Effects of Metformin and Rosiglitazone Monotherapy on Insulin-Mediated Hepatic Glucose Uptake and Their Relation to Visceral Fat in Type 2 Diabetes

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OBJECTIVE — Impaired insulin-mediated hepatic glucose uptake (HGU) has been implicated in the hyperglycemia of type 2 diabetes. We examined the effects of metformin (2 g/day) and rosiglitazone (8 mg/day) monotherapy on HGU and its relation to subcutaneous fat, visceral fat (VF), and whole-body insulin-mediated glucose metabolism in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — Glucose uptake was measured before and after 26 weeks of treatment using positron emission tomography with [^{18}F]2-fluoro-2-deoxyglucose during euglycemic hyperinsulinemia; fat depots were quantified by magnetic resonance imaging.

RESULTS — Fasting plasma glucose levels were significantly decreased after either rosiglitazone (-0.9 ± 0.5 mmol/l) or metformin treatment (-1.1 ± 0.5 mmol/l) in comparison with placebo; only metformin was associated with weight loss ($P < 0.02$ vs. placebo). When controlling for the latter, the placebo-subtracted change in whole-body glucose uptake averaged -1 ± 4 μmol · min^{-1} · kg^{-1} in metformin-treated patients (NS) and $+9 \pm 3$ μmol · min^{-1} · kg^{-1} in rosiglitazone-treated patients ($P = 0.01$). Both rosiglitazone and metformin treatment were associated with an increase in HGU; versus placebo, the change reached statistical significance when controlling for sex (placebo-subtracted values = $+0.008 \pm 0.004$ μmol · min^{-1} · kg^{-1} · pmol/l^{-1}, $P < 0.03$, for metformin; and $+0.007 \pm 0.004$, $P < 0.07$, for rosiglitazone). After treatment with either drug, insulin-mediated VF glucose uptake (VFGU) was higher than with placebo. In the whole dataset, changes in HGU were negatively related to changes in HbA_{1c} ($r = 0.43$, $P = 0.01$) and positively associated with changes in VFGU ($r = 0.48$, $P < 0.01$).

CONCLUSIONS — We conclude that both metformin and rosiglitazone monotherapy increase HGU in type 2 diabetes; direct drug actions, better glycemic control, and enhanced VF insulin sensitivity are likely determinants of this phenomenon.

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The ability of insulin to stimulate hepatic glucose uptake (HGU) is impaired in patients with type 2 diabetes (1), contributing to the development of hyperglycemia. The defect appears to involve the first steps of glucose uptake and metabolism in the liver, eventually leading to decreased glycogen synthesis (1). These findings are in line with the notion that glucokinase is rate-limiting for glucose entry into the liver (2) and that genetic defects of glucokinase activity associated with human maturity-onset diabetes of young (MODY-2) lead to decreased HGU and glycogen synthesis (3). In acquired forms of diabetes, hepatic glucokinase activity was decreased in liver biopsies obtained from obese type 2 diabetic individuals (4), and the direct HGU-mediated pathway of glycogen synthesis was reduced in poorly controlled type 1 diabetic individuals (5) and in modestly hyperglycemic type 2 diabetic patients (1). The mechanisms underlying these findings are not completely understood. Insulin has been hypothesized to be the main regulator of these enzymatic steps (1,6). Therefore, a primary impairment of insulin action is a putative culprit. In diabetic animals, defects of glucokinase activity and glycogen synthesis were partially reversed by normalization of glycemia (7), implicating glucose toxicity as a mechanism. Its relative contribution to the impairment of insulin-mediated HGU in human type 2 diabetes remains to be determined.

