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Actions of Insulin Beyond Glycemic Control: A Perspective on Insulin Detemir

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ABSTRACT

The physiologic effects of insulin on carbohydrate metabolism in health in general and in diabetes are well known. Less understood, but far more intriguing, are the extrapancreatic effects of insulin that go beyond glycemic control to help sense, integrate, and maintain energy balance. Virtually every organ, including the brain, is a target for insulin action. When exogenous insulin is administered directly into the brains of experimental animals, the net effect is anorectic; however, patients with type 2 diabetes who transition to insulin therapy often gain weight—a tendency that opposes good glycemic control and overall therapeutic goals. After the brief review of extrapancreatic insulin-signaling pathways presented here, the physiologic impact of developing insulin resistance in relation to body weight is considered. Attention is then focused on insulin detemir, a long-acting insulin analog that has consistently been associated with less weight gain than conventional formulations such as neutral protamine Hagedorn insulin. Mechanisms offered to explain this effect include the lower incidence of hypoglycemia and less within-patient variability associated with insulin detemir; however, recent observations and considerations of insulin-signaling pathways have shed light on other important properties of insulin detemir that may impart these weight-neutral effects. Namely, albumin binding, faster transport across the blood-brain barrier, and preferential activity in brain and liver are characteristics of insulin detemir that potentially explain the observed weight benefit seen in clinical trials, as well as in the real-world practice setting.

Keywords: glycemic control; brain; weight gain; insulin detemir; albumin binding

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INTRODUCTION

Perhaps best known as the primary regulator of blood glucose,[1] insulin is actually a pleiotropic (ie, "producing more than 1 genic effect") hormone that plays a role in virtually every tissue, including the brain.[2,3] In addition to its metabolic effects on carbohydrate metabolism, insulin stimulates cell growth and differentiation, including pancreatic β-cell growth and survival.[4] In peripheral targets such as fat, liver, and skeletal muscle, insulin is anabolic and acts to increase the intracellular storage of energy-rich compounds.[1] In the central nervous system (CNS), insulin helps maintain energy homeostasis,[2,5] although glucose utilization by brain cells is insulin independent.[6] In contrast to its anabolic role in peripheral tissues,[7] insulin activity in the brain is catabolic, inhibiting food intake and increasing energy expenditure.[8] Direct insulin administration into the brains of animals produces an appetite suppressant effect,[9] and animals that are made experimentally deficient in brain insulin receptors (IRs) become obese.[10] Thus, a complex interplay of signaling pathways constitutes peripherally mediated and CNS-mediated responses to insulin.[11] Defects in 1 or more of these control pathways might link type 2 diabetes with obesity.[8]

Patients with type 1 and type 2 diabetes who are treated with insulin typically gain weight.[12,13] A family history of type 2 diabetes, poor metabolic control, and weight loss before therapy intensification are associated with the greatest weight gain after insulin initiation.[13] Generally speaking, weight gain occurs regardless of the insulin formulation used,[13] although an interesting and unexplained phenomenon has been emerging from clinical trials with the new long-acting analog insulin detemir. Consistently less weight gain and occasional weight loss have been observed in patients using insulin detemir compared with other basal insulin formulations. The weight benefit persists despite comparable levels of glycemic control and occurs whether insulin detemir is part of a basal-bolus regimen or is combined with oral antidiabetic agents (OADs).[14-17] Robust enough to be sustained outside of clinical trials, these observations are supported by real-world data collected on patients who were using insulin detemir.[18] Several hypotheses, including reduced "defensive" snacking resulting from a lower risk of hypoglycemia and less within-patient variability,[19-21] have been postulated to explain these findings, although no definitive explanation has been found. Taking into account the profiles of insulin hormonal activity on various organ systems, this manuscript offers an alternative view into the mechanisms behind insulin detemir's weight-neutral effects.

ACTION OF INSULIN

In individuals without diabetes, insulin is secreted by the β-cells of the pancreas into the portal circulation in response to a glucose challenge.[22] The first target organ for circulating physiologic insulin is the liver, which serves as a primary site of insulin activity and clearance.[23] The diverse effects of insulin are mediated through IR binding in target tissues located in the periphery and in the CNS.[10,24] Binding of insulin to the IR, a member of a subfamily of tyrosine kinase receptors,[1] can activate multiple signaling pathways within a cell by coupling with a family of IR substrates. The IR substrate molecules are proteins, and each has a different role in the 2 main pathways of insulin that govern metabolism or growth (Table). In turn, IR substrate proteins bind other signaling molecules to mediate insulin action.[1,25]

Molecules Implicated in Insulin-Signaling Pathways

Metabolic Pathways	Growth Pathways
Akt (also known as protein kinase B)	Glycogen synthase kinase 3 (GSK3)
Glucose transporter (GLUT4)	Growth factor receptor binding protein 2 (GRB2)
Insulin-receptor substrates (IRS-1, -2, -3, -4)	GTPase-activating protein (GAP)
Phosphatidylinositol (PI) 3-kinase	PI-dependent protein kinase (PDK)
Tris-phosphorylated inositol (PIP_3)	Mitogen-activated protein kinase (MAPK)
	Mitogen-activated protein kinase kinase (MAPKK)
	Son of sevenless (SOS)

This table is intended to be a representative (and not necessarily comprehensive) sample; additional information can be found in references 1, 25, and 37.

