SHORT COMMUNICATION

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Syndrome X
10 Years After

Gerald Reaven

Stanford University School of Medicine, Stanford, California, USA

Resistance to insulin-mediated glucose disposal is present in the majority of patients with type 2 diabetes, a disease reaching epidemic proportions in many populations around the world. In addition, as many as 50% of all patients with high blood pressure are also insulin resistant. Furthermore, the ability of insulin to mediate glucose disposal varies approximately 10-fold in apparently healthy humans, and this defect in approximately 25% of these individuals approaches the magnitude of the insulin resistance seen in patients with type 2 diabetes or hypertension. Since approximately 50% of the variability in insulin action can be attributed to differences in behaviour, e.g. obesity, physical inactivity, and cigarette smoking all increase the degree of insulin resistance, the other 50% of the variability is likely to be related to genetic differences. In this context, the effect of ethnic differences is quite powerful, with individuals of European ancestry appearing to be the most insulin-resistant population.

Irrespective of the relative effects of nature versus nurture, insulin-resistant individuals can only remain glucose tolerant if the pancreas is capable of responding to this defect by secreting large amounts of insulin, and type 2 diabetes develops when insulin-resistant persons cannot sustain this state of compensatory hyperinsulinaemia. However, the ability of hyperinsulinaemia to prevent decompensation of glucose tolerance appears to be a mixed blessing. Individuals who are insulin resistant and hyperinsulinaemic are more likely to develop glucose intolerance, hypertension, and dyslipidaemia, characterised by high plasma triglyceride (TG) and low high density lipoprotein (HDL) cholesterol levels. All of these changes have been shown to increase the risk of coronary heart disease (CHD), and in 1988 were explicitly addressed and designated as comprising a syndrome X.

Since the introduction of the concept of syndrome X, several other abnormalities have been defined as being related to insulin resistance and/or compensatory hyperinsulinaemia and CHD. For example, it is now clear that the dyslipidaemia associated with insulin resistance and/or compensatory hyperinsulinaemia also includes the appearance of smaller, denser low density lipoprotein (LDL) particles and enhanced postprandial lipaemia; both of these latter changes have also been identified as increasing the risk of CHD. In addition, study of a normouricaemic population has defined significant correlations between resistance to insulin-mediated glucose uptake, the magnitude of the plasma insulin response to an oral glucose challenge, decreased urinary uric acid clearance, and serum uric acid concentration – thus providing an explanation for the well established association between elevated uric acid concentrations and CHD. Another link between insulin resistance and/or compensatory hyperinsulinaemia and CHD appears to involve plasminogen activator inhibitor-1 (PAI-1). PAI-1 levels have been shown to be associated with increased risk of CHD, and, more recently, evidence has been published demonstrating a significant relationship between PAI-1 levels and both insulin resistance and hyperinsulinaemia. Finally, there is evidence that insulin resistance

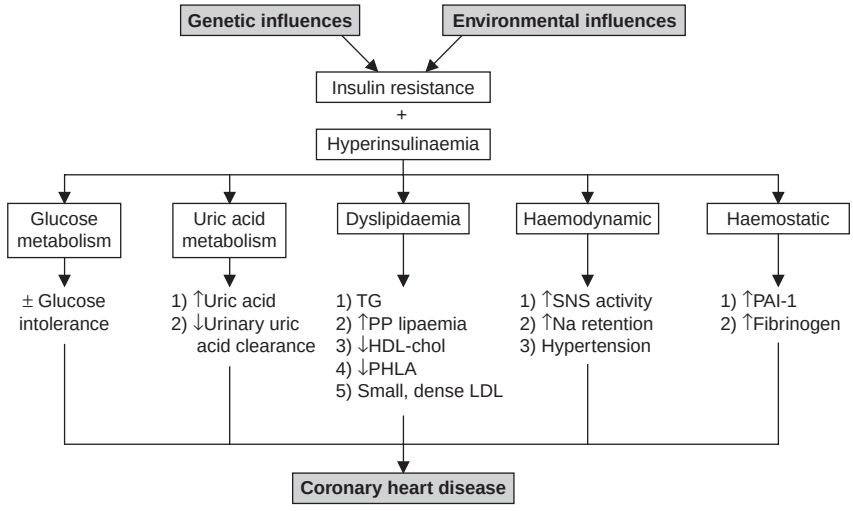

Fig. 1. Proposed role of insulin resistance and compensatory hyperinsulinaemia in coronary heart disease. **HDL-chol** = high density lipoprotein cholesterol; **LDL** = low density lipoprotein; **PAI-1** = plasminogen activator inhibitor-1; **PHLA** = post-heparin lipolytic activity; **PP** = post-prandial; **SNS** = sympathetic nervous system; **TG** = triglyceride.

and/or compensatory hyperinsulinaemia and sympathetic nervous system activity are highly correlated, providing an additional link to vascular disease.

In conclusion, the number of abnormalities associated with insulin resistance and/or compensatory hyperinsulinaemia has grown considerably during the 10 years since the notion of syndrome X was introduced. As summarised in figure 1, it includes abnormalities of glucose, uric acid, and lipid metabolism, as well as untoward haemodynamic and haemostatic changes. These abnormalities tend to cluster in the same individual, and represent major risk factors for CHD.

Correspondence and reprints: Prof. *Gerald Reaven*, Shaman Pharmaceuticals Inc., 213 East Grand Avenue, South San Francisco, CA 94080-4812, USA.