Biguanides and thiazolidinediones are commonly used in the management of type 2 diabetic patients. Both agents ameliorate glycemia and the lipid profile in

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Abbreviations: FDG, 2-fluoro-2-deoxyglucose; FFA, free fatty acid; HGU, hepatic glucose uptake; K_i, glucose influx rate constant; *M*, whole lean body mass glucose uptake; *M*/*I*, *M* normalized by the steady-state plasma insulin level of the clamp; MRI, magnetic resonance imaging; PET, positron emission tomography; PPAR-γ, peroxisome proliferator-activated receptor-γ; ROI, region of interest; SFGU, subcutaneous fat glucose uptake; VF, visceral fat; VFGU, VF glucose uptake.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

such patients by acting through different mechanisms (8–11).

The present study was undertaken to assess whether insulin-stimulated HGU can be upregulated by metformin or rosiglitazone monotherapy in patients with type 2 diabetes, and, if so, whether direct drug-specific mechanisms or indirect metabolic mediators are implicated. The response of HGU to treatment was compared with that of visceral and subcutaneous fat and that of total lean body mass. The data on adipose tissue glucose uptake presented in this analysis are part of a larger data set in patients with type 2 diabetes, which were previously published (12), and are here used to specifically investigate the hypothesis of their relationship with HGU.

RESEARCH DESIGN AND METHODS

Subjects

We recruited 30 patients in whom type 2 diabetes had been diagnosed 1–3 years before the study (13) and who had never been treated with drugs. Patients were excluded if they had a fasting plasma glucose value of <6.1 mmol/l or >11.0 mmol/l after the run-in period. Patients with cardiovascular disease, blood pressure >160/100 mmHg, abnormal hepatic or renal function, proliferative retinopathy, anemia, or corticosteroid treatment were excluded. Two patients were taking lipid-lowering medications (statin). The study protocol was approved by the ethics committee of the Hospital District of Varsinais-Suomi. Written informed consent was obtained from all subjects.

Study design

The first part of the study consisted of a 4-week run-in period with written diet instructions. Then, patients were randomized to treatment with rosiglitazone (2 mg b.i.d. for 2 weeks, thereafter 4 mg b.i.d.), metformin (500 mg b.i.d. for 2 weeks, thereafter 1 g b.i.d.), or placebo for a 26-week double-blinded trial. Positron emission tomography (PET) studies, in combination with [^{18}F]2-fluoro-2-deoxyglucose ([^{18}F]FDG) and the insulin clamp technique (14), were performed before the treatment and at week 26 to assess insulin-mediated whole lean body mass glucose uptake (*M*), glucose uptake in liver (HGU) and abdominal adipose tissue (visceral fat glucose uptake [VFGU] and subcutaneous fat glucose uptake [SFGU]), and glucose influx rate-constants (K_i) in liver (hepatic K_i) and adipose tissue (visceral fat K_i and subcutaneous fat K_i). All PET studies were performed after an overnight fast.

PET study protocol

An eight-ring ECAT 931/08-tomograph was used for image acquisition (Siemens/CTI, Knoxville, TN). A 5-min transmission scan was performed to correct subsequent emission scans for photon attenuation. Two catheters were inserted, one in an antecubital vein for infusion of glucose and insulin and for injection of [^{18}F]FDG and one in the opposite radial artery for blood sampling. At 0 min, a primed-continuous infusion of insulin (40 mU $\cdot$ min^{-1} $\cdot$ m^{-2}) was started. The study for each subject consisted of a 150-min normoglycemic hyperinsulinemic period (14). At 90 min, [^{18}F]FDG was injected, and consecutive 18-min dynamic scans (six × 180-s frame) of the abdominal area and of the liver were obtained at 20 min. Arterial plasma radioactivity was measured once during each time frame.

