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Is oxidative stress the missing link between insulin resistance and atherosclerosis?

Dear Sir,

It is noteworthy that the hypotheses which have been advocated to explain the pathogenesis of cardiovascular disease (CVD) have been largely focused on the atherogenic potential of insulin and glucose. Insulin, or more properly insulin resistance, i.e. the metabolic abnormality characterizing "syndrome X", has probably the most passionate supporters [1], but the evidence provided to affirm its involvement in the development of CVD is not univocal [2]. Independently of the blood insulin concentration and of the presence of diabetes, blood glucose level has been proven to be associated with CVD: subjects who have high-normal levels of blood glucose [3] and of glycated haemoglobin [4] but who are non-diabetic and non-insulin-resistant have an increased incidence of CVD.

When insulin resistance and glucose have been investigated separately, they have been demonstrated to act as independent determinants of several risk factors for CVD. Hypertension has been linked to insulin resistance [5], but data also support the hypothesis that it might be associated with an impaired carbohydrate metabolism [6]. The modifications of blood lipids typical of insulin resistance [1] are also present in patients with impaired glucose tolerance or diabetes [7]. Finally, plasma fibrinogen and PAI-1 concentrations have been shown to be increased in states of insulin resistance [8], but also during hyperglycaemia [9].

When two substances such as insulin and glucose, which appear so closely related physiologically, are implicated independently of each other in the development of CVD, it is legitimate to suspect that they may act by means of a third common mechanism.

It is now clear that impaired glucose metabolism leads to oxidative stress [10], and that the glycation of proteins produces free oxygen radicals [10]. The possibility that oxidative stress, i.e. the release of free radicals unbalanced by the protective effect of anti-oxidants, might have a pathogenetic role in the development of CVD has been recently raised [11]. Oxidative stress therefore might represent the biochemical mechanism through which the alteration of glucose metabolism might result in the development of CVD. Is it possible to also link such a mechanism to insulin resistance?

In our opinion, this sounds plausible. Preliminary findings in animal models indicate that rats with insulin resistance show signs of increased lipid peroxidation [12], while the administration of anti-oxidants improves the action of insulin in humans [13–14]. This last evidence is consistent with the finding that troglitazone, the structure of which is similar to that of vitamin E [15], improves insulin-resistance in non-diabetic obese subjects [16]. In adipocytes cultured in vitro, insulin increases the production of H_2O_2 [17], which has been shown to mimic the action of insulin [18]. Furthermore, the administration of vanadium reproduces the action of insulin [19] through the intercellular release of free radicals [20]. On the basis of this evidence, we propose oxidative stress as the best candidate for the role of final common mediator by which glucose and insulin resistance, via their action on risk factors, might contribute to the development of CVD. Experimental models of insulin resistance are available and it could be worth testing whether the administration of an anti-oxidant in this setting might result in the prevention of atherosclerosis and/or of its risk factors.

Yours sincerely,
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Could coenzyme Q10 and L-carnitine be a treatment for diabetes secondary to 3243 mutation of mtDNA?

Dear Sir,

Maternally-inherited "diabetes and deafness syndrome" has been related to a point mutation of mtDNA leading to an A to G transition at position 3243 in the tRNA leucine gene [1–9]. This mutation has been previously observed in patients with MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes). In this disease, as in other mitochondrial myopathies, treatment by coenzyme Q10 has been shown to dramatically improve muscle oxidative metabolism in some patients [10–14]. We wondered whether coenzyme Q10 or related compounds which improve mitochondrial oxidative processes might be useful in the treatment of this type of diabetes. Accordingly, we treated a diabetic patient who exhibited the 3243 mutation with a combination of coenzyme Q10 (150 mg/day) and L-carnitine (2 g/day) for 6 months in order to evaluate whether improvement of glucose tolerance as well as muscle oxidative functions could be observed.

The patient was a 49-year-old woman who had a 3243 mutation in the tRNA leucine gene identified with a combination of maternally-inherited diabetes, deafness and atypical pigmentary retinitis. Non-insulin-dependent diabetes was diagnosed at the age of 25 years and insulin treatment had to be introduced at the age of 40 years after oral hypoglycaemic agent failure. Of the total mtDNA, 11 % of that in blood cells and 74 % of that in muscle was found to be mutated. Muscle impairment had been diagnosed by pathology and ^{31}P nuclear magnetic resonance spectroscopy. The ^{31}P magnetic resonance spectroscopy data were recorded throughout a standardized rest-exercise-recovery protocol as previously described [15]. Low residual insulin secretion was assessed by C-peptide measurement before and after i. v. injection of 1 mg of glucagon (Novo Nordisk laboratory Gentofte, Denmark).

The effect of the treatment on glucose tolerance at 3 and 6 months is summarized in Table 1. During coenzyme Q10 and L-carnitine administration metabolic post-stimulative C-peptide values did not change. In contrast, at the muscular level the patient felt better and ^{31}P NMR spectroscopy showed an improvement in oxidative metabolism. Metabolic changes were recorded before and after 3 months of treatment. Decreased phosphocreatine/inorganic phosphate (PCr/Pi) ratio measured at rest, before treatment, indicated an impaired muscle energy state, while after palliative therapy, normalization of the value reflected the improvement of oxidative metabolism. Similarly, ADP concentration, calculated from the creatine kinase equilibrium, returned to normal after treatment (35.68 vs 9.87 μmol/l). During the 3-min exercise of the forearm flexor muscles, glycolysis-induced pH decrease was large (6.23) compared to the pre-treatment value (6.63) whereas a trend towards a limitation of the PCr breakdown (20.98 vs 15.36 mmol/l) was observed. Kinetics of PCr/Pi recovery, closely associated with the mitochondrial function, was slower than normal before treatment, as a manifestation of oxidative impairment. Taking into account the effect of end-of-exercise pH on recovery processes [16], the PCr/Pi kinetics returned to normal upon treatment, further confirming the positive effect of coenzyme Q palliative therapy upon muscular oxidative metabolism. Finally, the clinical tolerance was

Table 1. Effects of treatment by coenzyme Q10 (150 mg/day) and L-carnitine (2 g/day)

	Month of therapy			
	– 6	0	3	6
Daily insulin dose (IU/day)	92	100	92	106
Basal C-peptide (nmol/l)	0.17	0.22	0.15	0.10
Post-stimulative C-peptide (nmol/l)	0.23	0.22	0.30	0.15
HbA_{1c} (%)	8.1	7.9	8.2	8.1

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