Effect of IGF-I on FFA and glucose metabolism in control and type 2 diabetic subjects

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Received 24 July 2001; accepted in final form 24 February 2002

Am J Physiol Endocrinol Metab 282: E1360–E1368, 2002; 10.1152/ajpendo.00335.2001—The effects of insulin-like growth factor I (IGF-I) and insulin on free fatty acid (FFA) and glucose metabolism were compared in eight control and eight type 2 diabetic subjects, who received a two-step euglycemic hyperinsulinemic (0.25 and 0.5 mU·kg⁻¹·min⁻¹) clamp and a two-step euglycemic IGF-I (26 and 52 pmol·kg⁻¹·min⁻¹) clamp with [3-³H]glucose, [1-¹⁴C]palmitate, and indirect calorimetry. The insulin and IGF-I infusion rates were chosen to augment glucose disposal (Rd) to a similar extent in control subjects. In type 2 diabetic subjects, stimulation of Rd (second clamp step) in response to both insulin and IGF-I was reduced by ~40–50% compared with control subjects. In control subjects, insulin was more effective than IGF-I in suppressing endogenous glucose production (EGP) during both clamp steps. In type 2 diabetic subjects, insulin-mediated suppression of EGP was impaired, whereas EGP suppression by IGF-I was similar to that of controls. In both control and diabetic subjects, IGF-I-mediated suppression of plasma FFA concentration and inhibition of FFA turnover were markedly impaired compared with insulin (P < 0.01–0.001). During the second IGF-I clamp step, suppression of plasma FFA concentration and FFA turnover was impaired in diabetic vs. control subjects (P < 0.05–0.01). Conclusions: 1) IGF-I is less effective than insulin in suppressing EGP and FFA turnover; 2) insulin-resistant type 2 diabetic subjects also exhibit IGF-I resistance in skeletal muscle. However, suppression of EGP by IGF-I is not impaired in diabetic individuals, indicating normal hepatic sensitivity to IGF-I.

insulin-like growth factor I; insulin resistance; free fatty acid metabolism; type 2 diabetes mellitus

INSULIN-LIKE GROWTH FACTOR I (IGF-I) is a growth-promoting peptide that shares many structural and functional similarities with insulin. In the circulation, IGF-I is highly protein bound, and only free IGF-I is biologically active. In vitro, physiological concentrations of IGF-I stimulate glucose transport and metabolism in muscle, and these effects are mediated via a specific IGF-I receptor (28), although some effects of IGF-I may be mediated by insulin/IGF-I hybrid receptors (44). The IGF-I receptor is highly homologous to the insulin receptor (17, 36). Both ligands, IGF-I and insulin, activate receptor tyrosine kinase activity, leading to a cascade of intracellular events resulting in the stimulation of glucose utilization.

The effects of IGF-I on whole body and muscle glucose metabolism have been studied extensively in animals (21, 35, 37, 50) and in humans (2, 12, 19, 27, 38, 46). IGF-I augments glucose uptake, glucose oxidation, and nonoxidative glucose disposal in a dose-dependent fashion, similar to insulin (2, 12, 27, 38). IGF-I also suppresses endogenous (primarily hepatic) glucose production (EGP) (2, 12, 38), although it appears to be less effective than insulin in both animals (21, 22, 35) and humans (27). In animal models of type 2 diabetes mellitus (4, 23), the ability of IGF-I to augment glucose disposal is impaired. The acute effects of IGF-I on peripheral and hepatic glucose metabolism in type 2 diabetic humans have been less well characterized. Laagerand and Keller (26) demonstrated that the decline in plasma glucose concentration in response to intravenous IGF-I was impaired in type 2 diabetic individuals, but this study did not examine whether the IGF-I resistance was present in skeletal muscle, liver, or in both. In a previous study (7), we demonstrated that chronic subcutaneous IGF-I administration in type 2 diabetic patients inhibited EGP, reduced the fasting glucose concentration, and produced a small increase in insulin-mediated glucose disposal. In the present study, we have compared the effects of IGF-I and insulin on peripheral (muscle) and hepatic glucose metabolism by using doses of IGF-I and insulin that elicit a similar stimulation of whole body glucose disposal in healthy control subjects.

Much less is known about the effect of IGF-I on free fatty acid (FFA) metabolism. In vitro, an insulinomimetic effect of IGF-I on adipocytes is observed only at
high hormone concentrations and is believed to be mediated through a cross-reaction with the insulin receptor (1, 43, 51), because IGF-I receptors are not present on fat cells (1, 31). Consistent with these observations, several investigators (5, 21, 50) have failed to detect any decline in plasma FFA concentration, albeit with high doses of IGF-I. Little information is available about the effect of low, physiological concentrations of IGF-I on FFA metabolism in humans. In the present study, we have employed [1-14C]palmitate with indirect calorimetry and the euglycemic clamp technique to examine and contrast the effects of physiological levels of IGF-I and insulin on FFA metabolism in healthy control and type 2 diabetic individuals.