Peripheral Effects

Metabolic/glucose uptake and cell growth characterize the main peripheral effects of insulin.[1] In the metabolic pathway, the primary targets of insulin are fat, skeletal muscle, and liver cells. With a major role in regulating blood glucose concentration in a narrow physiologic range, insulin is the hormone responsible for increasing glucose uptake in skeletal muscle and fat cells. In these tissues, substrate glucose is converted to storage glycogen and lipid, respectively, for future use when energy is needed. Another peripheral fat–sparing effect of insulin is to inhibit lipolysis in fat cells. Insulin also increases protein synthesis in muscle and liver cells and lipoprotein uptake and synthesis in fat cells; it enhances cellular respiration and inhibits protein degradation in all 3 primary target tissues. Distinct from its effects in fat and muscle, insulin does not promote glucose uptake in the liver. Instead, its hepatic effects promote conversion of glucose to glycogen and oppose glucose output by blocking the breakdown of glycogen (glycogenolysis) and the synthesis of new glucose (gluconeogenesis).[1] Insulin's suppression of hepatic glucose output is largely (75%) indirect and is not due to insulin delivery to hepatocytes via the portal vein.[26] A brain-liver circuit exists such that glucose-homeostatic effects in the liver are dependent on insulin-mediated effects in the hypothalamus (see section below on CNS effects).[24,27] Thus, central and peripheral insulin pathways interact to cause maximal reductions in hepatic glucose production.

In addition to exhibiting high-affinity binding to the IR, insulin binds, albeit with ~1000-fold lower affinity, to receptors for insulin-like growth factor-1 (IGF-1).[28] IGF-1 is a member of the tyrosine kinase receptor family and is structurally similar to the IR.[1] By interacting with IGF-1, insulin becomes a growth factor for cells and promotes the induction of genes involved in cell proliferation and differentiation.[25] Along these lines, insulin is believed to be an important growth factor for fetal development.[29] These effects have raised questions about the mitogenic potential of higher than physiologic concentrations of insulin, long-term insulin exposure, or insulin molecules that have been structurally modified.[30] Research in the area of

insulin-related mitogenesis and IGF-1 receptor interactions is complex, however, with in vitro and in vivo results often conflicting. Although the potential for toxicologic implications (ie, tumor or vascular cell growth) is a possibility that should be acknowledged, there is no consistent evidence that exogenous insulin plays any clinically significant role in this regard.[30]

CNS Effects

Contrary to earlier opinion that insulin could not cross the blood-brain barrier because of its large size, and therefore could not exert CNS effects, it is now known that insulin and IRs are widely distributed in the brain.[3] Neuronal insulin signaling may play a role in diverse areas such as life span, growth, learning, memory, and reproduction.[2,10,31] Insulin is not synthesized by the brain to any extent,[7] but it enters the brain from the periphery via specific, saturable, and modifiable transporters on brain capillary endothelium and can also enter via regions of the brain (eg, circumventricular regions) that are unprotected by a blood-brain barrier.[3,7,32] The rate of insulin entry into brain tissue varies among brain regions and tends to correlate with IR density in the following order: olfactory > pons-medulla ≈ hypothalamus > spinal cord > whole brain.[7] The physical nature of the insulin transporter at the blood-brain barrier membrane is a mystery, and it remains undetermined whether this transporter is structurally related to the IR.[7]

Once in the brain, the actions of insulin oppose those of peripheral insulin. Insulin controls energy balance and body weight[31] by acting through CNS receptors to provide a negative feedback loop for postprandial inhibition of food intake.[3,33] Insulin signaling via stimulation of hypothalamic adenosine triphosphate–sensitive potassium (KATP) channels is believed to play a role in the normal control of hepatic glucose production.[27,31,34] By exerting actions via the hypothalamus, insulin reduces food intake and increases energy expenditure by enhancing fatty acid oxidation.[31,35] Additionally, disruption of the gene that encodes brain IR expression in mice causes increased adipose tissue mass, obesity, insulin resistance, and hypertriglyceridemia.[10] In healthy men (but not women), intranasal administration of insulin that delivered the hormone directly to the brain reduced body weight.[36]

CHANGES IN INSULIN SIGNALING IN TYPE 2 DIABETES, OBESITY, AND A PREDIABETES CONDITION

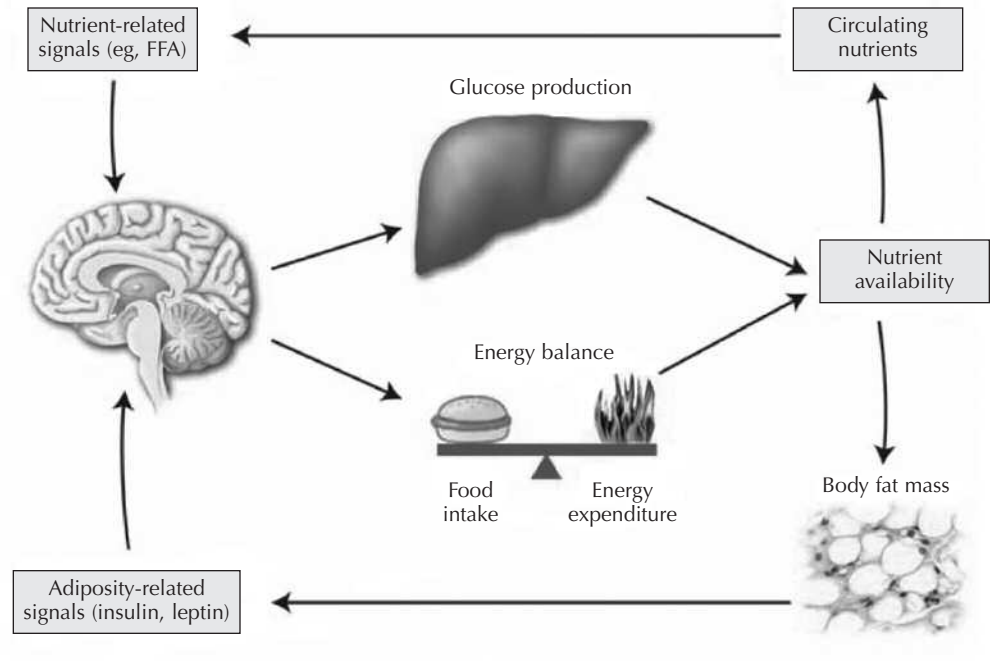
Given the complexities and myriad pathways involved in insulin transport, tissue receptor distribution, and intracellular signaling, opportunities for defects in insulin action abound.[4] In patients who have type 2 diabetes or are obese, the metabolic pathway is primarily affected without disruption of growth pathways.[1] For example, IR concentrations, phosphorylation of IR substrate-1 and -2 molecules, and phosphatidylinositol (PI) 3-kinase activity are reduced in obesity and type 2 diabetes, whereas growth pathways (eg, mitogen-activated protein kinase [MAPK] activation) are not. This imbalance of functional defects in metabolism versus growth pathways may be responsible for the pathologic vascular cell growth seen with chronic hyperinsulinemia.[1]

