DESCRIPTION OF INSULIN ACTION

Figure 1 shows a classic view of insulin action to promote glucose uptake. Glucose uptake by skeletal muscle is plotted against worsening glucose tolerance. When glucose tolerance deteriorates from normal to impaired, glucose uptake decreases because of worsening insulin resistance of glucose metabolism (1,2). The insulin level continuously increases as one becomes more insulin resistant because the β-cell tries to maintain normal glucose tolerance by increasing insulin secretion. Thus, hyperinsulinemia is a marker of insulin resistance. To understand whether insulin is atherogenic or antiatherogenic, based on its physiologic effects and its alteration in insulin resistant states, current knowledge of what insulin normally does, ie, how it acts in individuals with normal insulin sensitivity, will first be reviewed.

NORMAL ACTION OF INSULIN AND THE IMPACT OF INSULIN RESISTANCE

Figure 2 depicts a modern view of normal insulin action (2). Insulin affects multiple metabolic pathways in many tissues. In the liver, the main action of insulin is to inhibit the production of glucose and triglyceride-rich particles (very low-density lipoprotein 1 [VLDL₁]). In skeletal muscle and the heart, insulin stimulates glucose uptake. In addition, it has now been clearly demonstrated in various in vitro studies but also in human studies in

**Figure 1.** The classic glucocentric view of insulin action in vivo in humans. DM = diabetes mellitus; IGT = impaired glucose tolerance; NGT = normal glucose tolerance; OGTT = oral glucose tolerance test. Reprinted with permission (1).
vivo that insulin increases nitric oxide (NO) production in blood vessels (3) and thereby acts as a vasodilator, inhibits platelet aggregation (4,5), and is associated with low levels of type-1 plasminogen activator inhibitor (6). Thus, in a person with normal insulin sensitivity, insulin action can be considered antiatherogenic.

In individuals who are insulin resistant, insulin’s normal antiatherogenic actions are defective. The ability of insulin to stimulate glucose uptake and to inhibit glucose production is impaired, which promotes hyperglycemia. In the liver, insulin does not normally inhibit the production of triglyceride-rich lipoprotein particles, which results in hypertriglyceridemia (7). Hypertriglyceridemia in turn leads to the generation of small, dense low-density lipoprotein (LDL) particles, which are highly atherogenic, and the lowering of high-density lipoprotein (HDL) cholesterol concentration (8). Insulin resistant platelets have an increased tendency for aggregation and are more likely to attach to collagen (4,5). Less insulin-sensitive subjects also have impaired endothelial function compared with more insulin-sensitive subjects (9).

**EFFECT OF INSULIN THERAPY ON CARDIOVASCULAR RISK FACTORS**

**Hyperglycemia and Insulin Resistance**

Multiple studies have documented that exogenous insulin therapy ameliorates insulin resistance in patients with type 2 diabetes and therefore may have a beneficial effect on cardiovascular disease in these patients (10). In one study the effect of insulin therapy on insulin sensitivity and glucose uptake was investigated in 19 patients with type 2 diabetes who were poorly controlled by oral agents alone (11). After 4 weeks of insulin therapy, insulin sensitivity of glucose uptake had signifi-

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**Figure 2.** Modern view of insulin as a hormone affecting multiple functions in several tissues. SNS = sympathetic nervous system. Reprinted with permission (2).
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...cantly increased. This increase occurred even though the mean diurnal free insulin concentration was almost twice as high at the end of therapy compared with the concentration before insulin therapy was initiated (Figure 3). Improvement in insulin sensitivity was observed although body weight increased by ~5 kg within the 4-week period. This change can be attributed to correction of insulin deficiency and reduction of glucosuria, from which it can be predicted that body weight increases by 2 kg per every 1% decrease in glycated hemoglobin A (A1C) (12). This weight gain is observed with any glucose-lowering therapy and is not specific to insulin (13). These data reinforce that hyperinsulinemia itself is not harmful as it can be a marker of both insulin resistance (nondiabetic subjects) and enhanced insulin sensitivity (after insulin therapy).

Dyslipidemia
Successful insulin therapy appears to have a beneficial effect on dyslipidemia in patients with type 2 diabetes. In the study discussed above, where patients with type 2 diabetes were treated intensively with insulin for 4 weeks (11), an almost 50% decrease in the mass concentration of VLDL particles, a small decrease in LDL, and a highly significant increase in the mass concentration of HDL2 particles were observed (14). Serum total triglycerides, cholesterol, and phospholipid concentrations were also significantly reduced compared with baseline (P <0.001, P <0.01, and P <0.001, respectively). The activity of lipoprotein lipase, which hydrolyzes chylomicrons and VLDL particles and thereby promotes their removal, increased in each patient (11,14).

ENDOTHELIAL DYSFUNCTION
Definition and Measurement
As suggested by Cai and Harrison (15), endothelial dysfunction has been used to refer to several pathologic conditions, including altered anticoagulant and anti-inflammatory properties of the endothelium, impaired modulation of vascular growth, and dysregulation of vascular remodeling. However, in much of the literature this term has been used to

Figure 3. Effect of chronic insulin therapy on glycemic control in type 2 diabetes as measured by glycated hemoglobin (panel on the left), diurnal mean serum-free insulin concentrations (middle panel), and whole body insulin sensitivity of glucose metabolism (panel on the right). HbA1c = glycated hemoglobin A. Reprinted with permission (11).
refer to an impairment of endothelium-dependent vasorelaxation caused by a loss of NO bioactivity in the vessel wall.