**METHODS**

*Subjects.* Eight healthy nondiabetic and eight type 2 diabetic subjects participated in the study. Their clinical and biochemical characteristics are shown in Table 1. The diabetic subjects were slightly more obese than the nondiabetic subjects, and they were in reasonably good glycemic control, as demonstrated by a mean hemoglobin A_1C_ value of 6.8%. All nondiabetic subjects had a normal 75-g oral glucose tolerance test, and none had a family history of diabetes mellitus. Except for the presence of diabetes, all subjects were in good general health. Two diabetic subjects were treated with diet alone, and six diabetic subjects were receiving a sulfonylurea. The sulfonylurea was stopped 2 days before each study. Other than sulfonylureas, no subject was taking any medication known to affect glucose metabolism. None of the diabetic subjects had ever taken metformin, a thiazolidinedione, or insulin. Body weight was stable for 3 mo before study in all subjects. No subject participated in any strenuous exercise on a regular basis. Over the 3 days before study, subjects were instructed to consume a weight-maintaining diet containing 200–250 g of carbohydrate per day. The purposes, nature, and potential risks of the study were explained to all subjects before their written, voluntary consent to participate in the study was obtained. The protocol was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio.

*Study design.* All studies were conducted at the General Clinical Research Center of the University of Texas Health Science Center at San Antonio. Subjects refrained from eating or drinking anything except water after 2200 on the evening before study. All studies were carried out at 0700 in the postabsorptive state. Before study, catheters were placed into an antecubital vein for the infusion of all test substances, and retrogradely into a vein on the dorsum of the hand for blood withdrawal. The hand was then placed in a heated box (60°C) to provide arterialized venous blood. All subjects received both a two-step euglycemic hyperinsulinemic (0.25 and 0.5 mIU·kg⁻¹·min⁻¹) clamp and a two-step euglycemic IGF-I clamp (26 and 52 pmol·kg⁻¹·min⁻¹). The insulin and IGF-I clamp studies were performed in random sequence within a 7-day period. The insulin infusion rates were chosen to achieve steady-state plasma insulin concentrations on the steep part of the curve for the suppression of EGP and FFA turnover (18). The infusion rates of IGF-I were chosen on the basis of previous studies (16), which demonstrated that they increased total body glucose disposal in healthy nondiabetic subjects to a level comparable to that observed with insulin. On a molar basis, the dose of IGF-I is ~18-fold greater than that of insulin. Three hours before the insulin and IGF-I clamp studies, a primed (25 μCi × fasting plasma glucose/90-continuous (0.25 μCi/min) infusion of [3-3H]glucose (New England Nuclear, Boston, MA) was begun. At the same time, a primed (2.2 μCi)-continuous (0.1 μCi/min) infusion of [1-14C]palmitate and a 4-μCi bolus of [3-14C]sodium bicarbonate was given. After a 3-h isotope equilibration period, the two-step insulin or IGF-I infusion was started. Each clamp step lasted 120 min. During the last 30 min of the equilibration period, arterialized blood samples were obtained every 5–10 min for determination of plasma glucose, FFA, total IGF-I and insulin concentrations, and plasma tritiated glucose and [1-14C]palmitate radioactivity. During the two-step IGF-I and insulin clamp studies, plasma FFA and insulin concentrations and plasma FFA and glucose radioactivities were determined every 10–15 min. After the start of insulin or IGF-I infusion, arterialized blood samples were collected every 5 min for the determination of plasma glucose concentration, and the infusion of a 20% glucose infusion was appropriately adjusted to maintain euglycemia (8). In the diabetic patients, no exogenous glucose was infused until the plasma glucose concentration declined to ~100 mg/dl, at which level it was maintained. No tritiated glucose was added to the cold glucose infusate, because we previously have shown that, at the rates of whole body glucose disposal achieved with the steady-state plasma insulin and IGF-I concentrations, the tracer-derived rate of whole body glucose disposal closely approximates the rate of whole body glucose uptake (15).