Insulin resistance is a key finding in obesity and in prediabetes conditions,[37,38] and type 2 diabetes may result from a combination of defects in the metabolic signaling

pathways of insulin. The net result of insulin resistance is the disruption of transportation of glucose into the cell; this elevates fasting and postprandial glucose. Lipolysis is insufficiently suppressed and lipid levels in the blood are increased.[1,39] The presence of excess adipose tissue exacerbates these detrimental effects. Free fatty acids released into the portal circulation are a potent stimulus for glucose production in the liver.[1] This stimulus is insufficiently counteracted by insulin because of tissue resistance or inadequate insulin availability relative to demand in the portal circulation.[23] Proinflammatory cytokines (interleukin-6 [IL-6], tumor necrosis factor [TNF]-α and adipokines), which are increased during infection or are produced in fat cells, can worsen insulin resistance.[1,4]

The close association between diabetes and obesity may also result from defective insulin signaling within the CNS.[31] In the brain, both insulin and leptin (another peripheral hormone secreted in response to nutrient intake) act as "adiposity signals" that regulate body weight and food intake and help maintain metabolic homeostasis (Fig 1).[8] Reduced secretion or sensing of these hormones can lead to weight gain and

Fig 1. Schema outlining the control of energy homeostasis and hepatic glucose production by adiposity- (insulin, leptin) and nutrient-related signals in the brain.



FFA=free fatty acids.

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insulin resistance.[8] Several experimental examples support the role of CNS insulin as an anorexogenic hormone. For example, mice bred to be deficient in neuronal IRs are overweight, insulin resistant, and glucose intolerant.[10] Rats subjected to chronic blockade of hypothalamic IR signaling exhibit hepatic insulin resistance and increased hepatic glucose production.[40] On the other hand, stimulation of rat hypothalamic KATP channels, which are known to be activated by insulin and leptin, slows hepatic glucose production and thereby lowers blood glucose.[34] Magnetic imaging techniques have allowed observation of brain responses to peripheral insulin infusions administered to humans. At doses known to double cerebrospinal fluid (CSF) insulin concentrations, insulin exerts less pronounced effects in obese compared with lean individuals.[41]

PHYSIOLOGIC VERSUS THERAPEUTIC INSULIN

Under normal physiologic conditions, in response to a glucose load, insulin is secreted by pancreatic β-cells into the portal circulation, where its first main target organ is the liver. The liver extracts 60% of this physiologically secreted insulin, and liver cells are therefore exposed to insulin concentrations severalfold higher than those of fat or muscle cells.[22] One difference between physiologic and therapeutic insulin is that the absorption of subcutaneous (SC) insulin occurs via the systemic circulation rather than on a "first-pass" basis through the liver. Without the hepatic/systemic concentration gradient of physiologic insulin, SC insulin may exert relatively greater effects on peripheral fat and muscle cells than in the liver.[22]

Binding of insulin to the IR leads to metabolic and growth effects, and binding to IGF-1 further enhances the growth effects of insulin. Exposure of tissues to higher insulin concentrations is one possible scenario that could result in unwanted stimulation of IGF-1 and may exert mitogenic effects.[30] This theoretical concern is perhaps most relevant to inhaled insulin because its long-term effects on lung development are unknown.[42] With a specific activity of ~2.7 units/mg, approximately 3-fold to 10-fold more insulin by weight must be administered by inhalation[43] to achieve therapeutic effects equivalent to those produced by commonly used SC insulin preparations.[44,45] With its apparently low bioavailability, the amount of unabsorbed inhaled insulin that the lung retains, how long it is retained, and its effects remain to be discovered.

With insulin analogs, structural changes in the native insulin molecule have been made to improve the pharmacokinetic profiles and the predictability of insulin action.[30] The receptor-binding capabilities of these analogs might be expected to differ from one insulin formulation to another.[28,30] An in vitro comparison of the binding properties of insulin analogs versus human insulin to the human IR and IGF-1 receptors was performed to determine the relative metabolic and mitogenic potential, respectively, of the available insulin analogs.[28] In this study, the IR affinities of rapid-acting insulin analogs—insulin aspart and insulin lispro—were similar to those of human insulin; insulin lispro had slightly increased IGF-1 receptor affinity compared with neutral protamine Hagedorn (NPH) and insulin aspart.[28] On the basis of in vitro results, one can calculate the ratios of metabolic (lipogenesis)-to-mitogenic (IGF-1) potency for insulin aspart and lispro to be 1.7 and 1.2, respectively, relative to 1.0 for human insulin. Thus, although the clinical relevance of this property has not yet been determined, human insulin has slightly higher mitogenic potential than does insulin aspart or insulin lispro. With regard to the long-acting analogs, insulin glargine and