Release of NO from the endothelium induces vasorelaxation of adjacent smooth muscle cells via stimulation of guanylate cyclase (Figure 4) (16). Sodium nitroprusside (SNP) is an exogenous NO donor that induces vasodilatation by directly stimulating guanylate cyclase independently of the endothelium. Acetylcholine (ACh) triggers release of NO from endothelial cells via muscarinic receptors (17). When endothelial function is measured in vivo, the blood flow response to ACh (or the flow response to another endothelium-dependent vasodilator) is compared with the blood flow response to SNP (17).

In normal patients, blood flow responses to ACh in coronary arteries (18–20) and in the forearm vascular bed (21) have been shown to correlate with the severity of coronary heart disease and to be blunted in individuals with risk factors of cardiovascular disease such as in those with high LDL cholesterol (22), smokers (22), and patients with both type 1 (23) and type 2 diabetes (24).

**Effect of Insulin on Endothelial Function in vitro and Acutely in vivo in Normal Subjects**

Based on in vitro studies, insulin appears to have, at least acutely, a beneficial effect on endothelial function. It increases NO production in cultured endothelial cells (25) by increasing the expression and activity of endothelial NO synthase (eNOS) (26). Activation of insulin receptor substrate-1, phosphoinositide-3 kinase, and Akt appear necessary for this insulin action, which results in phosphorylation of eNOS at a serine residue (3,27). The ability of insulin to induce vasodilation increases slowly but steadily in vivo during several hours (28). The slow vasodilating effect has been

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**Figure 4.** Measurement of endothelial function. ACh = acetylcholine; cGMP = cyclic guanosine monophosphate; EDHF = endothelium derived hyperpolarizing factor; eNOS = endothelial nitric oxide synthase; GIP = gastric inhibitory polypeptide; GTN = glyceryl trinitrate; L-NMMA = L-n-monomethyl-L-arginine; M = macroangiopathy; NADPH = nicotinamide adenine dinucleotide phosphate; NO = nitric oxide; SNP = sodium nitroprusside. Reprinted with permission (16).
attributed to the insulin-induced increase in eNOS expression (26). In vivo in humans, acute studies have shown that a physiologic increase in the circulating insulin concentration potentiates ACh- but not SNP-induced vasodilatation (29).

**Effect of Insulin Therapy on Endothelial Function in Type 2 Diabetes**

Based on the data cited above, it is possible that in patients with type 2 diabetes, endothelial function could be beneficially affected by insulin therapy. Recently, this hypothesis has been supported by small-scale clinical studies (30,31). In the first of these studies, 18 patients with type 2 diabetes were studied before and after 6 months of insulin therapy, and their endothelial function was compared with that of 27 matched nondiabetic subjects (30). At study entry, patients with type 2 diabetes had mean fasting plasma glucose of 229 mg/dL and A1C of 9.0%. After receiving insulin (human isophane insulin at bedtime) for 6 months, fasting plasma glucose had decreased to 132 mg/dL and A1C to 7.6%. Insulin concentrations were significantly increased from 11±1 mU/L before insulin therapy to 14±1 mU/L after 6 months (P <0.05). This insulin concentration was considerably higher than the 6 mU/L found in the nondiabetic subjects in the study. Body weight remained unchanged, possibly because insulin therapy was started relatively early and metformin was used both before, during, and after the study as an adjunct to bedtime insulin. A significant decrease in triglycerides (P <0.05) was also observed. No changes in risk factors or vascular responses were observed in a control group who were taking chronic metformin therapy. Regarding vascular function, the blood flow response to SNP remained unchanged. The blood flow response to the endothelium-dependent vasodilator ACh was significantly blunted at study entry in the patients with type 2 diabetes compared with the normal subjects. After 6 months of insulin therapy, a significant increase in blood flow was observed in response to high-dose ACh (30). The response was no longer significantly different from that in the normal subjects (Figure 5).

**LONG-TERM EFFECTS OF INSULIN THERAPY IN TYPE 2 DIABETES**

Although a detailed discussion of the effects of long-term insulin therapy on cardiovascular disease is beyond the scope of this article, some comments may be appropriate. Insulin therapy in patients with type 2 diabetes can lead to improvement in insulin sensitivity, lipid profile, and endothelial function.
function, which may lessen the incidence and severity of cardiovascular disease in these patients. The United Kingdom Prospective Diabetes Study (UKPDS) (32,33) showed that modest improvements in glycemic control (decrease in A1C of 0.9%) reduced the risk of myocardial infarction (MI) by 16% ($P = 0.052$). The difference in mean A1C between patients receiving intensive therapy and patients receiving conventional therapy (7.0% vs 7.9%, respectively, $P < 0.001$) and the observed reduction in the incidence of MI (16%) were entirely consistent with epidemiologic data of the UKPDS, which predicted a 14% (95% CI, 8% to 21%) reduced risk of MI for every 1% lowering of A1C with no threshold value (34). This finding suggests that further reduction in the A1C value should reduce the risk of MI. However, proof of this hypothesis requires additional clinical outcome studies where improved glycemic control is sustained using the newer insulin treatment regimens.

REFERENCES


