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Is insulin vasculotoxic?

J.S. Yudkin

Centre for Diabetes and Cardiovascular Risk, Department of Medicine, University College London Medical School, London, UK

Insulin resistance is generally taken to imply insensitivity of insulin sensitive tissues to the glucose effects of insulin. These actions include stimulation of glucose uptake, mainly by skeletal muscle, and suppression of hepatic glucose output. Normal glucose tolerance can be maintained in such subjects by increased beta-cell output of insulin, but these people show several other phenotypic characteristics which are associated with increased cardiovascular risk. Thus, insulin resistance and hyperinsulinaemia cluster with elevated blood pressure, hypertriglyceridaemia and low concentrations of high density lipoprotein cholesterol, and elevated levels of plasminogen activator inhibitor-1, an inhibitor of fibrinolysis. These risk factors are individually associated with cardiovascular disease, but prospective epidemiological studies suggest an additional, independent, role for hyperinsulinaemia in predicting coronary heart disease. It has been proposed that insulin may exert pro-atherogenic effects, but it is also possible that hyperinsulinaemia represents a surrogate marker for insulin resistance, which has been put forward as the true culprit.

As an alternative explanation, insulin resistance and cardiovascular disease may both represent consequences of a common antecedent. Endothelial dysfunction plays an important role in both atherogenesis and coagulation, and the endothelium has recently also been shown to play an important role in insulin action. During a hyperinsulinaemic clamp, limb blood flow increases, and this enhances the delivery of both insulin and substrate to insulin sensitive tissues. It has been suggested that the haemodynamic action of insulin underlies as much as 40% of its effect on peripheral glucose uptake. The endothelium also acts as a barrier to insulin transport from the luminal to the interstitial compartment, where it can bind to insulin receptors, and this may offer a second mechanism of association of endothelial dysfunction with impaired insulin action. Our own experimental data have shown relationships between levels of von Willebrand factor, a marker of endothelial dysfunction, and impaired insulin mediated glucose uptake. Endothelial dysfunction is not a disease entity in its own right, and may be the consequence of other pathological processes. Although the proposed mechanisms could underlie the association of insulin resistance with microalbuminuria or cigarette smoking, no experimental data exist which show impaired transport in subjects with endothelial dysfunction.

We have previously reported associations between concentrations of fibrinogen, an acute phase marker, and hyperinsulinaemia in population studies, which are difficult to explain through the known actions of insulin. For this reason, we have explored the links between features of the insulin resistance cluster, markers of endothelial dysfunction, and acute phase markers and their determinants. We studied 107 Europid non-diabetic subjects (59 male, 48 female; age 59.0 ± 10.9 years). Standard cardiovascular risk factors were measured, together with albumin excretion rate, three serum markers of endothelial dysfunction, C-reactive protein, and circulating levels of tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6). We created sum scores for insulin resistance, endothelial dysfunction and acute phase response by calculating the mean value of each of the variables as Z-scores, so providing a unit-free score for the three clusters. The insulin resistance and endothelial scores correlated with a coefficient of 0.32 ($p = 0.0008$), but there was a strong relationship

Corresponding author: Professor J.S. Yudkin, Centre for Diabetes and Cardiovascular Risk, Department of Medicine, University College London Medical School, G Block, Archway Wing, Whittington Hospital, Archway Road, London N19 3UA, UK

Abbreviations: TNFα, Tumour necrosis factor-alpha; IL-6, interleukin-6.

between the insulin resistance and acute phase scores ($r = 0.59$, $p < 0.00005$). The third of these correlations, between endothelial and acute phase scores, is also significant ($r = 0.43$, $p < 0.00005$). If the acute phase and endothelial scores were included in the same model, the former remained significantly associated with insulin resistance score (partial $r = 0.61$, $p < 0.00005$) but not the latter (partial $r = -0.02$, $p = 0.82$). Circulating concentrations of TNF-α were related to all insulin resistance variables. Concentrations of IL-6 were also related to several of the insulin resistance cluster and endothelial markers, including albumin excretion rate, while the relationships for C-reactive protein were generally stronger. Both the acute phase score and concentrations of C-reactive protein correlated weakly with titres of helicobacter, chlamydia and cytomegalovirus antibodies but the acute phase score as a whole, and the concentrations of IL-6, TNF-α and C-reactive protein, were strongly related to measures of total, and particularly central, obesity.

In 24 healthy Caucasian subjects subcutaneous abdominal vein cannulation was used to study adipose tissue production of cytokines. Venous concentrations of IL-6 were consistently greater than arterial levels both fasting and at 1, 3 and 5 h following a high carbohydrate meal but there were no significant differences in the concentration of TNF-α between the abdominal venous and arterial samples. We calculated that adipose tissue produced 15–25 % of the systemic IL-6 in the fasting state and 30–45 % post-prandially.

Among the known metabolic effects of TNF-α are inhibition of the action of lipoprotein lipase and stimulation of lipolysis, these actions being shared with IL-6, perhaps affecting insulin action through Randle cycle mechanisms. TNF-α impairs the function of the insulin signalling pathway by effects on phosphorylation of both the insulin receptor and its substrate, IRS-1. In addition, cytokines have significant damaging effects on the endothelial cell. We postulate that the cluster of variables that have been attributed to insulin resistance (dyslipidaemia, hypertension and impaired fibrinolysis), as well as insulin resistance itself, might all result as consequences of a common antecedent. We found close relationships with each of the anthropometric measures of obesity, but no in vivo release of TNF-α by adipose tissue, suggesting that influences of adipocyte-generated TNF-α on insulin action occur in the interstitial compartment in adipose tissue, and perhaps within muscle, as autocrine or paracrine effects.

We conclude that circulating concentrations of the proinflammatory cytokines TNF-α and IL-6 are related to elevated levels of both insulin resistance variables and endothelial markers and may underlie the relationship between obesity and cardiovascular risk.