Insulin and atherosclerosis: villain, accomplice, or innocent bystander?

Initial descriptions of an association between insulinaemia and both atherosclerotic cardiovascular disease and its risk factors appeared nearly 30 years ago. In 1969, Stout and Vallance-Owen suggested a direct role for insulin in atherogenesis.1 Stout recently summarised laboratory studies supporting a direct atherogenic effect of insulin through stimulation of vascular smooth muscle proliferation and arterial wall lipid deposition.2 Insulin has also been implicated as an indirect cause of atherogenesis through promoting the development of hypertension and dyslipidaemia.3,4

Several risk factors for atherosclerosis which cluster in individuals at high risk of atherosclerotic cardiovascular disease are associated with hyperinsulinaemia and/or insulin resistance. Reaven in 1988, postulated that insulin resistance and compensatory hyperinsulinaemia underlie this clustering.5 He coined the term "syndrome X" (or the "insulin resistance syndrome") to describe the associations among insulin resistance, hyperinsulinaemia, glucose intolerance, dyslipidaemia, and hypertension, speculating that this syndrome may be an important cause of atherosclerotic cardiovascular disease in affluent societies.

Several mechanisms have been proposed for the association of insulin with atherosclerotic cardiovascular disease risk factor abnormalities. Insulin may contribute to the pathogenesis of hypertension by stimulating the sym pathetic nervous system, promoting renal sodium retention, modulating cardiac cation transport, and/or stimulating vascular smooth muscle hypertrophy.1 Insulin also may induce dyslipidaemia by stimulating hepatic synthesis of very low density lipoprotein (VLDL), leading to raised concentrations of triglyceride and depressed concentrations of high density lipoprotein (HDL) cholesterol.6

Indeed, hyperinsulinaemia is common in some populations with high rates of atherosclerotic cardiovascular disease such as Edinburgh or Gothenburg men.4,12 Pima Indians, who are markedly hyperinsulinaemic, have a low prevalence rate of atherosclerotic cardiovascular disease, and insulinaemia is not a predictor of ischaemic electrocardiographic abnormalities.13 Thus insulinaemia is not consistently associated with atherosclerotic cardiovascular disease.

The relation of insulin concentrations to atherosclerotic cardiovascular disease risk factors, especially hypertension, varies considerably. Nearly all studies showing a strong association between insulinaemia and blood pressure were conducted among groups of northern European origin.17-19 Studies in black subjects,20-21 Mexican-Americans,22 Nauruans,23 Pima Indians,19 and Asian Indians21 showed little or no association. Even among white subjects some data are discrepant. The CARDIA study showed comparable weak relations between blood pressure and fasting insulin concentrations among blacks and whites.20 The European Fat Distribution Study which was conducted among white women in Italy, the Netherlands, Sweden, and Poland found that diastolic blood pressure correlated with serum insulin in all countries except Sweden, whereas systolic blood pressure correlated with insulin only in Poland and southern Italy. After adjustment for body mass index, systolic and diastolic blood pressures were significantly correlated with insulinaemia only in subjects from southern Italy.21 Furthermore, Muller et al24 reported that insulinaemia accounted for less than 4% of the variance in blood pressure in an elderly white population in Baltimore. Although fewer data are available, associations between insulin concentrations and high concentrations of triglycerides and low concentrations of HDL cholesterol seem more consistent across populations.4,15

The failure to find a consistent association between insulinaemia and atherosclerotic cardiovascular disease and some of its risk factors suggest that the relation is not causal or that the effects of insulin are primarily permisive. Insulin may act to accelerate atherogenesis in the presence of other risk factors such as hyperlipidaemia or hypertension. Modan et al25 reported that the excess risk of atherosclerotic cardiovascular disease found in hyperinsulinaemic men was confined to those who had at least one of three conditions: obesity, glucose intolerance, or hypertension.27 The Pima Indians, who are markedly hyperinsulinaemic but have low total cholesterol concentrations and a low prevalence of hypertension, have a low prevalence rate of atherosclerotic cardiovascular disease despite a considerably increased prevalence of non-insulin dependent diabetes.14 Limited evidence from clinical trials suggests that inducing hyperinsulinaemia may not have adverse effects on rates of atherosclerotic cardiovascular disease. The Coronary Drug Project showed that the hypolipidaemic drug nicotinic acid decreased total
and cardiovascular mortality in men with previous myocardial infarction, though it causes insulin resistance and hyperinsulinaemia. The University Group Diabetes Program did not show any adverse effects of insulin treatment on cardiovascular complications.