PET image processing

All data were corrected for dead time, decay, and measured photon attenuation and were reconstructed iteratively (15). Liver tissue time-activity curves were derived from large circular regions of interest (ROIs) placed on two to four planes in the right lobe of the liver. Adipose tissue ROIs were drawn on magnetic resonance imaging (MRI) images and copied into [^{18}F]FDG images to cross-sectional slices from identical planes (12). Plasma and tissue time-activity curves were analyzed graphically to quantitate the fractional rate of tracer transport and phosphorylation (16), reflecting the glucose influx rate constant into the hepatic, visceral, and subcutaneous fat tissue components (K_i, ml $\cdot$ min^{-1} $\cdot$ ml^{-1}). Graphical analysis has been previously evaluated for in vivo application to liver [^{18}F]FDG-PET data (17,18). Rate-constant values were multiplied by steady-state plasma glucose concentrations achieved during the clamp to derive glucose uptake (μmol $\cdot$ min^{-1} $\cdot$ ml^{-1}) (19,20). For adipose tissue, a lumped constant of 1.14 was used (12). Whole-body glucose uptake was calculated during the period of PET scanning and normalized for lean body mass (*M*). To account for interindividual differences in steady-state plasma insulin concentrations, all parameters of insulin-mediated glucose uptake were normalized to an insulin concentration of 600 pmol/l. Body fat content and lean mass were obtained with the impedance method. Posthepatic insulin clearance rate was computed during the steady state of the clamp (21).

MRI

The abdominal region was imaged with a 0.23 T Outlook GP (Marconi Medical Systems, Vantaa, Finland) magnetic resonance imager using a body coil. Transverse T1-weighted field echo images with a time repetition value of 170 ms and a time echo value of 4 ms were obtained with the same pixel size as PET images. The level of the mid-slice and the upper and lower border of the area imaged were determined as earlier described (12). Abdominal adipose tissue masses were measured at the level of intervertebral disc L2/L3. Fat volume was converted to weight using a tissue density of 0.9196 mg/ml. Biochemical analyses were performed as previously detailed (12).

Statistical methods

Differences in paired data were evaluated using the Student's paired *t* test for single repeated measurements. One-way ANOVA was used for unpaired group comparisons. To test for the effects of treatment, mixed multivariate models were set up in which treatment-induced changes in any given parameter were the dependent variable and treatment group and baseline values were independent variables. In these models, comparison between any two treatments was carried out by contrasts, and potential confounders (such as imbalances in sex group distribution) were controlled for by entering them as additional independent variables. Regression analyses were carried out according to standard techniques; to avoid the influence of the common denominator, values of glucose uptake and K_i were used without normalization to insulinemia. All data are presented as means ± SEM. Statistical significance was set at $P \leq 0.05$.

RESULTS — At baseline, the three groups were well matched (Tables 1 and 2). At 26 weeks, BMI was significantly lower than at baseline in metformin-treated patients only. Fasting plasma glucose levels were significantly decreased after both rosiglitazone and metformin

Table 1—*Clinical characteristics of the study groups*

	Placebo	Metformin	Rosiglitazone
n	10	11	9
Sex (M/F)	6/4	7/4	7/2
Age (years)	57 ± 2	59 ± 2	57 ± 2
Before treatment			
BMI (kg/m^2)	31.5 ± 1.5	28.2 ± 1.1	29.2 ± 1.4
FM (%)	32.8 ± 3.1	31.9 ± 2.8	29.3 ± 3.4
WHR (cm/cm)	0.96 ± 0.02	0.95 ± 0.01	0.95 ± 0.01
SBP (mmHg)	147 ± 4	142 ± 5	148 ± 6
DBP (mmHg)	84 ± 3	84 ± 3	90 ± 3
HR (bpm)	63 ± 4	66 ± 3	70 ± 5
After treatment			
BMI (kg/m^2)	31.5 ± 1.5	27.1 ± 1.0*†	29.0 ± 1.4
FM (%)	32.8 ± 3.3	30.2 ± 2.6†	28.6 ± 3.3
SBP (mmHg)	143 ± 5	139 ± 5	143 ± 3
DBP (mmHg)	84 ± 4	82 ± 3	85 ± 3
HR (bpm)	63 ± 3	66 ± 3	71 ± 3