Continuous indirect calorimetry was carried out during the 45-min period before the start of the insulin/IGF-I clamp and during the last 45 min of each clamp step (41). Expired breath samples for determination of [14CO₂] specific activity were obtained every 10–15 min during the last 45 min of the basal equilibration period and of each clamp step (18). Percent fat mass and fat free mass were measured by the

**Table 1. Subject characteristics**

<table>
<thead>
<tr>
<th>Number</th>
<th>Control Subjects</th>
<th>Diabetic Subjects</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>2M/6F</td>
<td>4M/4F</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes duration, yr</td>
<td>NA</td>
<td>6±3</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>42±3</td>
<td>49±2</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>64.1±3.0</td>
<td>77.2±3.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Height, cm</td>
<td>163±1</td>
<td>163±NS</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.1±1.1</td>
<td>28.9±1.2</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>45.1±2.5</td>
<td>55.2±3.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FM, kg</td>
<td>18.9±1.1</td>
<td>22.2±2.0</td>
<td>0.20</td>
</tr>
<tr>
<td>FPI, μU/ml</td>
<td>9±1</td>
<td>16±1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>F-IGF-I, ng/ml</td>
<td>106±8</td>
<td>81±10</td>
<td>0.07</td>
</tr>
<tr>
<td>HbA_{1C}, %</td>
<td>5.2±0.1</td>
<td>6.8±0.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>181±14</td>
<td>211±9</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride, mg/dl</td>
<td>71±6</td>
<td>166±17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>52±3</td>
<td>42±3</td>
<td>0.03</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>115±14</td>
<td>136±8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE. BMI, body mass index; FPG, fasting plasma glucose concentration; FPI, fasting plasma insulin concentration; F-IGF-I, fasting plasma insulin-like growth factor I concentration; FFM, fat free mass; FM, fat mass; Hb, hemoglobin; HDL and LDL, high-density and low-density lipoprotein, respectively; NS, not significant.
bioelectrical impedance method (25) (RJL Systems, Clinton, MI) before the start of the insulin/IGF-I clamp.

Analytical determinations. Plasma glucose concentration was determined by the glucose oxidase method (Glucose Oxidase Analyzer, Beckman Instruments, Fullerton, CA). Plasma insulin concentration was determined by radioimmunoassay (Diagnostic Product, Los Angeles, CA) and plasma FFA concentration by an enzymatic method (Wako Pure Chemical Industry, Osaka, Japan). Plasma total IGF-I concentration was determined by radioimmunoassay (ALPCO, Windham, NH). Plasma IGF-binding protein-3 (BP-3) concentration was determined by immunoradiometric assay (DSL, Webster, TX). Plasma-tritiated glucose radioactivity was determined on barium hydroxide and zinc sulfate-precipitated plasma samples, as previously described (18). For determination of [1-14C]palmitate radioactivity, 1.5 ml of plasma was extracted with 10 ml of Dole’s solution. FFAs were isolated from the liquid phase by use of 0.02 N NaOH and reextracted with heptane after acidification (18). The heptane extraction was repeated three times, and 99.9% of the radioactivity was consistently recovered in the heptane phase. The extracts were combined and dissolved in scintillation liquid and counted in a beta scintillation counter (Beckman Instruments). 14CO2 radioactivity was determined by bubbling expired air through a CO2-trapping solution (1 M hyamine hydrochloride-absolute ethanol-0.1% phenolphthalein; 3:5:1) that was tritiated with 1 N HCl to trap 1 mmol of CO2 per 3 ml of solution. 14CO2 radioactivity was measured in a beta scintillation counter (LS 6000IC, Beckman Instruments).

Calculations. Basal EGP was calculated by dividing the tritiated glucose infusion rate (dpm/min) by the steady-state plasma tritiated glucose specific activity (dpm/mg) during the last 30 min of the basal equilibration period. During steady-state postabsorptive conditions, the rate of EGP equals the rate of whole body glucose disposal. During the insulin/IGF-I clamp, the glucose system is driven out of steady state, and the rates of glucose appearance and disappearance were calculated by Steele’s non-steady-state equation (45) by use of a volume of distribution of 250 ml/kg and a pool factor of 0.65 (6). Rates of whole body glucose disposal are expressed per kilogram of fat-free mass (FFM), because muscle is responsible for the disposal of the majority (80–90%) of glucose disposal under euglycemic conditions.

The plasma FFA turnover rate (expressed as μmol·kg⁻¹·min⁻¹) was calculated as the rate of [1-14C]palmitate infusion (dpm/min) divided by the steady-state plasma palmitate specific activity (dpm/μmol) and corrected for the contribution of palmitate to total plasma FFA concentration (18). Plasma FFA concentration and specific activity were constant during the last 30 min of the equilibration period and the last 40 min of the each insulin/IGF-I clamp step. Therefore, all calculated rates of FFA turnover pertain to steady-state conditions and are expressed per kilogram body weight, since lipolysis in adipose tissue represents the primary source of plasma-derived FFA, and both muscle and adipose tissue contribute to FFA oxidation and nonoxidative FFA disposal.

The rates of whole body glucose and lipid oxidation were calculated from the rates of CO2 production and O2 consumption from indirect calorimetry and the urine nitrogen excretion rate (41). Total lipid oxidation was converted to a molar equivalent, with the assumption of the average molecular weight of triglycerides to be 860 g/mol (41).

