CME CREDIT PROVIDED FOR THIS ARTICLE

Nonglycemic Effects of Insulin

Hannele Yki-Järvinen, MD, FRCP

Professor of Medicine
Department of Medicine
University of Helsinki
Helsinki, Finland

Insulin affects multiple metabolic pathways in many tissues. Nonglycemic effects include inhibiting production of triglyceride-rich particles and platelet aggregation and increasing vasodilatation. In persons with normal insulin sensitivity, these actions are considered antiatherogenic. However, insulin's normal antiatherogenic actions are defective in persons who are insulin resistant, which results in hypertriglyceridemia, increased platelet aggregation, and endothelial dysfunction. Insulin therapy in patients with type 2 diabetes can lead to improved glycemic control, insulin sensitivity, lipid profile, and endothelial function and may impact the incidence and severity of cardiovascular disease. Clinical Cornerstone® Supplement 4.

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.

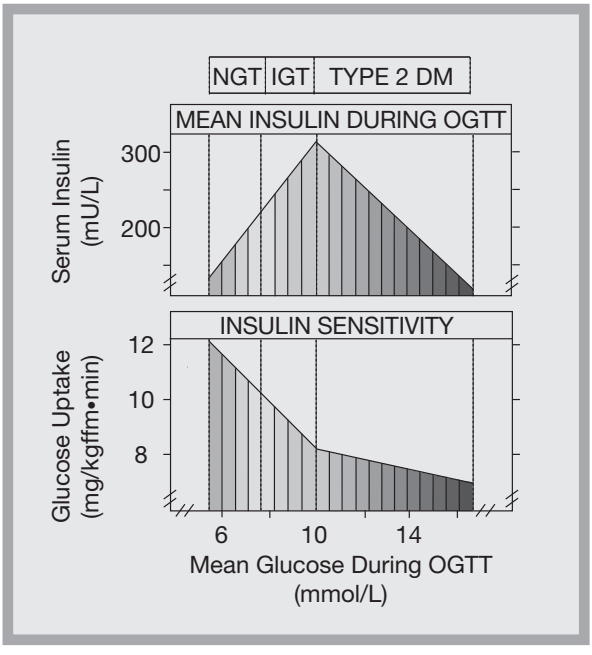

Figure 1. *The classic glucocentric view of insulin action in vivo in humans. DM = diabetes mellitus; IGT = impaired glucose tolerance; NGT = normal glucose tolerance; OGTT = oral glucose tolerance test. Reprinted with permission (1).*

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 [$VLDL_1$]). 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

