accumulates at the site of the endothelial lesion. Fibrinogen may contribute to plaque buildup or par-ticipate in blood clot-induced block-age of an artery after an unstable atherosclerotic plaque ruptures.[30]

Glucose at even high-normal levels may accelerate the glyca-tion process that causes arterial stiffening, while high-normal fasting insulin inflicts direct damage to the endothelium.[31-36]

High levels of iron promote LDL oxidation in the damaged endothe-lium, while low levels of testoster-one appear to interfere with normal endothelial function.[9,11,14]

C-reactive protein is not only an inflammatory marker, but also directly damages the endothelium. Chronic inflammation, as evidenced by persistent high levels of C-reac-tive protein, creates initial injuries to the endothelium and also ac-celerates the progression of existing atherosclerotic lesions.[3,27]

In response to numerous published studies, health-conscious people are altering their diets, taking drugs, hormones, and dietary supplements, and trying to exercise regularly in or-der to reduce these atherosclerosis risk factors. However, these efforts alone cannot be completely success-ful because age itself is a major risk factor for atherosclerosis.

Atherosclerotic risk conferred by age is attributable in large measure to pathological endothelial dysfunc-tion.[37,38] As noted earlier, endothelial

dysfunction is not synonymous with atherosclerosis, but the two processes are increasingly intertwined with advancing age.

Endothelial dysfunction markers:
1. VEGF (Vascular endothelial growth factor)
2. ADMA (Asymmetric dimethyl-arginine)
3. VCAM-1 (vascular cell adhesion molecules)
4. NOS (Nitric oxide synthase)

ADMA is involved in the pathogenesis of hypertension and atherosclerosis through its inhibition of the formation of the endogenous vasculoprotective molecule, nitric oxide (NO). Determination of ADMA can thus help to predict both the likelihood of developing cardiovascular disease and its prognosis. A new competitive ELISA test for ADMA is a useful and fully validated tool suitable for routine laboratory use.

Available tests to detect endothelial dysfunction in South Africa include :
a) Ultra sensitive CRP
b) Von Willebrand Factor (WF)
c) PAI-1 (Plasminogen activator inhibitor-1)
d) FDP (Fibrinogen degradation products) – as D-dimer
e) NT-proBNP
f) Homocysteine
g) Active renin
h) Lipids (lipogram) and lipo-proteins
i) ACE (angiotensin converting enzyme)

An article published online on October 21, 2008 in the journal Nutrition & Metabolism reported the discovery of Italian researchers of an association between decreased plasma levels of several antioxidants and early carotid atherosclerotic lesions in asymptomatic middle-aged individuals.

"Atherosclerosis remains clinically mute for a long time and frequently manifests itself with an acute cardiovascular event; therefore, the possibility of detecting the disease in a subclinical phase and reducing or reversing its progression is an issue of relevance," the authors write. "Antioxidants, which may inhibit lipid peroxidation, could play an important protective role against the formation of simple and complex atherosclerotic lesions, which progressively protrude into the arterial lumen, causing stenosis or occlusion. In particular, increased carotid intima-media thickness represents an early phase of the atherosclerotic process and is widely used as a marker of subclinical atherosclerosis which correlates with established coronary heart disease."

Two hundred and twenty men and women between the ages of 45 and 65 without history of transient ischemic attack, stroke, or other conditions related to carotid artery disease were enrolled at the San Camillo de Lellis Hospital, in Manfredonia, Italy. Participants underwent ultrasonographic evaluation of the extracranial carotid arteries, and blood samples were analysed for lipids, C-reactive protein and other factors, in addition to plasma levels of vitamin A, vitamin E, beta-carotene and lycopene.

One hundred and twenty-five participants were found to have carotid atherosclerosis as determined by carotid intima-media thickness of 0.8 millimeters or more. Body mass index, plasma hemoglobin, and high-density lipoprotein cholesterol were marginally higher among those diagnosed with atherosclerosis, and all of the nutrients measured were significantly reduced. Vitamin A, vitamin E, and lycopene levels were decreased by 50 percent or more among those with atherosclerosis compared with participants who were not diagnosed with the condition, and beta-carotene levels were less than a third of those without atherosclerosis.

Oxidative stress resulting from the oxidation of low-density lipoprotein (LDL) cholesterol in the wall of the artery results in inflammation which stimulates the differentiation of immune system cells called monocytes into macrophages. Macrophages accumulate lipids to form foam cells which thicken the walls of the artery. Antioxidants such as those evaluated in the current study could help protect against this process by preventing LDL oxidation.

