# Reactive oxygen species, anti-oxidant enzymes and smoldering chronic inflammation: Relevance to diabetes mellitus, atherosclerosis, and menopausal metabolic syndrome

In the present issue of the journal the role of glutathione peroxidase (GPx) activity in obese and non-obese diabetic patients has been investigated *vis-a-vis* insulin therapy.[1] The authors conclude that there is a persistent higher level of oxidative stress in obese diabetics after control of hyperglycemia, as compared to non-obese diabetics. Even the basal levels of GPx are almost half in the obese group as compared to the non-obese group. Over the last decade, reactive oxygen species (ROS), that have been inadequately dealt with by the body's defense mechanisms, have led to a chronic release of proinflammatory cytokines and a smoldering chronic inflammation.[2] The nature of such an inflammation is being actively investigated in diverse metabolic diseases, namely, obesity, Polycystic ovary syndrome (PCOS), type 2 diabetes mellitus, atherosclerosis, and even malignancy.[2-7] Besides the direct cellular and cytokine pathogenetic factors, a long list of other risk factors is emerging. The proclivity to unresolved oxidant and inflammatory damage has multiple genetic, epigenetic, environmental, and lifestyle determinants. As a consequence, any cross-sectional study monitors the effects of intervention by only a small number of variables, as markers have limitations. These limitations become obvious particularly in conditions like obesity and diabetes mellitus, which are syndromes of immense complexity. The authors have expressed their inability to monitor basally and serially the levels of glycosylated hemoglobin — a hall mark of glycemic control. Similarly in a longitudinal study like this, both at 24 and 48 weeks, the evaluation of the lipid profile and other markers of oxidant damage would have been desirable. However, this article opens up the need to investigate the impact of adiposity in diverse disorders affecting mature women.

Earlier, gender-related differences in erythrocyte GPx activity had been demonstrated in a large cohort of healthy subjects — 150 women (90 premenopausal and 60 postmenopausal) and 150 age-matched healthy men.[7] The erythrocyte GPx was significantly higher in the premenopausal group as compared to the other two groups. However, there was no difference in the GPx activity between postmenopausal group and age-matched men. Estrogen replacement (ERT) administered by the transdermal route significantly increased the GPx activity in postmenopausal women receiving the treatment, as compared to non-treated postmenopausal women. The antioxidant and lipid modulating effects of Soya isoflavones were observed by us in peri-/postmenopausal women.[8] There was a significant decline in plasma lipid-peroxides (LPO), notwithstanding any change in the body mass index, after three months. We had not studied the effects of phytoestrogens on glucose metabolism. In another study on women with surgical menopause ($N=26$), physiological menopause ($N=54$), and premenopausal controls ($N=40$), the effects of estradiol and estroprogestin were investigated on the erythrocyte enzyme antioxidant system.[9] These authors also observed a higher level of LPO in postmenopausal women that decreased after hormone replacement therapy. The effect was accompanied by a rise in GPx and glutathione (GSH). However, there were no significant baseline or post interventional changes in catalase and superoxide dismutase. Neither this group nor our study had focused on the baseline and the subsequent alterations in glucose metabolism. In a CSIR-NMITLI program, *Curcuma longa* and *Phyllanthus embelica* were investigated for insulin sensitizing and other antidiabetic activities. An active principle of *P. embelica* — galic acid, was shown to significantly increase MnSOD mRNA along with marked cytoprotective activity on islet beta cells against palmitic acid and glucose.[10] Therefore, in future, interventions should focus on not only free scavenging, but also on activating genes for antioxidant enzymes. It is only then that normalizing mitochondrial superoxide production can block the pathways of hyperglycemic lesions.

In metabolic syndrome, obesity, and diabetes, the role of elevated homocysteine has emerged as a cardiovascular risk factor. Homocysteine, besides its harmful effect on inadequate methylation of DNA, has other effects.[11] Although less investigated, homocysteine decreases bioavailable nitric oxide by a mechanism involving glutathione peroxidase, thus further aggravating the endothelial dysfunction induced by oxidant damage and proinflammatory cytokines. It has been shown that overexpression of cellular GSH rescues homocysteine-induced endothelial dysfunction. Hence, one wonders how the massive vitamin B-12 deficiency in our women and subsequent hyperhomocystenemia would be important contributory factors in chronic smoldering inflammatory disease processes.

One should not forget that glutathione peroxidases have multiple forms.[12] The factors that can upregulate GPx-1 can downregulate proatherogenic gene expression in human endothelial cells.[13] The loss of hetrozygocity of the human cytosolic *GSHI* gene has been demonstrated in lung cancer, another consequence of long-term smoldering inflammation.[14]

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## REFERENCES

1. Goyal R, Singhai M and Abul Faiz Faizy. Glutathione peroxidase activity in obese and non-obese diabetic patients and role of hyprglycemia in oxidative stress. Journal of Midlife health 2011;2:72-6.
2. Wise RE. The inflammatory syndrome: The role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol 2004;15:2792-800.
3. Pandey S, Srinivas M, Agashe S, Joshi J, Galvankar P, Prakasam CP, *et al*. Menopause and metabolic syndrome: A study of 498 urban women from western India. J Midlife Health 2010;1:63-9.
4. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, *et al*. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 2003;112:1821-30.
5. Moller DE. Potential role of TNF-alpha in the pathogenesis of insulin resistance and type 2 diabetes. Trends Endocrinol. Metab 2000;11:212-7.
6. Skurk T, Kolb H, Müller-Scholze S, Röhrig K, Hauner H, Herder C. The proatherogenic cytokine interleukin-18 is secreted by human adipocytes. European Journal of Endocrinology 2005;152:863-8.
7. Seth Rakoff-Nahoum. Why Cancer and Inflammation? Yale J Biol Med 2006;79:123-30.
8. PPandey SN, Vaidya AB, Vaidya RA, Joshi JV, Agashe SV, Chandrashekar S, *et al*. Evaluation of anti-oxidant and lipid-modulating effects of soy isoflavones and root powder of *Glycyrrhiza glabra linn* in peri/postmenopausal women. Indian Drugs 2006;43:130-135.
9. Bednarek-Tupikowska G, Tworowska U, Jedrychowska I, Radomska B, Tupikowski K, Bidzinska-Speichert B, *et al*. Effects of oestradiol and oestroprogestin on erythrocyte antioxidative enzyme system activity in postmenopausal women. Clin Endocrinol (Oxf) 2006;64:463-8.
10. Pandey SN, Vaidya ADB, Vaidya RA, Talwalkar S. Hyperhomocysinemia as a cardiovascular risk factor in Indian women: Determinents and directionality. J Assoc Physicians India 2006;54:769-74.
11. Wang X, Cui L, Joseph J, Jiang B, Homocysteine induces cardiomyocyte dysfunction and apoptosis through p38 MAPK-mediated increase in oxidant stress. J Mol Cell Cardiol 2011;29:Epub ahead of print].
12. Artur JR. The glutathione peroxidases. Cell Mol life Sci 2000;57:1825-35.
13. Weiss N, Zhang YY, Heydrick S, Bierl C, Loscalzo J. Overexpression of cellular glutathione peroxidase rescues homocystiene-induced endothelial dysfunction. Proc natl Acad Sci U S2001;A98:12503-12508.
14. Ketterer B, Harris JM, Talaska G, Meyer DJ, Pemble SE, Taylor JB, *et al*. The human glutathione S-transferase supergene family, its polymorphism, and its effects on susceptibility to lung cancer. Environ Health Perspect 1992;98:87-94.

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