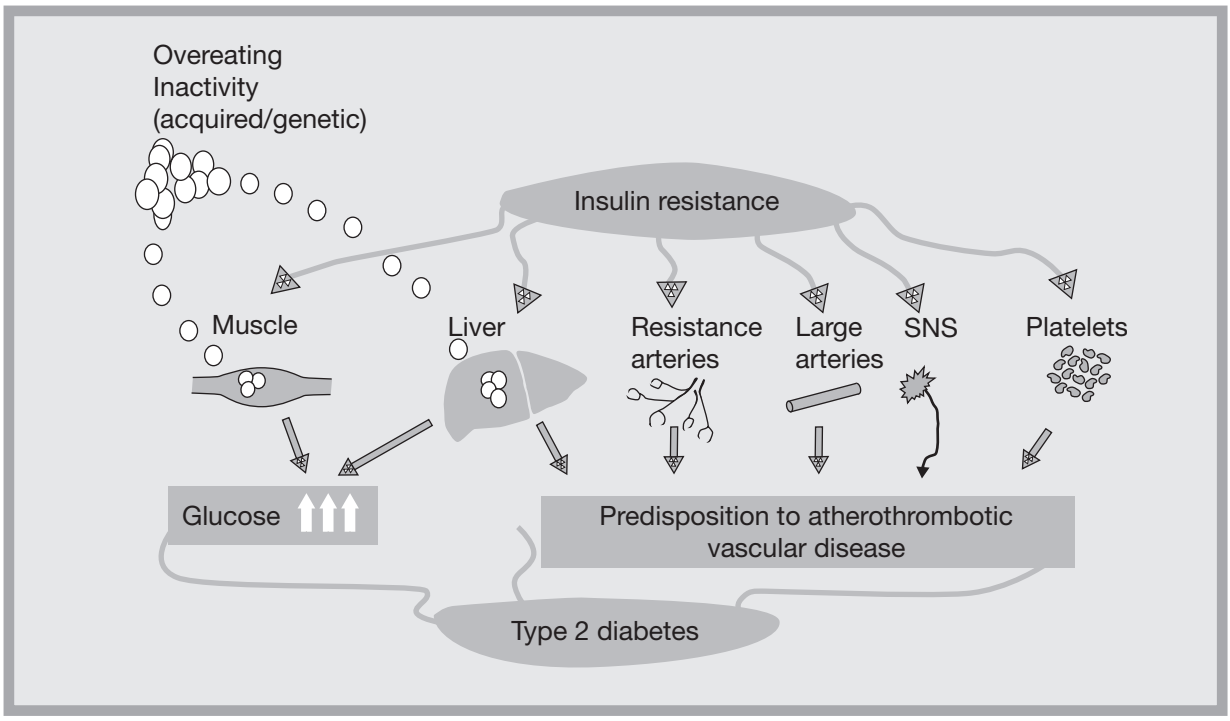

Figure 2. *Modern view of insulin as a hormone affecting multiple functions in several tissues. SNS = sympathetic nervous system. Reprinted with permission (2).*

vivo that insulin increases nitric oxide (NO) production in blood vessels (3) and thereby acts as a vasodilatator, 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-

KEY POINT

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.

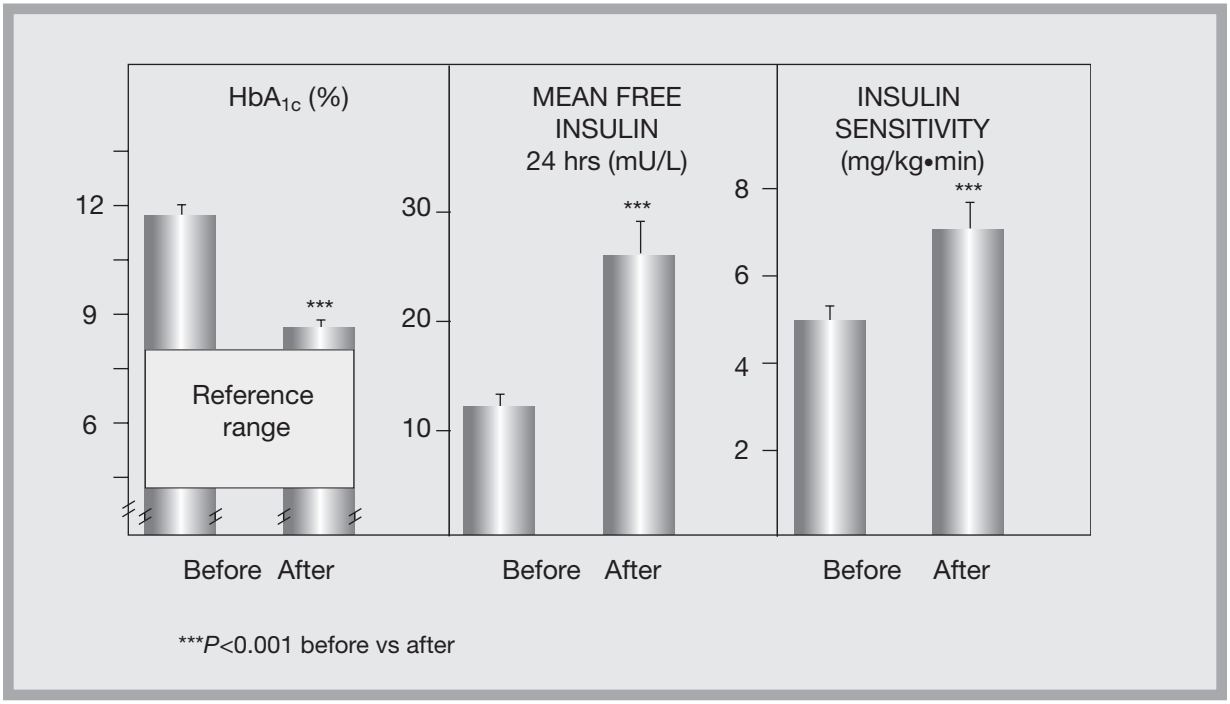

Figure 3. *Effect of chronic insulin therapy on glycemic control in type 2 diabetes as measured by glycated hemoglobin (panel on the left), diurnal mean serum-free insulin concentrations (middle panel), and whole body insulin sensitivity of glucose metabolism (panel on the right). HbA_{1c} = glycated hemoglobin A. Reprinted with permission (11).*