"Regular intake of foods rich in lycopene and other antioxidant vitamins may slow the progression of atherosclerotic processes and modify the early stages of atherosclerosis, with a consequent reduction in cardiovascular events," the authors conclude.

Oxidative stress profile (blood)
1. Malondialdehyde
2. Glutathione
3. CoEnzyme Q10
4. Vitamin C
5. b-Carotene (including cryptoxanthin and lycopene)

REFERENCES :
1. Selnes OA, Grega MA, Borowicz LM, Jr., et al. Self-reported memory symptoms with coronary artery disease: a prospective study of CABG patients and nonsurgical controls. Cogn Behav Neurol. 2004 Sep;17(3):148-56.
2. Toner I, Peden CJ, Hamid SK, et al. Magnetic resonance imaging and neuropsychological changes after coronary artery bypass graft surgery: preliminary findings. J Neurosurg Anesthesiol. 1994 Jul;6(3):163-9.
3. Rasouli ML, Nasir K, Blumenthal RS, et al. Plasma homocysteine predicts progression of atherosclerosis. Atherosclerosis. 2005 Jul;181(1):159-65.
4. Xie LQ, Wang X. C-reactive protein and atherosclerosis. Sheng Li Ke Xue Jin Zhan. 2004 Apr;35(2):113-8.
5. Verma S. C-reactive protein incites atherosclerosis. Can J Cardiol. 2004 Aug;20 Suppl B29B-31B.
6. Stochmal E, Szurkowska M, Czarnecka D, et al. Association of coronary atherosclerosis with insulin resistance in patients with impaired glucose tolerance. Acta Cardiol. 2005 Jun;60(3):325-31.
7. Sharrett AR, Patsch W, Sorlie PD, et al. Associations of lipoprotein cholesterols, apolipoproteins A-I and B, and triglycerides with carotid atherosclerosis and coronary heart disease. The Atherosclerosis Risk in Communities (ARIC) Study. Arterioscler Thromb. 1994 Jul;14(7):1098-104.
8. Muis MJ, Bots ML, Bilo HJ, et al. High cumulative insulin exposure: a risk factor of atherosclerosis in type 1 diabetes? Atherosclerosis. 2005 Jul;181(1):185-92.

9. Malkin CJ, Pugh PJ, Jones RD, Jones TH, Channer KS. Testosterone as a protective factor against atherosclerosis—immunomodulation and influence upon plaque development and stability. J Endocrinol. 2003 Sep;178(3):373-80.

10. Howes PS, Zacharski LR, Sullivan J, Chow B. Role of stored iron in atherosclerosis. J Vasc Nurs. 2000 Dec;18(4):109-14.

11. Jones RD, Nettleship JE, Kapoor D, Jones HT, Channer KS. Testosterone and atherosclerosis in aging men: purported association and clinical implications. Am J Cardiovasc Drugs. 2005;5(3):141-54.

12. de Valk B, Marx JJ. Iron, atherosclerosis, and ischemic heart disease. Arch Intern Med. 1999 Jul 26;159(14):1542-8.

13. Drexel H, Amann FW, Beran J, et al. Plasma triglycerides and three lipoprotein cholesterol fractions are independent predictors of the extent of coronary atherosclerosis. Circulation. 1994 Nov;90(5):2230-5.

14. Chau LY. Iron and atherosclerosis. Proc Natl Sci Counc Repub China B. 2000 Oct;24(4):151-5.

15. Bolad I, Delafontaine P. Endothelial dysfunction: its role in hypertensive coronary disease. Curr Opin Cardiol. 2005 Jul;20(4):270-4.

16. Chakraphan D, Sridulyakul P, Thipakorn B, et al. Attenuation of endothelial dysfunction by exercise training in STZ-induced diabetic rats. Clin Hemorheol Microcirc. 2005;32(3):217-26.

17. Harvey PJ, Picton PE, Su WS, et al. Exercise as an alternative to oral estrogen for amelioration of endothelial dysfunction in postmenopausal women. Am Heart J. 2005 Feb;149(2):291-7.

18. Hink U, Tsilimingas N, Wendt M, Munzel T. Mechanisms underlying endothelial dysfunction in diabetes mellitus: therapeutic implications. Treat Endocrinol. 2003;2(5):293-304.

19. Lteif AA, Han K, Mather KJ. Obesity, insulin resistance, and the metabolic syndrome: determinants of endothelial dysfunction in whites and blacks. Circulation. 2005 Jul 5;112(1):32-8.