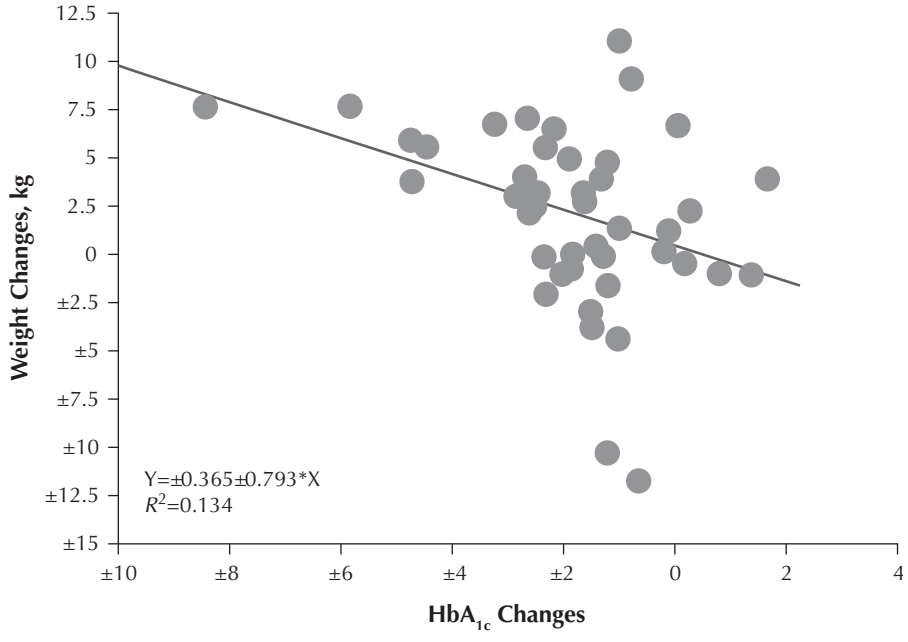
insulin detemir were found to have very different receptor affinity profiles for IR and IGF-1 compared with human insulin.[28] Specifically, insulin glargine exhibited 1.5-fold and 6.4-fold higher affinity for the IR and IGF-1 receptor, respectively, than human insulin. Insulin detemir, in contrast, exhibited lower affinity for the IR (0.46-fold to 0.18-fold) and for the IGF-1 receptor (0.16-fold). Insulin detemir also had a 2-fold faster dissociation rate from the IR compared with human insulin.[28] Relative to a metabolic-to-mitogenic ratio of 1.0 for human insulin, the ratio for insulin glargine was 0.08 and for insulin detemir it was 2.5, thus ordering the mitogenic potential as follows: insulin detemir < human insulin < insulin glargine. Because insulin detemir has lower binding affinity and a faster off-rate for the IR than human insulin, it is formulated at a higher concentration (in milligrams per milliliter) to provide equivalent glucose-lowering potential per unit. This increase in insulin detemir concentration, however, would not be expected to alter its metabolic-to-mitogenic potency ratio.

WEIGHT GAIN AND THERAPEUTIC INSULIN: CLINICAL OBSERVATIONS AND UNSOLVED MYSTERIES

Exogenous insulin administration is generally associated with weight gain that correlates with improved glycemic control, as exemplified in Figure 2.[19,46-48] Several potential mechanisms have been proposed to explain why weight gain occurs, especially in new users of insulin.[12,48] Decreased glycosuria from improved metabolic control, inhibition of catabolism in poorly controlled diabetes, increased fat and protein deposition from insulin's anabolic effects, reduction of energy expenditure caused by reduction in hepatic glucose output, and increased intake of food attributed to prevention of hypoglycemia or overcorrection after a hypoglycemic episode have been proposed.[12] Insulin-induced weight gain might reflect the body's tendency to "catch up" and return to its set point after a patient experiences weight loss when glycemic control is poor.[49] Insulin-associated weight gain was independent of baseline body mass index (BMI) in a study of patients with type 2 diabetes.[50] Body composition studies (of fat content and fat-free body mass comprising muscle, bone, and total body water) have been performed to elucidate the nature of weight-gain changes with insulin. In patients with type 2 diabetes who are receiving basal insulin glargine along with mealtime insulin lispro, aspart, or regular human insulin, weight gain was characterized by increases in fat and fat-free mass.[48] Based on the contribution that adipose tissue makes to insulin resistance, the fat to fat-free body composition changes in type 2 diabetes are more worrisome than those that occur in type 1 diabetes, where weight gain is attributed to increases in fat-free mass.[48] Despite the fact that this is an active area of considerable research interest and speculation, no definitive single cause or underlying mechanism for weight gain in insulin users has yet been established.

Clinical evaluation of insulin detemir, the newest long-acting analog, has revealed weight-related findings that also defy explanation at present. Clinical trials in type 1 and type 2 diabetes have consistently shown that patients gain less weight and sometimes experience net weight loss when they are treated with insulin detemir compared with NPH insulin and, recently, with insulin glargine as well (Fig 3).[14-16,20,51] For example, in a 26-wk treat-to-target study in which insulin detemir or NPH insulin was added to OADs, patients gained 1.2 versus 2.8 kg, respectively ($P<.001$).[14] The weight

Fig 2. Correlation of weight gain with improved glycemic control in a study of 69 insulin-treated patients with type 2 diabetes.