The rate of plasma FFA oxidation was calculated by dividing the 14CO2 production rate (dpm/min) by the plasma FFA specific activity (dpm/μmol). Under steady-state conditions, the 14CO2 production rate is obtained from the product of the 14CO2 specific activity (dpm/mmol) and the CO2 excretion rate (mmol/min; determined by indirect calorimetry) divided by 0.81, which represents the correction factor for the amount of labeled CO2 that is not recovered from the bicarbonate pool in humans. It has been suggested that the acetate, not bicarbonate, correction factor should be employed to calculate rates of plasma FFA oxidation (40). Use of the acetate correction factor would result in slightly greater rates of plasma FFA oxidation than reported herein, but this would not influence any of the present conclusions. The oxidation rate of nonplasma FFA (i.e., intramuscular FFA and plasma triglycerides) was calculated as the difference between the rates of total body lipid oxidation (indirect calorimetry) and plasma FFA oxidation.

Statistics. Differences between the basal and insulin/IGF-I-mediated rates of glucose and FFA metabolism within a group were determined by the paired t-test. Differences in glucose and FFA turnover rates between the insulin and IGF-I clamp studies and between type 2 diabetic and control subjects were compared by ANOVA. When statistically significant differences were obtained, they were confirmed by the Bonferroni test. Differences were considered to be statistically significant if the P value was <0.05. All data are presented as means ± SE.

RESULTS

Plasma glucose, insulin, IGF-I, and IGFBP-3 concentrations. The fasting plasma glucose and insulin concentrations were significantly greater in the diabetic vs. control subjects (P < 0.01) (Table 1 and Fig. 1). During the first and second steps of the insulin clamp, the steady-state plasma insulin concentrations were similarly increased in the control and diabetic groups. During the first and second steps of the IGF-I clamp, the plasma insulin concentrations declined slightly and similarly in the diabetic and control groups. In the basal state, the plasma IGF-I concentration was slightly lower (P = 0.07) in the diabetic than in the control group (Table 1). The increment in IGF-I was similar in the control and diabetic groups during the first and second steps of the IGF-I clamp (Table 2). In the control group, the plasma glucose concentrations during the first and second steps of the insulin (96 ± 2 mg/dl) and IGF-I (95 ± 2 mg/dl) clamps were maintained close to the fasting value, with a coefficient of

![Fig. 1. Plasma insulin concentrations in control (A) and type 2 diabetic (B) subjects during the 1st (0–120 min) and 2nd (120–240) minutes of the insulin/IGF-I clamps.](http://ajpendo.physiology.org/DownloadedFrom/10.1152/ajpendo.00021.2002)
controls) nor IGF-I (P = 0.01) suppressed EGP (0.29 ± 0.14 vs. 1.50 ± 0.19 mg·kg FFM⁻¹·min⁻¹, P < 0.01; Fig. 3). During the second clamp step in control subjects, both insulin and IGF-I suppressed EGP by >90% (0.05 ± 0.04 vs. 0.24 ± 0.10 mg·kg FFM⁻¹·min⁻¹, P = 0.15). In the diabetic group, insulin and IGF-I suppressed EGP similarly during both the first (1.40 ± 0.14 vs. 1.26 ± 0.16 mg·kg FFM⁻¹·min⁻¹, P = NS) and second (0.56 ± 0.13 vs. 0.52 ± 0.18 mg·kg FFM⁻¹·min⁻¹, P = NS) clamp steps. The ability of insulin to inhibit EGP in type 2 diabetic vs. control subjects was significantly impaired (Fig. 2). During the second clamp step in diabetic subjects, both insulin and IGF-I significantly increased total body glucose uptake above that observed in the basal state, but the rates of glucose disposal with both insulin (3.31 ± 0.19 vs. 6.43 ± 0.45 mg·kg FFM⁻¹·min⁻¹, P < 0.001) and IGF-I (3.46 ± 0.41 vs. 5.86 ± 0.75 mg·kg FFM⁻¹·min⁻¹, P = 0.02) were reduced compared with those in the control group (Fig. 2). Both diminished glucose oxidation and nonoxidative glucose disposal contributed to the defects in insulin-mediated and IGF-I-mediated whole body glucose disposal in the diabetic subjects. EGP. In the control group during the first clamp step, insulin was five times more potent than IGF-I in suppressing EGP (0.29 ± 0.14 vs. 1.50 ± 0.19 mg·kg FFM⁻¹·min⁻¹, P < 0.01; Fig. 3). During the second clamp step in control subjects, both insulin and IGF-I suppressed EGP by >90% (0.05 ± 0.04 vs. 0.24 ± 0.10 mg·kg FFM⁻¹·min⁻¹, P = 0.15). In the diabetic group, insulin and IGF-I suppressed EGP similarly during both the first (1.40 ± 0.14 vs. 1.26 ± 0.16 mg·kg FFM⁻¹·min⁻¹, P = NS) and second (0.56 ± 0.13 vs. 0.52 ± 0.18 mg·kg FFM⁻¹·min⁻¹, P = NS) clamp steps. The ability of insulin to inhibit EGP in type 2 diabetic vs. control subjects was significantly impaired

