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For debate

Diabetes mellitus and hypertension: the possible role of hyperglycaemia through oxidative stress

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It is estimated that 30% of the adult population may have arterial hypertension [1], and that 30–60% of diabetic patients have associated hypertension [2]. A series of observations has provoked much speculation and interest in the phenomenon of insulin resistance as a common factor underlying the link between obesity, diabetes mellitus and hypertension [3].

Epidemiological data linking hyperinsulinaemia, obesity and hypertension seem to be associative rather than causal, but this is inconsistent [4]. It has become increasingly evident that the relationship between insulin, insulin-resistance and blood pressure varies according to racial group [5]. On the other hand, chronic and marked hyperinsulinism in patients with insulinomas is not associated with elevated blood pressure values [6]. Although the causal relationship between insulin and blood pressure is still inconclusive, recent evidence suggests that a reduced hepatic insulin clearance may contribute to increased insulin levels in hypertension [7, 8]. To summarize, current experimental findings linking hyperinsulinaemia or insulin resistance to hypertension have been provocative: many inconsistencies remain and causal relationships have not been established.

Although diabetes is a well-established risk factor for macrovascular disease, the role of hyperglycaemia is less clear, perhaps because a strong relationship between glucose levels and cardiovascular risk factors has not been consistently found [9]. However, evaluating the relationship between HbA_{1C} and cardiovascular disease in the survivors of the original cohort of the Framingham Heart Study, Singer et al. [10] found that HbA_{1C} was significantly related to prevalent cardiovascular disease among women but not men. We found a positive correlation between HbA_{1C} and established risk factors for cardiovascular disease, particularly systolic blood pressure and total cholesterol [11]. This may indicate that the impact of hyperglycaemia on cardiovascular risk factors may be stronger than previously thought.

It is now well-established that a reduction of anti-oxidant defence is an important cardiovascular risk factor [12] and much evidence has been accumulated indicating that an increased free radical generation is present in diabetes [13, 14], hyperglycaemia and non-enzymatic glycation of proteins themselves being important sources of free radicals [15, 16].

Endothelial cells play a major role in arterial relaxation. The factor released by the endothelium that causes vascular relaxation is called endothelium-derived relaxing factor, and nitric oxide is believed to be one such factor [17]. The half-life of nitric oxide is only a few seconds since it is rapidly degraded by the oxygen-derived free radical superoxide anion. An imbalance of this system has been hypothesized to play a role in the development of arterial hypertension [18]. Since an increased serum superoxide generation, correlated with glucose and glycated protein plasma levels has been found in diabetic subjects [19], the raised prevalence of hypertension in diabetes might be linked to this increased generation of free radicals. This hypothesis is supported by the following observations: glucose alters some endothelial cell functions through free radicals [20], free radicals specifically abolish endothelium-dependent relaxation in the aorta of diabetic and hypertensive rats [21, 22], an anti-oxidant deficiency in the diet contributes to the aetiology of hypertension in populations [23], an elevated plasma glucose concentration impairs endothelium-dependent relaxation in the rabbit [24], anti-oxidant drugs ameliorate the abnormal arterial vasomotion in diabetes [25] and also show a blood pressure lowering effect in both diabetic and hypertensive subjects [26].

Many studies have confirmed the existence of a genetic contribution to the determination of blood pressure [27]. In this respect, the balance between hyperglycaemia and the different, genetically-determined anti-oxidant cellular defence may account for a different effect of hyperglycaemia-related increased free radical production in the development of hypertension in diabetic patients. This point of view is supported, for example, by the evidence that, in carcinogenesis, the genetically-determined level of cellular anti-oxidant defences may condition the neoplastic tranformation of cells induced by the free radicals [28].

Although more than one factor is probably implicated in the development of hypertension in diabetes, the present hypothesis puts in perspective the crucial role of glucose in the aetiology of diabetic complications [29]. Anti-oxidants have blood pressure lowering effects [26] and also reduce one source of free radicals, protein glycation [30]. Anti-oxidant supplementation might be advantageously used to support anti-hypertensive therapy in diabetic patients.

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