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Corticosteroids and endothelial dysfunction

Assessment of endothelial-mediated relaxation in situ is rapidly becoming the standard gauge of individual susceptibility to future cardiovascular dysfunction (Hadi et al 2005).

In this issue of *Vascular Health and Risk Management*, Turner and colleagues (2005), in a pilot investigation, have proposed the concept that endothelial dysfunction in patients with systemic lupus erythematosus, but with no known cardiovascular disease, is the result of exposure to corticosteroids. Even though the study by Turner and colleagues (2005) has a small sample size and may not have the desired power to conclusively indicate the relationship between endothelial dysfunction and corticosteroids use, it is worth considering the possible basis for such an association.

An interesting angle of this hypothesis is the impact of corticosteroids on the plasma glucose levels and insulin. The metabolic actions of corticoid steroid, namely cortisol, are well recognized, and it is counted among the counter-regulatory stress hormones. Infusion of hydrocortisone is believed to increase plasma glucose, free fatty acid, and insulin concentrations, and is thus believed to increase metabolic rate in healthy individuals (Brillon et al 1995). Moreover, despite an elevated insulin concentration, hypercortisolemia results in a significantly higher plasma glucose concentration (Nielsen et al 2003). In addition, during the infusion of glucose in healthy subjects, the integrated glycemic response above baseline is higher in the presence of hydrocortisone than saline infusion, which suggests that plasma glucose level is less rigorously controlled and seems to remain elevated for a longer duration in presence of the glucocorticoid (Nielsen et al 2003). Of interest, is that treatment with prednisolone, which reportedly causes insulin resistance, hyperinsulinemia, and hyperglucagonemia (Gravholt et al 2002), as well as infusion of hydrocortisone, also seems to result in insulin resistance (Nielsen et al 2003).

There is now ample evidence in the literature that provides both an acute and a chronic link between glucose and endothelial dysfunction in animals and humans (Ceriello 2004; Triggle et al 2005). Some compelling early evidence was presented by Kawano and colleagues (1999), which indicated that flow-mediated vasodilation is decreased after glucose loading in normal subjects and patients with type 2 diabetes mellitus, and it was suggested that suppression of endothelium-dependent vasodilation was probably due to the production of oxygen-derived free radicals. Moreover, Title et al (2000) reported that the acute transient decrease in flow-mediated dilation in healthy subjects by oral glucose could be prevented by vitamins C and E. It has also been reported that administration of (6R)-5,6,7,8-tetrahydrobiopterin, but not (6S)-5,6,7,8-tetrahydrobiopterin, can reverse the transient glucose-induced endothelial dysfunction in healthy individuals (Ihlemann et al 2003).

Among the mechanisms that have been postulated to explain endothelial dysfunction during elevation of plasma glucose levels are glycosylation of the insulin receptor substrate, which eventually leads to an impediment in the ability of protein kinase B (Akt) to enhance endothelial nitric oxide (NO) synthase activity, which then manifests as a lower amount of NO being produced by the endothelial cells. Another proposed mechanism is that an elevation of oxidative stress due to hyperglycemia results in reduced levels of tetrahydrobiopterin, which subsequently

leads to an uncoupling of NO synthase that acts to produce superoxide rather than NO (Triggles et al 2005). Both the former and the latter mechanisms can account for the decrease in NO generation and reduced vasodilation.

Recently, experimental data from rabbits seem to suggest that glucose levels observed in daily clinical practice can induce endothelial dysfunction in both macro- and micro-circulation (Gomes et al 2004). Collectively, the majority of the evidence in the literature seems to support the concept that a spike in plasma glucose levels and/or uncontrolled high plasma glucose levels have detrimental effects on vascular function and clearly seem to cause impairment in endothelial-mediated vasorelaxation, resulting in endothelial dysfunction over the long-term. It may not be a far fetched hypothesis that the basis for endothelial dysfunction in patients with lupus erythematosus treated with glucocorticoids is a lack of rigorous control of plasma glucose levels due to insulin resistance caused by glucocorticoid use. It seems that stress-related endothelial dysfunction can be prevented by blocking cortisol production with metyrapone in subjects without coronary heart disease risk factors, thus presenting a direct facilitative role for cortisol in endothelial dysfunction (Broadley et al 2005). This can be linked to significant changes in plasma glucose level, among other things. It is clear that the paper by Turner and colleagues (2005) is hypothesis generating and obviously a much larger study is warranted. However, it is also worthwhile to consider whether glucose has a role and is the link between endothelial dysfunction and glucocorticoid use in this population of patients.

Cortisol also has a permissive effect in enhancing vasoactive actions of catecholamines through glucocorticoid receptors, and has been suggested to have pathogenic role in secondary hypertension. The role of cortisol in hypertension is the subject of an elegant review by Whitworth et al (2005), also in this issue of *Vascular Health and Risk Management*. This review also reaches the conclusion that cortisol may affect the cardiovascular tree by having a negative impact on the vasodilator actions of

NO. This would agree with the concept that glucocorticoids have a protagonist and pivotal role in aiding and perhaps inducing endothelial dysfunction in patients with lupus erythematosus that are treated with this class of compounds.

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