Table 2. Plasma total IGF-I and IGFBP-3 concentrations in control and type 2 diabetic subjects during the basal state and during the 1st and 2nd steps of the insulin and IGF-I clamp studies

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>1st Step</th>
<th>2nd Step</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IGF-I clamp</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>108 ± 9</td>
<td>315 ± 18</td>
<td>529 ± 23</td>
</tr>
<tr>
<td>Diabetic</td>
<td>83 ± 11*</td>
<td>299 ± 20</td>
<td>496 ± 26</td>
</tr>
<tr>
<td>IGFBP-3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2,584 ± 206</td>
<td>2,555 ± 279</td>
<td>2,725 ± 303</td>
</tr>
<tr>
<td>Diabetic</td>
<td>2,107 ± 326†</td>
<td>2,284 ± 387</td>
<td>2,431 ± 433‡</td>
</tr>
<tr>
<td><strong>Total IGF-I</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>104 ± 7</td>
<td>103 ± 9</td>
<td>98 ± 9</td>
</tr>
<tr>
<td>Diabetic</td>
<td>80 ± 10*</td>
<td>86 ± 10</td>
<td>80 ± 10</td>
</tr>
<tr>
<td>IGFBP-3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2,345 ± 337</td>
<td>2,319 ± 344</td>
<td>2,379 ± 304</td>
</tr>
<tr>
<td>Diabetic</td>
<td>2,065 ± 289†</td>
<td>2,168 ± 321</td>
<td>1,849 ± 308</td>
</tr>
</tbody>
</table>

Values are means ± SE expressed as ng/ml. IGFBP-3, IGF-binding protein 3. *P = 0.07, diabetic vs. control subjects; †P = 0.10 diabetic vs. control subjects; ‡P = 0.07 vs. basal.

variation of <5%. The basal plasma IGFBP-3 concentration in the diabetic subjects was slightly less than in control subjects (Table 2). During the second IGF-I clamp study, there was a tendency for the IGFBP-3 levels to increase in both diabetic and control groups (Table 2). There was no significant change in the IGFBP-3 levels in either group during the insulin clamp study (Table 2). There was a strong correlation between the plasma IGF-I and plasma IGFBP-3 levels during the basal state in both the diabetic and control groups (r = 0.80, P < 0.001). In the diabetic group, the fasting plasma glucose concentration (142 ± 12 mg/dl) was reduced to 114 ± 8 and 101 ± 1 mg/dl, respectively, during the first and second insulin clamp steps and to 107 ± 9 and 101 ± 1 mg/dl, respectively, during the first and second IGF-I clamp steps.

Whole body glucose uptake, glucose oxidation, and nonoxidative glucose uptake. During the first clamp step in control subjects, insulin (from 2.59 ± 0.15 to 3.21 ± 0.20 mg·kg FFM⁻¹·min⁻¹) and IGF-I (from 2.68 ± 0.13 to 3.01 ± 0.25 mg·kg FFM⁻¹·min⁻¹) increased the rate of total body glucose disposal to similar values [P = nonsignificant (NS), insulin vs. IGF-I]. Likewise, during the second clamp step in control subjects, insulin (from 3.21 ± 0.20 to 6.43 ± 0.45) and IGF-I (from 3.01 ± 0.25 to 5.86 ± 0.75 mg·kg FFM⁻¹·min⁻¹) increased total body glucose to similar values (P = NS, insulin vs. IGF-I). During the second clamp step (Fig. 2), the increase in total body glucose disposal with both insulin and IGF-I was accounted for approximately equally by increases in both glucose oxidation (P < 0.01) and nonoxidative glucose disposal (P < 0.01) (Fig. 2).

In the diabetic group, neither insulin (P < 0.05 vs. controls) nor IGF-I (P < 0.05 vs. controls) increased whole body glucose uptake, glucose oxidation, or nonoxidative glucose disposal during the first clamp step.
during both clamp steps (1st step: 1.40 ± 0.14 vs. 0.29 ± 0.14, P < 0.01; 2nd step: 0.56 ± 0.13 vs. 0.05 ± 0.04 mg·kg FFM⁻¹·min⁻¹, P < 0.01). In contrast to insulin, the ability of IGF-I to suppress EGP was similar in type 2 diabetic and control subjects (1st step 1.50 ± 0.19 vs. 1.26 ± 0.16, P = NS; 2nd step 0.24 ± 0.10 vs. 0.42 ± 0.18 mg·kg FFM⁻¹·min⁻¹, P = NS).

