A complex relationship: glucose, insulin and coronary artery disease

Endothelial dysfunction is thought to be an early precursor of atherosclerosis. Thus, the non-invasive detection of endothelial dysfunction in high-risk subjects is attractive and has been the subject of many recent studies. Endothelial synthesized and released nitric oxide (NO) is a potent vasodilator and plays a key role in normal endothelial function. Increases in intra-arterial shear and stress force result in the release of NO with consequent increases in arterial diameter and blood flow. After a period of limb ischaemia, changes in arterial diameter (measured by high-resolution ultrasound) or blood flow (measured by plethysmography), reflect peripheral artery endothelial function and may provide a surrogate measure of coronary artery endothelial function[1].

Endothelial function is influenced by physiological variables including age, gender, phase of the menstrual cycle, menopausal status, and unexplained individual day to day variation[2,3]. Risk factors for atherosclerosis such as hypercholesterolaemia, active and passive smoking, hypertension and diabetes cause endothelial dysfunction[1]. On the other hand interventions such as anti-oxidant supplementation and lipid lowering improve endothelial function[1].

Glucose and insulin both have effects on endothelial function. Animal studies have shown that acute profound hyperglycaemia (without hyperinsulinaemia) impairs endothelial function[4,5]. Studies looking at the effect of acute hyperglycaemia on endothelial function in healthy individuals have shown conflicting results with some studies showing an adverse effect and others a neutral one[6,7]. While abnormal endothelial function found in subjects with type 1[8] and type 2[9] diabetes may be mediated by hyperglycaemia, other factors such as hypertension and dyslipidaemia are likely to play a role. Insulin is known to cause increases in blood flow via NO, irrespective of the prevailing glucose concentration[10] and thus understanding the mechanisms of abnormal endothelial function with changing insulin and glucose concentrations is difficult.

In the novel study by Leyva et al.[11] reported in this issue, subjects with coronary artery disease demonstrated a paradoxical decrease in forearm blood flow in response to an intravenous bolus of dextrose, while in healthy individuals the opposite response was seen. The authors draw the parallel between the observed findings and the paradoxical vasoconstrictor response induced by acetylcholine seen in atherosclerotic coronary arteries. Without detailing mechanisms, the authors suggest that one explanation for the decrease in forearm blood flow is failure of the NO system to respond to insulin. The provocative conclusion of this paper is that forearm blood flow response to intravenous glucose has the potential for use as a non-invasive procedure for the diagnosis of clinically occult coronary artery disease.

Subjects with impaired glucose tolerance and insulin resistance have twice the risk of cardiovascular disease[12] but, in addition to increased circulating insulin concentrations, they are also hyperglycaemic, dyslipidaemic, centrally obese and exhibit a procoagulant state — all of which are associated with increased cardiovascular risk. Studies aimed at reducing the vascular risk associated with diabetes have convincingly demonstrated that a lower level of glycaemia, using intensive insulin therapy, reduces the burden of microvascular disease[13,14]. There has been much debate as to whether or not intensive insulin use in subjects with type 2 diabetes may increase the coronary artery disease risk via potential adverse effects of insulin on the myocardium or coronary arteries due to growth stimulating effects or adverse effects on blood pressure, weight or lipids. However, in a feasibility study of intensive therapy with insulin compared with standard care in 153 men with type 2 diabetes on cardiovascular events, no differences in the rate of new events were detected between groups over a 2 year follow-up period[15]. Furthermore the Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) study, with 620 diabetic subjects, showed that intensive insulin treatment was associated with a lower mortality rate than standard treatment in subjects with acute myocardial
infarction (18.6% vs 26.1%, P = 0.03) [16]. The United Kingdom Prospective Diabetes Study also showed that intensive treatment with insulin or oral sulphonylureas reduced the risk of myocardial infarction (15.8% vs 18.1%, P = 0.052), a reduction of borderline statistical significance. Insulin treatment did not increase the risk of cardiovascular disease [14]. These studies suggest that the macrovascular complications of diabetes are also related to the degree of prevailing hyperglycaemia or its associated cardiovascular risk factors and are not due to the administration of exogenous insulin.

Leyva et al. [11] agree that hyperglycaemia alone may have accounted for their findings. Williams et al. [13] administered octreotide (which prevents insulin secretion) to non-diabetic subjects during hyperglycaemia and euglycaemia, and demonstrated a significant attenuation in vasodilatation to meta-choline during hyperglycaemia, suggesting that acute hyperglycaemia independent of hyperinsulinaemia does impair endothelium-dependent vasodilatation. It is debated if hyperglycaemia per se is causally related to cardiovascular disease or merely a marker for some underlying risk factor that causes both diabetes and cardiovascular disease. While there is a definite association between the level of glycaemia both above and below the threshold for diabetes and cardiovascular risk, proof that hyperglycaemia causes coronary artery disease is less convincing. Establishing a causal link between hyperglycaemia and coronary artery disease is likely to be difficult given that both are complex conditions.

The significant differences in the forearm blood flow response in the study by Leyva et al. [11] may be due to the effects of insulin and/or glucose on the endothelium in the presence or absence of endothelial damage. However there are caveats. The gender of the study subjects is not stated and important differences were present between the study groups with respect to age, body mass index, blood pressure, and medication being taken, factors known to affect endothelial function. Inclusion of the older age and lower body mass index in the subjects with coronary artery disease as covariates in ANOVA did not influence the significance of the results. In addition the rise in glucose and insulin concentration are expressed as the area under the curve which does not denote the level of glycaemia or insulin attained in the study or any potential difference between the groups. It is possible that the coronary artery disease group attained a higher peak glucose level that accounted for the impaired endothelial function. Despite these methodological issues the study is of interest and should stimulate further discussion and research about the complex relationship of glucose and insulin with respect to coronary artery disease.

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References


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