These observations and the stronger associations of insulin resistance than insulinemia with blood pressure and lipid abnormalities in several studies suggest that insulin resistance rather than insulin may be the key factor with insulin as an innocent bystander merely reflecting insulin resistance. Several mechanisms have been proposed. Decreased insulin sensitivity in adipose tissue, especially visceral fat, can cause accelerated lipolysis and excessive delivery of free fatty acids to the liver resulting in increased VLDL production and hypertriglyceridaemia. Insulin resistance may reduce plasma triglyceride clearance (because of an associated reduction in lipoprotein lipase activity within the vasculature) further amplifying the increase in the concentrations of triglyceride rich lipoprotein. When the plasma residence time of these lipoproteins is increased they become cholesterol enriched and presumably more atherogenic, with reductions in HDL cholesterol concentrations. Insulin resistance could lead to the development of hypertension through blunting of insulin induced vasodilatation. Insulin resistance also is associated with increased concentrations of plasminogen activator inhibitor-1 which inhibits fibrinolysis. These changes could accelerate development of atherosclerosis and predispose to thrombosis, leading to an increased risk of atherosclerotic cardiovascular disease.

Alternatively, the association between hyperinsulinaemia or insulin resistance and atherosclerotic cardiovascular disease may not be causal but merely linked through common underlying factors. Both insulinemia and insulin resistance are strongly correlated with adiposity, and much of the impact of insulin on risk of atherosclerotic cardiovascular disease could be related to amounts of body fat and its distribution. Increased sensitivity to glucocorticoids could produce an association. Glucocorticoids favour deposition of central fat and can induce insulin resistance, hypertension, and hyperlipidaemia. Increased activity of the sympathetic nervous system could lead to hypertension, insulin resistance, and hyperlipidaemia.

Hyperinsulinaemia and insulin resistance are related to atherosclerotic cardiovascular disease and to the clustering of its risk factors in individuals. Their roles as independent atherosclerotic cardiovascular disease risk factors are, however, less certain. At present, it can be concluded that neither hyperinsulinaemia nor insulin resistance is a major risk factor for the development of atherosclerotic cardiovascular disease in the absence of other risk factors. Further laboratory research and prospective population studies of insulin resistance are needed to determine whether the observed relations are part of a causal chain for the development of atherosclerosis.

For now, what are the therapeutic implications of the insulin resistance syndrome? Should individuals be screened for hyperinsulinaemia or insulin resistance? Can either be modified? Should conventional drug regimens for treatment of diabetes and other risk factors for atherosclerotic cardiovascular disease be modified?

Practising physicians need to be aware of the interrelated features of the insulin resistance syndrome to avoid overlooking abnormalities that increase the risk of atherosclerotic cardiovascular disease. Routine determination of fasting insulin concentrations or attempts to measure insulin resistance are not justified. Though insulin resistance is partially genetically determined, it worsens with aging, weight gain, physical inactivity, and possibly a high fat diet. Maintenance of normal body weight is recommended. Obese people should be encouraged to lose weight and to maintain the weight loss because this will benefit all features of the insulin resistance syndrome. Exercise also is beneficial because it increases insulin sensitivity.

Some have recommended avoiding use of diuretics and β blockers in the treatment of hypertension, particularly in obese subjects at high risk of developing diabetes. The United States Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends these drugs still be used as initial therapy for hypertension, but points out that caution is needed with antihypertensive treatment in diabetics. Recent results from the Systolic Hypertension in the Elderly Study showed reduced incidence of stroke and coronary heart disease when hypertension was treated with these drugs. Therefore, a prudent course is to initiate antihypertensive therapy with a low dose of one of these drugs, monitor patients for significant shifts in risk factors for atherosclerotic cardiovascular disease, and use more expensive drugs only when they have specific advantages. In patients with non-insulin dependent diabetes mellitus there is no reason to withhold insulin treatment that is needed to control hyperglycaemia. It is advisable, however, to emphasise the role of diet and exercise in treatment of non-insulin dependent diabetes mellitus and avoid inducing hyperinsulinaemia by overzealous use of long acting insulins or sulphonylureas.

Preliminary data indicate that some drugs improve insulin sensitivity and further developments in this area may be of great importance in the treatment of both the insulin resistance syndrome and the prevention of non-insulin dependent diabetes mellitus. The biguanide metformin is useful for diabetic patients because it reduces glucose concentrations without increasing insulin secretion and may increase insulin sensitivity. It may have a role in subjects with impaired glucose tolerance and in normoglycaemic obese subjects. A new group of drugs that improve insulin sensitivity "thiazolidinediones" is undergoing clinical trials to determine long-term safety and efficacy. In addition, patients with hyperlipidaemia and high concentrations of free fatty acids may benefit from the nicotinic acid analogue acipimox which inhibits lipolysis and improves insulin sensitivity. Though these new drugs seem promising, their ability to reduce the risk of atherosclerotic cardiovascular disease needs to be established by clinical trials. For now, diet and exercise remain the mainstays of treatment.

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