**Plasma FFA concentration and turnover.** In control subjects, the decline in basal plasma FFA concentration was greater with insulin than with IGF-I during both clamp steps (1st step: 123 ± 25 vs. 562 ± 53, P < 0.001; 2nd step: 77 ± 17 vs. 182 ± 47 μmol/l, P < 0.05). In type 2 diabetic subjects, the suppression of plasma FFA concentration by insulin also was significantly greater than with IGF-I during both insulin clamp steps (1st step: 203 ± 35 vs. 571 ± 94, P < 0.01; 2nd step: 118 ± 15 vs. 347 ± 98 μmol/l, P < 0.05).

In type 2 diabetic patients, insulin was less effective in decreasing the plasma FFA concentration than it was in controls during the first clamp step: 123 ± 25 vs. 203 ± 34, P < 0.05. During the second clamp step, suppression of plasma FFA by insulin in the diabetic subjects was slightly but not significantly impaired. In diabetic patients, suppression of plasma FFA concentration by IGF-I during the first (562 ± 53 vs. 123 ± 25, P < 0.001) and second (182 ± 47 vs. 77 ± 17 μmol/l, P = 0.06) clamp steps was impaired compared with insulin (Fig. 4).

In control subjects, IGF-I (1st clamp step) had no significant effect on total body FFA turnover rate, whereas insulin (1st clamp step) reduced the FFA turnover rate by 69% (5.78 ± 0.57 vs. 1.84 ± 0.36 μmol·kg⁻¹·min⁻¹, P < 0.001) (Fig. 5). During the second clamp step in control subjects, suppression of whole body FFA turnover by insulin also was greater than with IGF-I (1.27 ± 0.30 vs. 2.42 ± 0.38 μmol·kg⁻¹·min⁻¹, P < 0.05). In type 2 diabetic patients, insulin-mediated suppression of whole body FFA turnover was greater than that observed with IGF-I during both the first and second clamp steps (P < 0.01) (Fig. 5). In type 2 diabetic patients, the ability of insulin to reduce whole body FFA turnover was impaired compared with control subjects during both the first and second insulin clamp steps. Suppression of plasma FFA concentration by IGF-I in type 2 diabetic subjects also was significantly reduced compared with control subjects (P < 0.05) during the second clamp step.

Basal nonoxidative FFA disposal was similar during the insulin and IGF-I clamp studies in both control (4.17 ± 0.49 vs. 4.19 ± 0.67 μmol·kg⁻¹·min⁻¹) and type 2 diabetic (3.64 ± 0.24 vs. 3.54 ± 0.24) subjects. In both the control and diabetic groups, the ability of IGF-I to reduce nonoxidative FFA disposal was markedly reduced compared with insulin (P < 0.001) (Fig. 5).

**Total lipid oxidation, plasma FFA oxidation, and nonplasma FFA oxidation.** In both the control and diabetic groups during basal conditions, total body lipid oxidation (2.84 ± 0.26 vs. 2.72 ± 0.25 μmol·kg⁻¹·min⁻¹, respectively, P = NS) was ~75% greater than the plasma FFA oxidation rate (1.60 ± 0.24 and 1.60 ± 0.16 μmol·kg⁻¹·min⁻¹, respectively). In both control and type 2 diabetic subjects, inhibition of total body lipid oxidation and plasma FFA oxidation (Fig. 6) was significantly greater during both the first and second insulin clamp steps vs. the first and second IGF-I clamp steps (P < 0.05–0.001). In type 2 diabetic patients compared with control subjects, the ability of both insulin and IGF-I to inhibit plasma FFA and total lipid oxidation was significantly impaired during both clamp steps (Fig. 6).

In control subjects, nonplasma FFA oxidation did not change during the first step of either the insulin or IGF-I clamp studies, and it decreased similarly during the second step of the insulin (from 1.24 ± 0.23 to 0.45 ± 0.22 μmol·kg⁻¹·min⁻¹, P < 0.05) and IGF-I (from 1.12 ± 0.27 to 0.69 ± 0.22 μmol·kg⁻¹·min⁻¹, P < 0.05) clamps (Fig. 6). In type 2 diabetic subjects, neither insulin nor IGF-I significantly reduced the nonplasma FFA oxidation during the first clamp steps; during the second clamp step, both insulin and IGF-I reduced the nonplasma FFA oxidation slightly and similarly.
DISCUSSION

No previous study has employed the euglycemic clamp technique in type 2 diabetic patients to compare the effects of IGF-I and insulin on glucose and FFA metabolism at doses of the two hormones that produce a similar stimulation of glucose disposal in nondiabetic subjects. Importantly, the insulin infusion rates (0.25 and 0.50 mU/kg·min) were selected because they produced plasma insulin concentrations (20–25 and 35–40 µU/ml) that are on the steep part of the dose-response curve relating the hormone concentration to the suppression of EGP and plasma FFA turnover.