20. Newby DE, McLeod AL, Uren NG, et al. Impaired coronary tissue plasminogen activator release is associated with coronary atherosclerosis and cigarette smoking: direct link between endothelial dysfunction and atherothrombosis. Circulation. 2001 Apr 17;103(15):1936-41.

21. Panus C, Mota M, Vladu D, Vanghelie L, Raducanu CL. The endothelial dysfunction in diabetes mellitus. Rom J Intern Med. 2003;41(1):27-33.

22. Papamichael CM, Aznaouridis KA, Stamatelopoulos KS, et al. Endothelial dysfunction and type of cigarette smoked: the impact of 'light' versus regular cigarette smoking. Vasc Med. 2004 May;9(2):103-5.

23. Suvorava T, Lauer N, Kojda G. Physical inactivity causes endothelial dysfunction in healthy young mice. J Am Coll Cardiol. 2004 Sep 15;44(6):1320-7.

24. Toikka JO, Ahotupa M, Viikari JS, et al. Constantly low HDL-cholesterol concentration relates to endothelial dysfunction and increased in vivo LDL-oxidation in healthy young men. Atherosclerosis. 1999 Nov 1;147(1):133-8.

25. Vakkilainen J, Makimattila S, Seppala-Lindroos A, et al. Endothelial dysfunction in men with small LDL particles. Circulation. 2000 Aug 15;102(7):716-21.

26. Apetrei E, Ciobanu-Jurcut R, Rugina M, Gavrila A, Uscatescu V. C-reactive protein, prothrombotic imbalance and endothelial dysfunction in acute coronary syndromes without ST elevation. Rom J Intern Med. 2004;42(1):95-102.

27. Kunes P. C-reactive protein in the pathogenesis of atherosclerosis: advantage and pitfalls of the "Mainz hypothesis." Cas Lek Cesk. 2005;144(1):25-31.

28. Targher G, Bertolini L, Zoppini G, Zenari L, Falezza G. Increased plasma markers of inflammation and endothelial dysfunction and their association with microvascular complications in Type 1 diabetic patients without clinically manifest macroangiopathy. Diabet Med. 2005 Aug;22(8):999-1004.

29. Sainani GS, Sainani R. Homocysteine and its role in the pathogenesis of atherosclerotic vascular disease. J Assoc Physicians India. 2002 May;50 Suppl16-23.

30. Drouet L, Bal dit SC. Is fibrinogen a predictor or a marker of the risk of cardiovascular events? Therapie. 2005 Mar;60(2):125-36.

31. Caballero AE, Arora S, Saouaf R, et al. Microvascular and macrovascular reactivity is reduced in subjects at risk for type 2 diabetes. Diabetes. 1999 Sep;48(9):1856-62.

32. Ceriello A. Hyperglycaemia: the bridge between non-enzymatic glycation and oxidative stress in the pathogenesis of diabetic complications. Diabetes Nutr Metab. 1999 Feb;12(1):42-6.

33. Cubeddu LX, Hoffmann IS. Insulin resistance and upper-normal glucose levels in hypertension: a review. J Hum Hypertens. 2002 Mar;16 Suppl 1S52-5.

34. Nowak A, Stankiewicz W, Szczesniak L, Korman E. Glucosamine in the blood serum of young people with diabetes mellitus type 1. Endokrynol Diabetol Chor Przemiany Materii Wieku Rozw. 1999;5(2):97-101.

35. Steinbaum SR. The metabolic syndrome: an emerging health epidemic in women. Prog Cardiovasc Dis. 2004 Jan;46(4):321-36.

36. Woodman RJ, Chew GT, Watts GF. Mechanisms, significance and treatment of vascular dysfunction in type 2 diabetes mellitus: focus on lipid-regulating therapy. Drugs. 2005;65(1):31-74.

37. Brandes RP, Fleming I, Busse R. Endothelial aging. Cardiovasc Res. 2005 May 1;66(2):286-94.

38. Kravchenko J, Goldschmidt-Clermont PJ, Powell T, et al. Endothelial progenitor cell therapy for atherosclerosis: the philosopher's stone for an aging population? Sci Aging Knowledge Environ. 2005 Jun 22;2005(25):e18.

39. Rubanyi GM. The role of endothelium in cardiovascular homeostasis and diseases. J Cardiovasc Pharmacol. 1993;22 Suppl 4:S1-14.

40. Available at: http://www.medreviews.com/ pdfs/articles/RIU_5Suppl7_S21.pdf. Accessed April 20, 2005.