Data are *n* or means ± SEM. DBP, diastolic blood pressure, FM, fat mass; HR, heart rate, SBP, systolic blood pressure, WHR, waist-to-hip ratio. *$P < 0.002$ *vs.* placebo and $P = 0.01$ *vs.* rosiglitazone; †$P < 0.01$ or less *vs.* baseline study (Student paired *t* test in individual groups).

treatment in comparison with placebo. Metformin treatment was also associated with a significant drop in HbA_{1c}, whereas the corresponding change with rosiglitazone treatment fell just short of statistical significance ($P = 0.12$). Fasting plasma free fatty acid (FFA) levels were similar before and after either treatment. Fasting plasma insulin concentrations were lower after both rosiglitazone and metformin but not after placebo.

On the baseline clamp, there were no significant differences in steady-state plasma glucose, FFA, and insulin levels and in *M* and *M* normalized by the steady-state plasma insulin level of the clamp (*M/I*) across treatment groups (Table 3). Plasma FFA concentrations were significantly suppressed in all groups during the clamp. Percentage-wise, FFA suppression was higher after rosiglitazone than after placebo or metformin, whereas posthepatic insulin clearance was higher after metformin only.

Whole-body, liver, and fat glucose uptake

Rosiglitazone and metformin both enhanced whole-body glucose uptake (both as *M* and *M/I*), whereas placebo had no significant effect on this variable. However, only the changes induced by rosiglitazone were significant when compared with placebo (Table 3). When controlling for the concurrent changes in BMI, the change in *M* averaged -1 ± 4 μmol · min^{-1} · kg^{-1} in metformin-treated patients (NS) and $+9 \pm 3$ μmol · min^{-1} · kg^{-1} in rosiglitazone-treated patients ($P = 0.01$ vs. placebo).

By bioimpedance, changes in total fat mass averaged -2.9 ± 1.0 kg in metformin-treated patients ($P < 0.001$ vs. placebo) and -1.3 ± 1.0 kg in rosiglitazone-treated patients (NS). In the metformin group, placebo-subtracted MRI estimates of changes in subcutaneous and visceral depots were -0.55 ± 0.29 kg ($P = 0.07$ vs. placebo and $P = 0.03$ vs. rosiglitazone) and -0.11 ± 0.09 kg (NS), respectively. In the rosiglitazone group, the corresponding changes in fat depots were 0.11 ± 0.31 kg (NS) and -0.18 ± 0.09 ($P = 0.06$ vs. placebo) in the subcutaneous and visceral depots, respectively. After either metformin or rosiglitazone treatment, insulin-mediated VFGU was higher than with placebo; a smaller change in SFGU was observed, but it did not reach statistical significance, likely due to a sample size limitation (Fig. 1).

Both rosiglitazone and metformin treatments were associated with a significant increase in HGU ($P = 0.018$ and $P = 0.001$, respectively; Student paired *t* test for single groups); versus placebo, the change reached statistical significance in the metformin group when controlling for sex (placebo-subtracted values = $+0.008 \pm 0.004$ μmol · min^{-1} · kg^{-1} · pmol/l^{-1}, $P < 0.03$, for metformin and $+0.007 \pm 0.004$, $P < 0.07$, for rosiglitazone; sex-unadjusted levels of significance $P = 0.06$ and $P = 0.2$, respectively) (Fig. 1). In the whole dataset, sex-adjusted changes in HGU were negatively related to changes in HbA_{1c}; changes in HGU were positively associated with changes in VFGU and in percent FFA suppression (Fig. 2).