Consistent with many previous publications, our results demonstrate that type 2 diabetic patients are resistant to insulin and that the defect in insulin-stimulated total body glucose uptake is accounted for primarily by impaired nonoxidative glucose disposal, which reflects glycogen synthesis (39). Several studies have demonstrated that IGF-I can restore normoglycemia in severely insulin-resistant individuals (34, 49), and it has been suggested that IGF-I can bypass the defect in insulin action in type 2 diabetic patients, thereby eliciting a normal increase in tissue glucose disposal. In the present study, IGF-I augmented whole body glucose disposal in healthy lean nondiabetic control subjects to levels that were similar to those observed with insulin. Under euglycemic hyperinsulinemic clamp conditions, the great majority (~80–90%) of infused glucose is taken up and metabolized in muscle (8). However, in our type 2 diabetic patients, the ability of IGF-I to increase glucose disposal was markedly reduced, indicating that the muscle in diabetic patients is resistant to the effects of both IGF-I and insulin. Like insulin, both the oxidative and nonoxidative pathways of glucose disposal are resistant to IGF-I (Fig. 2).

Because the plasma IGF-I concentrations achieved during the two clamp steps were in the physiological range, it is unlikely that the hormone could be acting through the insulin receptor. Thus our results argue for primary resistance of the IGF-I signal transduction system to circulating plasma IGF-I levels. In insulin-resistant animal models of type 2 diabetes mellitus, the ability of IGF-I to phosphorylate its own receptor has been shown to be intact (4), but stimulation of phosphoinositide 3-kinase has been reduced (24), accounting for the observed defects in glucose uptake (23, 29) and glycogen synthesis (11, 30). Consistent with a postreceptor defect in IGF-I action, IGF-I binding and IGF-I receptor tyrosine phosphorylation (30) in cultured skeletal muscle cells from type 2 diabetic patients have been shown to be normal despite a marked reduction in IGF-I-stimulated muscle glucose uptake. These observations are most consistent with a postbinding, postreceptor defect in IGF-I action, possibly involving the IGF-I signal transduction system.

Our results in healthy diabetic subjects demonstrate that IGF-I inhibited EGP by 44 and 92% during the first and second clamp steps, respectively (Fig. 2). This effect of IGF-I was significantly less than doses of insulin that produced a similar stimulation of whole body (primarily muscle) glucose uptake in the same individuals (Fig. 3). Previous investigators have shown that, in nondiabetic subjects, the ability of IGF-I to inhibit EGP is less potent than that of insulin (27), and similar observations have been made in rodents (35, 37). The blunted effect of IGF-I to suppress EGP has been attributed to the lack of IGF-I receptors on hepatocytes (3, 48). However, it is possible that a low IGF-I receptor number could be present in the liver but not have been detected in these earlier studies (3, 48) because of receptor loss during the triton extraction that was employed. Although hybrid IGF-I/insulin receptors have been found in adipocytes (13, 44, 45) and muscle (14), such receptors have not been reported in liver. Nonetheless, this remains a potential explanation for the observed suppressive effect of IGF-I on EGP. Interpretation of the IGF-I-mediated suppression of EGP in control subjects in the present study thus depends on whether the liver possesses IGF-I receptors. If such receptors are present but exist in low concentration, this could explain the diminished ability of IGF-I compared with insulin to suppress hepatic glucose production in healthy nondiabetic subjects. It also is possible that the suppressive effect of IGF-I on hepatic glucose production is, in part, indirect and mediated via changes in circulating substrate levels. Recent studies have demonstrated that approximately one-half of the inhibitory effect of insulin on hepatic glucose production is mediated via a reduction in plasma FFA and glucagon concentrations (42). During the first IGF-I clamp step, EGP declined by 48%, yet there was no change in the plasma FFA concentration (Fig. 4). During the second IGF-I clamp step, the plasma FFA declined by 69%, but we failed to observe a significant correlation between the decrease in plasma FFA concentration and reduction in EGP (r = 0.32, P = 0.24). Therefore, the present results do not support a role for reduced plasma FFA concentrations...
in the IGF-I-mediated suppression of hepatic glucose production. Plasma glucagon concentrations were not measured in the present study. Finally, IGF-I caused a small decline in circulating plasma insulin concentration (Fig. 1), and a parallel decline in portal insulin concentration would be expected. Although it could be argued that this small decline in portal insulin was in part responsible for the lack of potency of IGF-I on the suppression of EGP, we believe that this is unlikely, because insulin infusion would be expected to cause a similar inhibition of endogenous insulin secretion (9).