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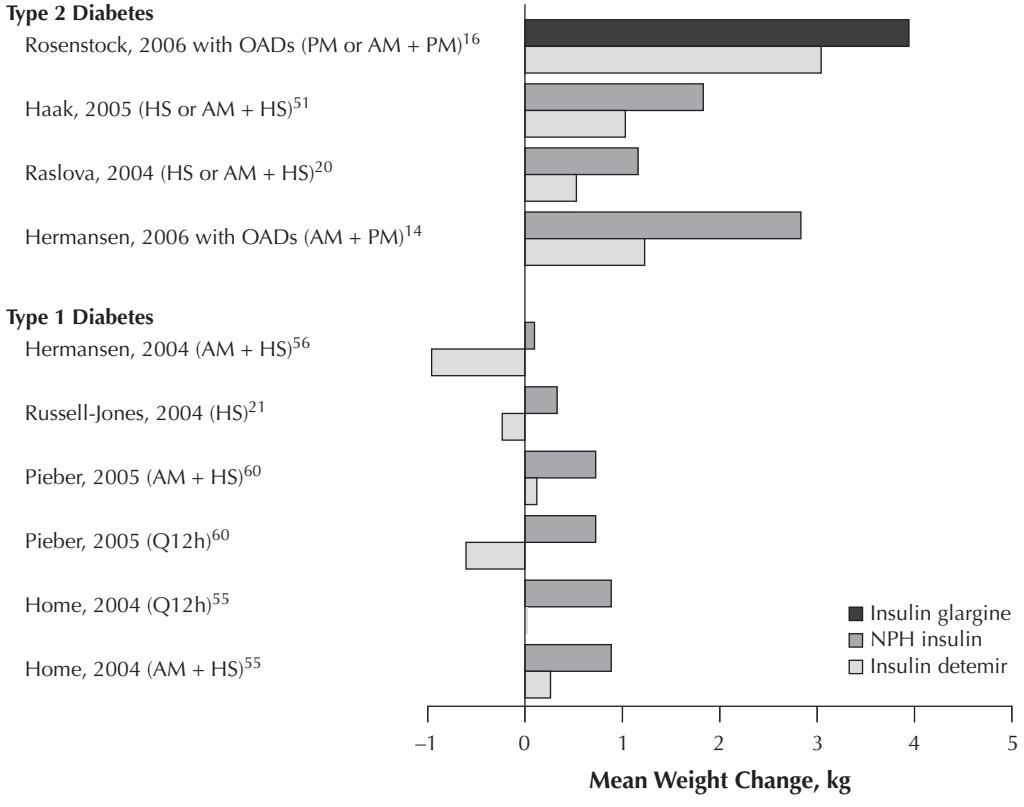
benefit of insulin detemir was more pronounced in patients with a higher BMI at baseline.[52] Glycemic control between treatments was comparable, and hypoglycemia incidence was 47% lower with insulin detemir than with NPH (P<.001). In a study of similar design that compared insulin detemir with insulin glargine (added to OADs),[16] patients gained 3.0 kg with insulin detemir versus 3.9 kg with insulin glargine (P=.012). Reductions in glycated hemoglobin (HbA_{1c}) and hypoglycemia incidence were similar between groups.

Dosing regimens, clinical trial design and duration, and patient populations have differed, and these differences have foiled attempts to conduct meta-analyses, although every study to date has shown significantly less weight gain with insulin detemir than with its comparator.[53] These clinical data are consistent with experimental data in animals. In diabetic rats, significantly greater increases in body weight and whole body fat mass relative to body weight were observed in human insulin–treated rats compared with insulin detemir–treated animals.[54] There is currently no definitive explanation for these observations; however, some aspects of insulin detemir's profile of activity beyond glycemic control are relevant to consider.

Fig 3. Changes in weight observed in clinical studies of insulin detemir compared with NPH or with insulin glargine.



HS=bedtime (hora somni).

Information (in parentheses) indicates dosing regimen of insulin detemir.

POTENTIAL MECHANISMS FOR INSULIN DETEMIR WEIGHT EFFECTS

As was noted earlier, patients with diabetes treated with insulin may tend to engage in "reactive overeating" to avoid hypoglycemia.[14,21,55-57] Insulin detemir has been associated with reduced hypoglycemia compared with human insulin formulations,[14,15,56,58,59] so this has been postulated to account for reduced "defensive snacking" and, subsequently, less weight gain. Several points argue against this as a sole hypothesis, however. First, even in studies that showed a similar hypoglycemia risk when insulin detemir and NPH were compared,[51,60] the weight benefit of insulin detemir persisted at similar or better levels of glycemic control. Secondly, other insulin analogs—including rapid-acting insulin analogs,[61] premixed analogs,[62] and insulin glargine[63]—also demonstrated a reduced risk of hypoglycemia over human

insulin formulations. In these cases, however, evidence of a weight benefit was less consistent.[64] For example, a 6-mo comparative study with insulin glargine reported less weight gain relative to NPH (0.4 kg vs 1.4 kg; *P*=.0007) in patients with type 2 diabetes mellitus,[65] but data collected after 1 y of treatment demonstrated that the hypoglycemia reduction persisted compared with that seen with NPH, although patients on both treatment arms gained similar amounts of weight (ie, 2.6 kg and 2.3 kg, on average, respectively).[66]

Finally, in an attempt to determine whether hypoglycemic episodes were correlated with weight gain, an analysis by Davies and colleagues[57] found a significant relationship between hypoglycemia and weight gain for NPH but not for insulin detemir. In the absence of such a relationship, this suggests that some other mechanism must be contributing to insulin detemir's weight benefit.[67]

The existence of a brain-liver circuit that maintains weight and glucose homeostasis may provide some clues.[27,34] As mentioned previously, delivery of insulin to the brain is anorexogenic in mammals under experimental conditions.[10,35] It is interesting to note that insulin detemir exerts more pronounced signaling effects in the brain than do other exogenously administered insulin formulations.[68,69] When intravenous (IV) insulin detemir or human insulin was injected into experimental mice (at doses selected to achieve comparable peripheral signaling and glucose-lowering effects), brain insulin concentrations were higher in animals treated with insulin detemir than in animals given human insulin.[68] Brain insulin concentrations also correlated with cerebrocortical activity recorded in awake mice. Tyrosine phosphorylation of IR and IRS-2 proteins in mouse hypothalamic tissue occurred faster and was enhanced by insulin detemir compared with human insulin, despite similar phosphorylation of the IR in peripheral tissues (muscle and liver). These results suggest that insulin detemir enters brain tissue faster than human insulin and exhibits greater selectivity for brain over peripheral tissues. In a crossover study in which magnetoencephalographic techniques were used in 10 obese human subjects with normal glucose tolerance, Tschritter et al[69] demonstrated a higher degree of neuronal activation in human cerebral cortex after IV infusion of insulin detemir compared with human insulin. These experiments also documented that the peripheral effects of human insulin were more pronounced than those of insulin detemir.