Table 2—*Metabolic parameters in the fasting state*

	Placebo	Metformin	Rosiglitazone
Before treatment			
Glucose (mmol/l)	7.14 ± 0.25	8.23 ± 0.52	7.39 ± 0.37
Insulin (pmol/l)	67 ± 11	63 ± 12	53 ± 15
FFA (mmol/l)	0.66 ± 0.07	0.51 ± 0.06	0.64 ± 0.05
HbA_{1c} (%)	6.11 ± 0.22	6.95 ± 0.27	6.80 ± 0.33
TG (mmol/l)	2.19 ± 0.95	1.31 ± 0.14	1.50 ± 0.29
Cholesterol (mmol/l)	4.77 ± 0.37	4.56 ± 0.25	4.68 ± 0.15
LDL (mmol/l)	2.71 ± 0.34	2.79 ± 0.25	2.86 ± 0.12
HDL (mmol/l)	1.10 ± 0.06	1.17 ± 0.09	1.13 ± 0.08
After treatment			
FPG (mmol/l)	7.23 ± 0.31	6.72 ± 0.38*†	6.76 ± 0.34†‡
Insulin (pmol/l)	61 ± 7	43 ± 5*†	40 ± 4*†
FFA (mmol/l)	0.56 ± 0.06	0.54 ± 0.06	0.58 ± 0.08
HbA_{1c} (%)	6.12 ± 0.19	6.27 ± 0.22†§	6.44 ± 0.34
TG (mmol/l)	1.52 ± 0.41	1.22 ± 0.38	1.39 ± 0.33
Cholesterol (mmol/l)	4.71 ± 0.32	4.44 ± 0.19	5.01 ± 0.23
LDL (mmol/l)	2.99 ± 0.33	2.59 ± 0.16	3.21 ± 0.14
HDL (mmol/l)	1.18 ± 0.07	1.28 ± 0.09†	1.23 ± 0.08†

Data are means ± SEM. FPG, fasting plasma glucose, TG, triglyceride. *$P < 0.01$ vs. placebo, †$P < 0.05$ vs. baseline study (Student paired *t* test in individual groups), ‡$P < 0.09$ vs. placebo, §$P < 0.03$ vs. placebo.

Table 3—*Metabolic parameters during the clamp*

	Placebo	Metformin	Rosiglitazone
Before treatment			
Glucose (mmol/l)	5.09 ± 0.06	5.33 ± 0.10	5.14 ± 0.05
Insulin (pmol/l)	507 ± 24	517 ± 26	517 ± 54
FFA (mmol/l)	0.17 ± 0.03	0.16 ± 0.03	0.15 ± 0.02
FFA suppression (%)	75 ± 5	65 ± 5	76 ± 5
ICR (ml/min)	985 ± 46	967 ± 54	988 ± 89
M (μmol · min^{-1} · kg^{-1})	17.6 ± 2.1	20.8 ± 3.6	21.3 ± 3.6
M/I	21.2 ± 2.7	24.2 ± 3.4	27.8 ± 6.1
After treatment			
Glucose (mmol/l)	5.07 ± 0.06	5.15 ± 0.05	5.10 ± 0.04
Insulin (pmol/l)	470 ± 29	393 ± 17*	431 ± 31*
FFA (mmol/l)	0.13 ± 0.02	0.12 ± 0.02*	0.08 ± 0.01*
FFA suppression (%)	76 ± 3	77 ± 3*	86 ± 3*†
ICR (ml/min)	1,080 ± 72	1,243 ± 66*‡	1,157 ± 93*
M (μmol · min^{-1} · kg^{-1})	17.2 ± 1.6	22.6 ± 3.0	29.4 ± 4.7*§
M/I	22.6 ± 2.3	34.9 ± 4.6*	44.0 ± 9.8†‖

Data are means ± SEM. Glucose and insulin are plasma levels during the steady-state plasma insulin level of the clamp; *M* is during the steady state of the clamp. ICR, insulin clearance rate; *M/I*, *M* normalized by the steady-state plasma insulin concentration. *$P < 0.05$ vs. baseline study (Student paired *t* test in individual groups); †$P = 0.02$ vs. placebo; ‡$P < 0.05$ vs. placebo; §$P < 0.01$ vs. placebo and $P = 0.05$ vs. metformin; ‖$P < 0.03$ vs. placebo.