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 HDL_2 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

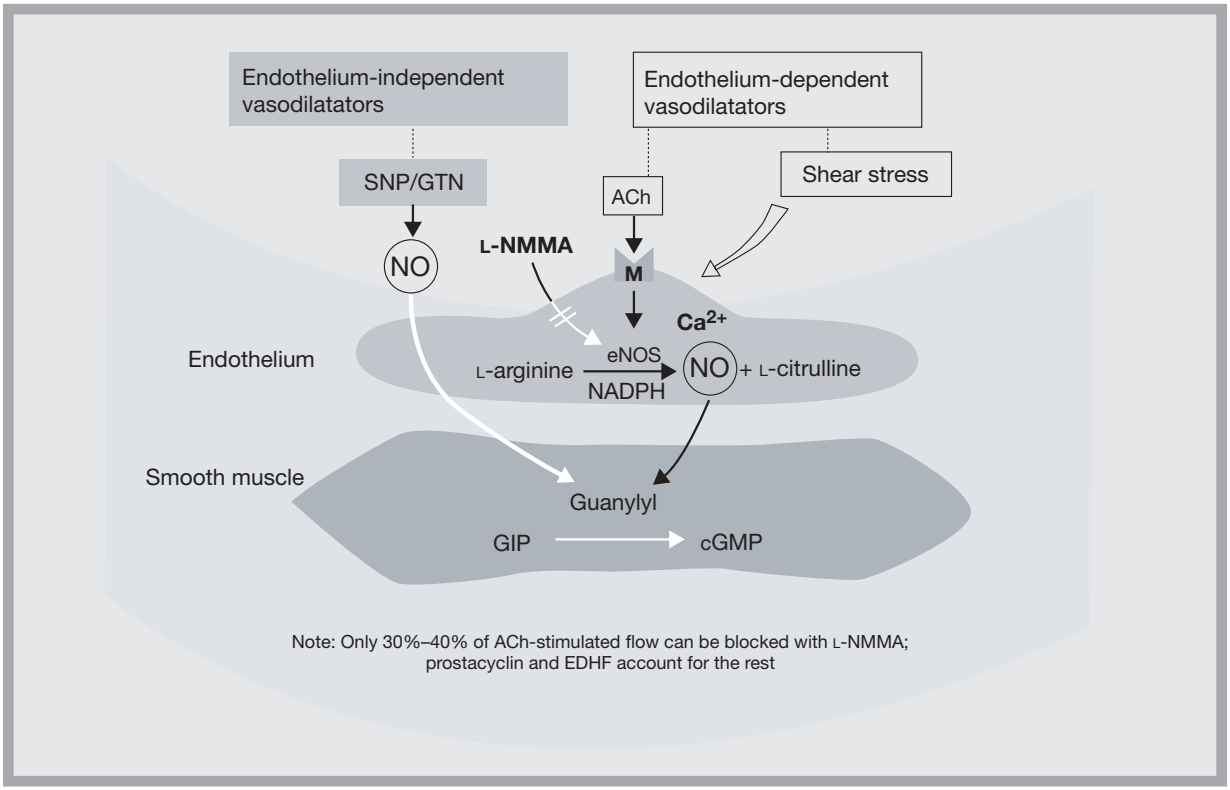

Figure 4. *Measurement of endothelial function. ACh = acetylcholine; cGMP = cyclic guanosine monophosphate; EDHF = endothelium derived hyperpolarizing factor; eNOS = endothelial nitric oxide synthase; GIP = gastric inhibitory polypeptide; GTN = glyceryl trinitrate; L-NMMA = L-n-monomethyl-L-arginine; M = macroangiopathy; NADPH = nicotinamide adenine dinucleotide phosphate; NO = nitric oxide; SNP = sodium nitroprusside. Reprinted with permission (16).*

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 vasodilatator) 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 vasodilatation increases slowly but steadily in vivo during several hours (28). The slow vasodilating effect has been

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 vasodilatator 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