Increased CNS tissue selectivity of insulin detemir may be explained by its albumin-binding properties and fatty acid chain.[68] Albumin is known to cross the blood-brain barrier via the choroid plexus and might facilitate transfer of insulin detemir into brain tissue. Once across, low concentrations of both substances in the CSF would favor dissociation; free insulin detemir would be available to exert physiologic (ie, anorectic) activity on brain IRs. Additionally, molecules with lipophilic properties (ie, those possessing fatty acid moieties) partition into brain tissue more rapidly than do more hydrophilic molecules, and they might also facilitate transfer of insulin detemir into the brain. Although these speculations would require further study for confirmation, they provide an intriguing notion that is consistent with the anorexogenic properties of brain-insulin effects and clinical observations with insulin detemir.

In addition to brain effects, other experimental angles may be worth exploring. Decreased affinity for the IR and faster dissociation from the receptor seen with insulin detemir[28] may contribute to a fat-sparing effect in peripheral tissues. Compared with

NPH, insulin detemir is preferentially available to hepatocytes[22] because of its albumin-binding properties. Albumin binding of insulin detemir could limit its transfer from the circulation to extravascular spaces in adipose and muscle tissue, allowing relatively greater exposure of insulin detemir in the liver. A higher concentration of insulin detemir in the liver would more closely mimic physiologic hepatic insulin levels, and the close proximity of liver sinusoids and hepatocytes would presumably result in greater suppression of hepatic glucose production, thus limiting the availability of glucose in fat cells.

Implications for Patients

Speculation about the mechanisms of insulin detemir–associated weight benefits aside, insulin detemir offers several advantages over NPH insulin through its direct impact on patients. With a similar time-action profile to insulin glargine[70] and more predictable time-action effects than NPH,[15] insulin detemir has been shown to reduce the risk of hypoglycemic episodes in number and in severity compared with NPH.[15,57] It is most important that significantly less weight gain and even weight loss has been observed in clinical trials with insulin detemir.[15] These effects have been reproduced in a real-world setting. In OAD-treated insulin-naive patients with type 2 diabetes (n=1321), initiation of insulin detemir improved glycemic control without weight gain.[18] In another cohort of patients with type 1 and type 2 diabetes from the same study, switching from a basal-bolus regimen with NPH to one that contained insulin detemir resulted in improvements in glycemic control, fewer hypoglycemic episodes, and no associated weight gain.[71]

Many pharmacologic agents have proved enormously beneficial before full knowledge of their mechanisms and therapeutic potential has been attained (eg, aspirin, coumarins, adrenergic blockers); this may also apply to the actions of insulin detemir that go beyond glycemic control.

SUMMARY/CONCLUSION

Endogenous insulin has many target organs, including the brain, and plays a vital role in diverse metabolic processes, including the maintenance of energy balance. Therapeutic insulin formulations that mimic normal physiologic mechanisms, such as preferential delivery to liver and brain tissue, would be expected to produce more physiologic effects and to minimize undesirable effects, including weight gain. Insulin detemir, when compared with other therapeutic insulin formulations, possesses characteristics that more closely mimic physiologic insulin. Although this will require further study, these characteristics may explain the beneficial effects on weight seen with this long-acting insulin analog.

DISCLOSURE

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REFERENCES

1. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature.* 2001;414:799-806.
2. Plum L, Belgardt BF, Bruning JC. Central insulin action in energy and glucose homeostasis. *J Clin Invest.* 2006;116:1761-1766.
3. Gerozissis K. Brain insulin: regulation, mechanisms of action and functions. *Cell Mol Neurobiol.* 2003;23:1-25.
4. White MF. Insulin signaling in health and disease. *Science.* 2003;302:1710-1711.
5. Obici S, Rossetti L. Minireview: nutrient sensing and the regulation of insulin action and energy balance. *Endocrinology.* 2003;144:5172-5178.
6. Seaquist ER, Damberg GS, Tkac I, Gruetter R. The effect of insulin on in vivo cerebral glucose concentrations and rates of glucose transport/metabolism in humans. *Diabetes.* 2001;50:2203-2209.
7. Banks WA. The source of cerebral insulin. *Eur J Pharmacol.* 2004;490:5-12.
8. Schwartz MW, Porte D Jr. Diabetes, obesity, and the brain. *Science.* 2005;307:375-379.
9. Gerozissis K. Brain insulin and feeding: a bi-directional communication. *Eur J Pharmacol.* 2004; 490:59-70.
10. Bruning JC, Gautam D, Burks DJ, et al. Role of brain insulin receptor in control of body weight and reproduction. *Science.* 2000;289:2122-2125.
11. Smith RM, Harada S, Jarett L. Insulin internalization and other signaling pathways in the pleiotropic effects of insulin. *Int Rev Cytol.* 1997;173:243-280.
12. Jacob AN, Salinsa K, Adams-Huet B, Raskin P. Weight gain in type 2 diabetes mellitus. *Diabetes Obes Metab.* 2007;9:386-393.
13. Larger E. Weight gain and insulin treatment. *Diabetes Metab.* 2005;31:4S51-4S56.
14. Hermansen K, Davies M, Derezinski T, Ravn GM, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetes Care.* 2006; 29:1269-1274.
15. Home P, Kurtzhals P. Insulin detemir: from concept to clinical experience. *Expert Opin Pharmacother.* 2006;7:325-343.
16. Rosenstock J, Davies M, Home PD, Larsen J, Tamer SC, Schernthanr G. Insulin detemir added to oral anti-diabetic drugs in type 2 diabetes provides glycemic control comparable to insulin glargine with less weight gain [abstract]. *Diabetes.* 2006;55(suppl 1):A132.
17. Raslová K, Tamer SC, Clauson P, Karl D. Insulin detemir results in less weight gain than NPH insulin when used in basal-bolus therapy for type 2 diabetes mellitus, and this advantage increases with baseline body mass index. *Clin Drug Investig.* 2007:27:279-285.
18. Meneghini LF, Rosenberg KH, Koenen C, Merilainen MJ, Luddeke H-J. Insulin detemir improves glycaemic control with less hypoglycaemia and no weight gain in patients with type 2 diabetes who were insulin naive or treated with NPH or insulin glargine: clinical practice experience from a German subgroup of the PREDICTIVE study. *Diabetes Obes Metab.* 2007;9:418-427.
19. Fritsche A, Haring H. At last, a weight neutral insulin? *Int J Obes Relat Metab Disord.* 2004; 28(suppl 2):S41-S46.