In summary, we believe that the most likely explanation for IGF-I's ability to suppress EGP in control subjects is related to the presence of small numbers of IGF-I receptors, or possibly to the presence of hybrid IGF-I/insulin receptors on human hepatocytes.

Only one previous study has examined the effect of IGF-I on the suppression of EGP (primarily hepatic) in type 2 diabetic subjects (7). In this study, diabetic subjects received 80 μg/kg of IGF-I subcutaneously, twice daily for 7 days. Chronic IGF-I treatment caused a significant decline in basal hepatic glucose production, which was closely related to the reduction in fasting plasma glucose concentration. No previous study has examined the acute effect of IGF-I on EGP in type 2 diabetic individuals. In the present study, IGF-I caused a reduction in EGP in type 2 diabetic patients that was similar to that observed in healthy control subjects (Fig. 3). Thus, regardless of the mechanism(s) by which IGF-I inhibits EGP, there is no resistance to the suppressive effect of IGF-I on hepatic glucose output in type 2 diabetic patients. This is in contrast to insulin, where marked resistance to the suppressive effect of the hormone on hepatic glucose production was observed in type 2 diabetic patients during both the first and second insulin clamp steps.

Previous studies that have examined the effect of IGF-I on plasma FFA levels have yielded conflicting results. In studies in which IGF-I was infused at rates <52 pmol·kg⁻¹·min⁻¹, no demonstrable effect of IGF-I on the plasma FFA concentration was observed (12, 32, 38). In studies (2, 20, 27, 46) in which IGF-I was infused at rates greater than or equal to 52 pmol·kg⁻¹·min⁻¹, a modest reduction in circulating plasma FFA concentration was observed. Our results are generally in good agreement with these previous studies. When IGF-I was infused at 26 pmol·kg⁻¹·min⁻¹ in healthy nondiabetic subjects, no change in the plasma FFA concentration was demonstrable. However, at the higher IGF-I infusion rate (52 pmol·kg⁻¹·min⁻¹), the plasma FFA concentration fell by 69% (Fig. 4). The decline in plasma FFA concentration most likely reflects an inhibition of lipolysis, because the primary source of plasma FFA is from triglycerides that are stored in fat cells. In nondiabetic control subjects, the decline in plasma FFA concentration and FFA turnover was associated with reductions in both plasma FFA oxidation and nonoxidative FFA disposal, which primarily reflects reesterification. During the first clamp step, IGF-I had no effect on plasma FFA turnover or plasma FFA concentration. This is in contrast to the 68% suppression observed with insulin. During the second clamp step, the suppression of plasma FFA and FFA turnover with IGF-I was approximately one-half of that observed with insulin. Because inhibition of lipolysis is very sensitive to insulin (18), it is possible that the small decline in peripheral insulin concentration could explain, in part, the weak inhibitory effect of IGF-I on FFA turnover. However, we believe that it is unlikely that a 2–3 μU/ml decline in plasma insulin concentration can account for the threefold greater suppression of FFA turnover (5.8 vs. 1.8 μmol·kg⁻¹·min⁻¹) by insulin (compared with IGF-I) during the first clamp step and the nearly twofold greater suppression by insulin during the second clamp step. The difference between the effects of IGF-I and insulin on the suppression of lipolysis by fat cells most likely is explained by two factors: 1) the lack of, or at least fewer, IGF-I vs. insulin receptors on human fat cells (1, 31) and 2) the greater intrinsic potency of insulin vs. IGF-I on suppression of lipolysis (47). In type 2 diabetic patients, IGF-I also was less effective than insulin in suppressing total body FFA turnover, FFA oxidation, nonoxidative FFA disposal, and the plasma FFA concentration compared with insulin. During the first clamp step, IGF-I had no effect on the plasma FFA concentration or FFA turnover in the diabetic (or control) group. During the second IGF-I clamp step, the ability of IGF-I to inhibit plasma FFA turnover and to reduce the plasma FFA concentration was impaired in the diabetic compared with the control group, indicating that the adipocyte is resistant to both IGF-I and insulin in patients with type 2 diabetes mellitus.

In summary, the present results indicate that the ability of IGF-I (when given in doses that produce a comparable stimulation of total body glucose disposal to insulin in nondiabetic control subjects) to suppress EGP, to reduce plasma FFA levels, and to inhibit total FFA turnover is significantly less than that of insulin. In type 2 diabetic patients, the ability of IGF-I to augment total body glucose disposal and to suppress plasma FFA concentration total FFA turnover is impaired compared with nondiabetic control subjects, indicating that both muscle and fat tissues are resistant to the action of IGF-I. In contrast, the ability of IGF-I to suppress hepatic glucose production (EGP) is similar in nondiabetic control and type 2 diabetic patients.

REFERENCES

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