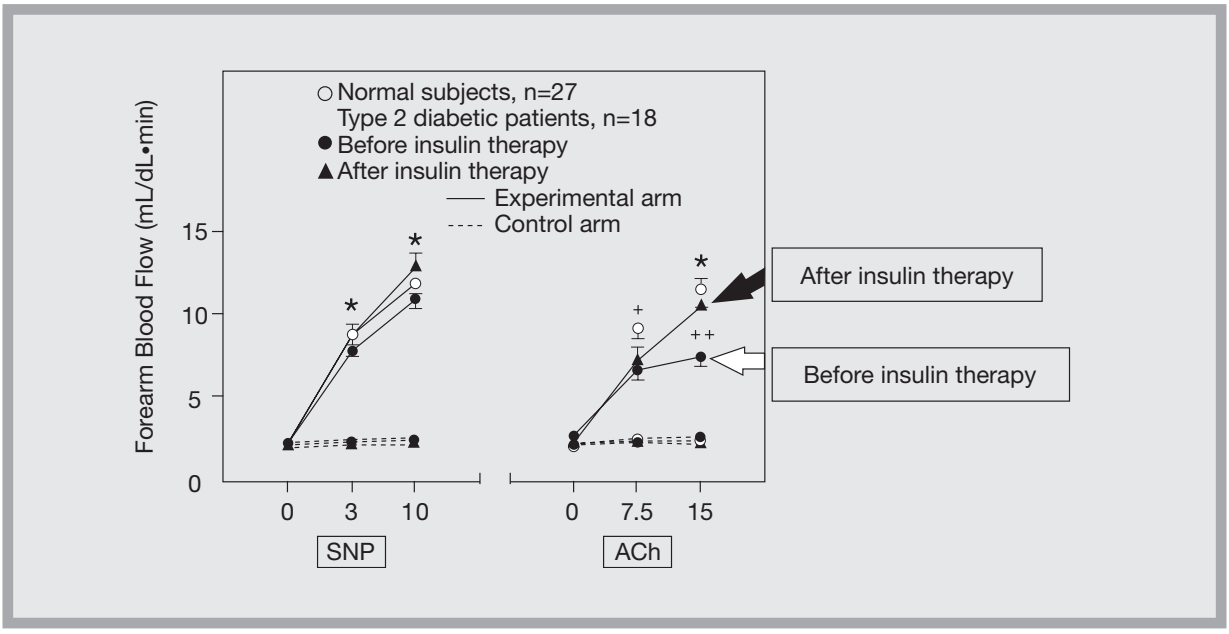

Figure 5. *Effects of 6 months of insulin therapy on endothelial function in patients with type 2 diabetes. ACh = acetylcholine; SNP = sodium nitroprusside. Reprinted with permission (30).*

KEY POINT

The UKPDS suggested 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.

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

1. Lillioja S, Mott DM, Spraul M, et al. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329:1988–1992.
2. Yki-Järvinen H. Insulin resistance in type 2 diabetes. In: Pickup JC, Williams G, eds. *Textbook of Diabetes.* Oxford, England: Blackwell; 2003:22.1
3. Montagnani M, Ravichandran LV, Chen H, et al. Insulin receptor substrate-1 and phosphoinositide dependent kinase-1 are required for insulin-stimulated production of nitric oxide in endothelial cells. *Mol Endocrinol.* 2002;16:1931–1942.
4. Trovati M, Anfossi G. Insulin, insulin resistance and platelet function: similarities with insulin effects on cultured vascular smooth muscle cells. *Diabetologia.* 1998;41:609–622.
5. Westerbacka J, Yki-Järvinen H, Turpeinen A, et al. Inhibition of platelet-collagen interaction: an in vivo action of insulin abolished by insulin resistance in obesity. *Arterioscler Thromb Vasc Biol.* 2002;22:167–172.
6. Juhan-Vague I, Alessi MC, Vague P. Thrombogenic and fibrinolytic factors and cardiovascular risk in noninsulin-dependent diabetes mellitus. *Ann Med.* 1996;28:371–380.
7. Malmstrom R, Packard CJ, Caslake M, et al. Defective regulation of triglyceride metabolism by insulin in the liver in NIDDM. *Diabetologia.* 1997;40:454–462.
8. Syvanne M, Taskinen MR. Lipids and lipoproteins as coronary risk factors in non-insulin-dependent diabetes mellitus. *Lancet.* 1997;350(Suppl 1): S120–S123.
9. Vakkilainen J, Mäkimattila S, Seppälä-Lindroos A, et al. Endothelial dysfunction in men with small LDL particles. *Circulation.* 2000;102:716–721.
10. Yki-Järvinen H. Glucose toxicity. *Endocr Rev.* 1992;13:415–431.
11. Yki-Järvinen H, Nikkilä E, Helve E, Taskinen M-R. Clinical benefits and mechanisms of a sustained response to intermittent insulin therapy in type 2 diabetic patients with secondary drug failure. *Am J Med.* 1988;84:185–192.
12. Mäkimattila S, Nikkilä K, Yki-Järvinen H. Causes of weight gain during insulin therapy with and without metformin in patients with type II diabetes mellitus. *Diabetologia.* 1999;42:406–412.
13. Yki-Järvinen H. Comparison of insulin regimens for patients with type 2 diabetes. *Curr Opin Endocrinol Diabetes.* 2000;7:175–183.
14. Taskinen M-R, Kuusi T, Helve E, et al. Insulin therapy induces antiatherogenic changes in serum lipoproteins in non-insulin-dependent diabetes mellitus. *Arteriosclerosis.* 1988;8:168–177.
15. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. *Circ Res.* 2000;87:840–844.
16. Ignarro LJ, Lippton H, Edwards JC, et al. Mechanism of vascular smooth muscle relaxation by organic nitrates, nitrites, nitroprusside and nitric oxide: evidence for the involvement of S-nitrosothiols as active intermediates. *J Pharmacol Exp Ther.* 1981;218:739–749.
17. Baron AD. Insulin resistance and vascular function. *J Diabetes Complications.* 2002;16:92–102.
18. Suwaidi JA, Hamasaki S, Higano ST, et al. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation.* 2000;101:948–954.
19. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation.* 2000;101:1899–1906.
20. Halcox JP, Schenke WH, Zalos G, et al. Prognostic value of coronary vascular endothelial dysfunction. *Circulation.* 2002;106:653–658.