20. Raslova K, Bogoev M, Raz I, Leth G, Gall MA, Hancu N. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes [correction appears in Raslova K, et al. *Diabetes Res Clin Pract.* 2006;72:112]. *Diabetes Res Clin Pract.* 2004;66:193-201.

21. Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen. *Clin Ther.* 2004;26:724-736.

22. Hordern SV, Wright JE, Umpleby AM, Shojaee-Moradie F, Amiss J, Russell-Jones DL. Comparison of the effects on glucose and lipid metabolism of equipotent doses of insulin detemir and NPH insulin with a 16-h euglycaemic clamp. *Diabetologia.* 2005;48:420-426.

23. Nigro J, Osman N, Dart AM, Little PJ. Insulin resistance and atherosclerosis. *Endocr Rev.* 2006;27:242-259.

24. Plum L, Schubert M, Bruning JC. The role of insulin receptor signaling in the brain. *Trends Endocrinol Metab.* 2005;16:59-65.

25. Kido Y, Nakae J, Accili D. Clinical review 125: the insulin receptor and its cellular targets. *J Clin Endocrinol Metab.* 2001;86:972-979.

26. Bergman RN. New concepts in extracellular signaling for insulin action: the single gateway hypothesis. *Recent Prog Horm Res.* 1997;52:359-385.

27. Pocai A, Obici S, Schwartz GJ, Rossetti L. A brain-liver circuit regulates glucose homeostasis. *Cell Metab.* 2005;1:53-61.

28. Kurtzhals P, Schaffer L, Sorensen A, et al. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. *Diabetes.* 2000;49:999-1005.

29. Boileau P, Cauzac M, Pereira MA, Girard J, Hauguel-De MS. Dissociation between insulin-mediated signaling pathways and biological effects in placental cells: role of protein kinase B and MAPK phosphorylation. *Endocrinology.* 2001;142:3974-3979.

30. Zib I, Raskin P. Novel insulin analogue and its mitogenic potential. *Diabetes Obes Metab.* 2006;8:611-620.

31. Porte D, Baskin DG, Schwartz MW. Insulin signaling in the central nervous system: a critical role in metabolic homeostasis and disease from *C. elegans* to humans. *Diabetes.* 2005;54:1264-1276.

32. Banks WA. The blood-brain barrier as a regulatory interface in the gut-brain axes. *Physiol Behav.* 2006;89:472-476.

33. Jobst EE, Enriori PJ, Cowley MA. The electrophysiology of feeding circuits. *Trends Endocrinol Metab.* 2004;15:488-499.

34. Pocai A, Lam TK, Gutierrez-Juarez R, et al. Hypothalamic K(ATP) channels control hepatic glucose production. *Nature.* 2005;434:1026-1031.

35. McGowan MK, Andrews KM, Kelly J, Grossman SP. Effects of chronic intrahypothalamic infusion of insulin on food intake and diurnal meal patterning in the rat. *Behav Neurosci.* 1990;104:373-385.

36. Hallschmid M, Benedict C, Schultes B, Fehm HL, Born J, Kern W. Intranasal insulin reduces body fat in men but not in women. *Diabetes.* 2004;53:3024-3029.

37. Khan AH, Pessin JE. Insulin regulation of glucose uptake: a complex interplay of intracellular signaling pathways. *Diabetologia.* 2002;45:1475-1483.

38. Vollenweider P, Menard B, Nicod P. Insulin resistance, defective insulin receptor substrate 2-associated phosphatidylinositol-3′ kinase activation, and impaired atypical protein kinase C (zeta/lambda) activation in myotubes from obese patients with impaired glucose tolerance. *Diabetes.* 2002;51:1052-1059.

39. Pessin JE, Saltiel AR. Signaling pathways in insulin action: molecular targets of insulin resistance. *J Clin Invest.* 2000;106:165-169.

40. Obici S, Feng Z, Karkanias G, Baskin DG, Rossetti L. Decreasing hypothalamic insulin receptors cause hyperphagia and insulin resistance in rats. *Nat Neurosci.* 2002;5:566-572.

41. Tschritter O, Preissl H, Hennige AM, et al. The cerebrocortical response to hyperinsulinemia is reduced in overweight humans: a magnetoencephalographic study. *Proc Natl Acad Sci U S A.* 2006;103:12103-12108.

42. Teeter J, Becker R. The clinical relevance of inhaled insulin in the diabetic lung. *Am J Med.* 2006; 119:184-185.

43. Pfizer Inc. Exubera® (insulin human [RDNA origin]) Inhalation Powder and Exubera® Inhaler [prescribing information]. New York, NY: Pfizer Inc; January 2006.

44. Novo Nordisk Inc. Levemir® (insulin detemir [RDNA origin] injection) [product information]. Princeton, NJ: Novo Nordisk; 2005.

45. Aventis Pharmaceuticals Inc. Lantus® (insulin glargine [RDNA origin] injection). Kansas City, Mo: Aventis Pharmaceuticals; 2004.

46. Wing RR, Klein R, Moss SE. Weight gain associated with improved glycemic control in population-based sample of subjects with type I diabetes. *Diabetes Care.* 1990;13:1106-1109.

47. DCCT Research Group. Weight gain associated with intensive therapy in the Diabetes Control and Complications Trial. *Diabetes Care.* 1988;11:567-573.

48. Sallé A, Guilloteau G, Ryan M, Bouhanick B, Ritz P. Effect of insulin treatment on the body composition of type 2 diabetic patients. *Diabet Med.* 2004;21:1298-1303.

49. Larger E, Rufat P, Dubois-Laforgue D, Ledoux S. Insulin therapy does not itself induce weight gain in patients with type 2 diabetes. *Diabetes Care.* 2001;24:1849-1850.

50. Biesenbach G, Raml A, Alsaraji N. Weight gain and insulin requirement in type 2 diabetic patients during the first year after initiating insulin therapy dependent on baseline BMI. *Diabetes Obes Metab.* 2006;8:669-673.

51. Haak T, Tiengo A, Draeger E, Suntum M, Waldhausl W. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes Obes Metab.* 2005;7:56-64.

52. Hermansen K, Tamer SC. The advantage of less weight gain increases with baseline obesity when insulin detemir rather than NPH insulin is added to oral agents in type 2 diabetes [abstract]. *Diabetes.* 2005;54(suppl 1):A67.

53. Hermansen K, Mathieu C. Insulin detemir is weight sparing compared to NPH insulin in type 1 and type 2 diabetes [abstract]. *Diabet Med.* 2006;23:329-330.

54. Fledelius C, Damgaard J, Endahl L, Ribel U, Sturis J. Insulin detemir causes less gain in body weight and relative fat mass than human insulin in the STZ rat for the same degree of glycemic control [abstract]. *Diabetes.* 2006;55(suppl 1):A470.

55. Home P, Bartley P, Russell-Jones D, et al. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. *Diabetes Care.* 2004;27:1081-1087.

56. Hermansen K, Fontaine P, Kukolja KK, Peterkova V, Leth G, Gall MA. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia.* 2004;47: 622-629.

57. Davies M, Derezinski T, Kim H, Clauson P. No correlation between weight gain and number of hypoglycemic events in patients with type 2 diabetes treated with insulin detemir as compared to NPH insulin [abstract]. *Diabetes.* 2006;55(suppl 1):A466.

58. Kolendorf K, Ross GP, Pavlic-Renart I, et al. Insulin detemir lowers the risk of hypoglycaemia and provides more consistent plasma glucose levels compared with NPH insulin in type 1 diabetes. *Diabet Med.* 2006;23:729-735.

59. Kolendorf K, Kim H, Clauson P. Insulin detemir incurs a lower risk of hypoglycaemia than NPH insulin for any level of HbA1c when added to oral agents in a treat-to-target protocol for patients with type 2 diabetes [abstract]. *Diabetologia.* 2005;48(suppl 1):A833.

60. Pieber TR, Draeger E, Kristensen A, Grill V. Comparison of three multiple injection regimens for type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir vs. morning plus bedtime NPH insulin. *Diabet Med.* 2005;22:850-857.

61. Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. *Cochrane Database Syst Rev.* 2006;CD003287.

62. Garber AJ. Premixed insulin analogues for the treatment of diabetes mellitus. *Drugs.* 2006;66:31-49.

63. Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. *Diabetes Care.* 2005;28:950-955.

64. Dunn CJ, Plosker GL, Keating GM, McKeage K, Scott LJ. Insulin glargine: an updated review of its use in the management of diabetes mellitus. *Drugs.* 2003;63:1743-1778.

65. Rosenstock J, Schwartz SL, Clark CM Jr, Park GD, Donley DW, Edwards MB. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. *Diabetes Care.* 2001;24:631-636.

66. Yki-Jarvinen H, Dressler A, Ziemen M. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. *Diabetes Care.* 2000;23:1130-1136.

67. Davies M. Less weight gain with insulin detemir compared to NPH insulin in type 2 diabetes is not directly correlated to lower risk of hypoglycemia. Presented at: the 19th World Congress of the International Diabetes Foundation, December 3–7, 2006. Cape Town, South Africa.

68. Hennige AM, Sartorius T, Tschritter O, et al. Tissue selectivity of insulin detemir action in vivo. *Diabetologia.* 2006;49:1274-1282.

69. Tschritter O, Porubska K, Hennige AM, et al. Neuronal activation of the human cerebral cortex by administration of insulin detemir compared to human insulin [abstract]. *Diabetologia.* 2005; 48:A256.

70. Klein O, Lynge J, Endahl L, Damholt B, Nosek L, Heise T. Albumin-bound basal insulin analogues (insulin detemir and NN344): comparable time-action profiles but less variability than insulin glargine in type 2 diabetes. *Diabetes Obes Metab.* 2006;1-10.

71. Ruhnau K-J, Hansen JB, Dornhorst A. Switching from basal-bolus therapy with NPH insulin to basal-bolus therapy with the analog insulin detemir improves glycemic control and reduces hypoglycemic episodes, without weight gain, in type 1 and type 2 diabetes patients: results from German subgroup of the PREDICTIVE Study [abstract]. *Diabetes.* 2006;55(suppl 1):A133.