21. Heitzer T, Schlinzig T, Krohn K, et al. Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. *Circulation.* 2001;104:2673–2678.
22. Heitzer T, Ylä-Herttuala S, Luoma J, et al. Cigarette smoking potentiates endothelial dysfunction of forearm resistance vessels in patients with hypercholesterolemia. Role of oxidized LDL. *Circulation.* 1996;93:1346–1353.
23. Mäkimattila S, Virkamäki A, Groop P-H, et al. Chronic hyperglycemia impairs endothelial function and insulin sensitivity via different mechanisms in insulin-dependent diabetes mellitus. *Circulation.* 1996;94:1276–1282.
24. Mäkimattila S, Liu M-L, Vakkilainen J, et al. Impaired endothelium-dependent vasodilatation in type 2 diabetes. Relation to LDL size, oxidized LDL and antioxidants. *Diabetes Care.* 1999; 22:973–981.
25. Zeng G, Quon MJ. Insulin-stimulated production of nitric oxide is inhibited by Wortmannin. Direct measurement in vascular endothelial cells. *J Clin Invest.* 1996;98:894–898.
26. Kuboki K, Jiang ZY, Takahara N, et al. Regulation of endothelial constitutive nitric oxide synthase gene expression in endothelial cells and in vivo: a specific vascular action of insulin. *Circulation.* 2000;101:676–681.
27. Du XL, Edelstein D, Dimmeler S, et al. Hyperglycemia inhibits endothelial nitric oxide synthase activity by posttranslational modification at the Akt site. *J Clin Invest.* 2001;108:1341–1348.
28. Utriainen T, Malmström R, Mäkimattila S, Yki-Järvinen H. Methodological aspects, dose-response characteristics and causes of interindividual variation in insulin stimulation of limb blood flow in normal subjects. *Diabetologia.* 1995;38:555–564.
29. Taddei S, Virdis A, Mattei P, et al. Effect of insulin on acetylcholine-induced vasodilatation in normotensive subjects and patients with essential hypertension. *Circulation.* 1995;92:2911–2918.
30. Vehkavaara S, Mäkimattila S, Schlenzka A, et al. Insulin therapy improves endothelial function in type 2 diabetes. *Arterioscler Thromb Vasc Biol.* 2000;20:545–550.
31. Rask-Madsen C, Ihlemann N, Krarup T, et al. Insulin therapy improves insulin-stimulated endothelial function in patients with type 2 diabetes and ischemic heart disease. *Diabetes.* 2001; 50:2611–2618.
32. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998;352:837–853.
33. Wright A, Burden AC, Paisey RB, et al. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). *Diabetes Care.* 2002;25:330–336.
34. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ.* 2000; 321:405–412.