CONCLUSIONS — In the present study carried out in obese patients with mild type 2 diabetes, 26 weeks of metformin treatment (2 g/day) resulted in the expected lowering of fasting plasma glucose and HbA_{1c} levels; this was associated with a modest weight reduction that was largely accounted for by loss of subcutaneous fat. Rosiglitazone monotherapy (8 mg/day), on the other hand, resulted in a somewhat lesser reduction in fasting glycemia and HbA_{1c} as compared with metformin, with no significant change in body weight. The MRI estimates of regional fat depots were compatible with a reduction in subcutaneous fat in metformin-treated patients and in visceral fat (VF) in rosiglitazone-treated patients.

From the metabolic standpoint, metformin treatment was accompanied by a marginal increase in whole-body insulin sensitivity, most likely determined by weight and HbA_{1c} reduction. Rosiglitazone treatment led to a more pronounced improvement in whole-body insulin sensitivity, which included insulin-mediated glucose disposal and insulin suppressibility of lipolysis. This pattern of responses is typical of peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists (10,11).

The novel finding is that both metformin and rosiglitazone monotherapy increased insulin-mediated HGU. The sex difference in the response to treatment may be related to the different body fat distribution, the ratio of visceral to subcutaneous fat mass being generally lower in women (in our series, 25 vs. 33%, $P = 0.05$). However, the small sample size and some imbalance in sex distribution among treatment groups prevents any firm conclusion on the mechanisms mediating the influence of sex on HGU response to treatment.

The clinical relevance of the finding of improved HGU stems from the observation that HGU, either insulin- or glucose-stimulated, is markedly impaired in patients with type 2 diabetes, and hepatic insulin resistance is likely to contribute to their hyperglycemia, both through inappropriately high glucose output and reduced glucose uptake (1,9). In the whole data set, the improvement in HGU was significantly related to the decrease in HbA_{1c} (Fig. 2), indicating that chronic glycemic control is a likely mechanism for the observed enhancement in HGU. Rosiglitazone and metformin were equally effective in increasing HGU, despite the fact that the former was more effective and more specific (i.e., independent of changes in body weight and glycemia)

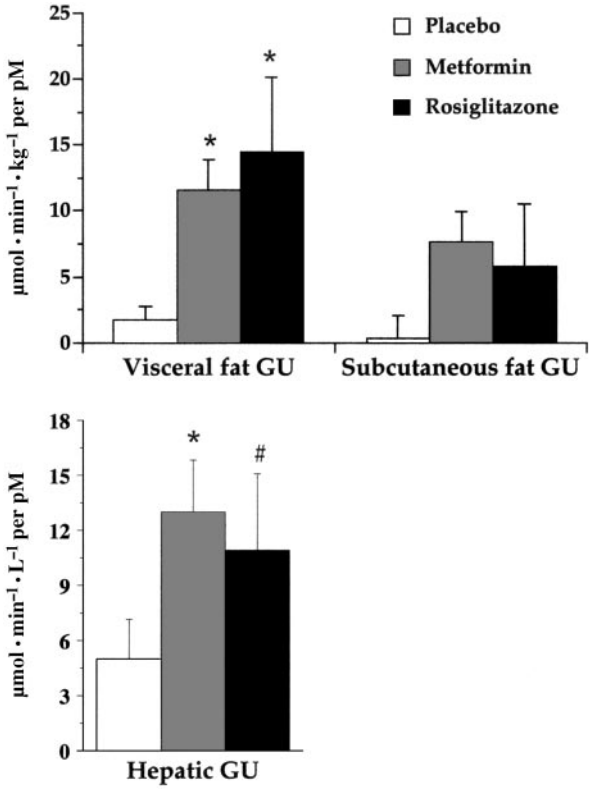

Figure 1—*Changes in VFGU and SFGU and changes in HGU after 26 weeks of treatment with placebo, metformin, or rosiglitazone. GU, glucose uptake. *$P \leq 0.05$ and $P = 0.07$ difference from placebo.*

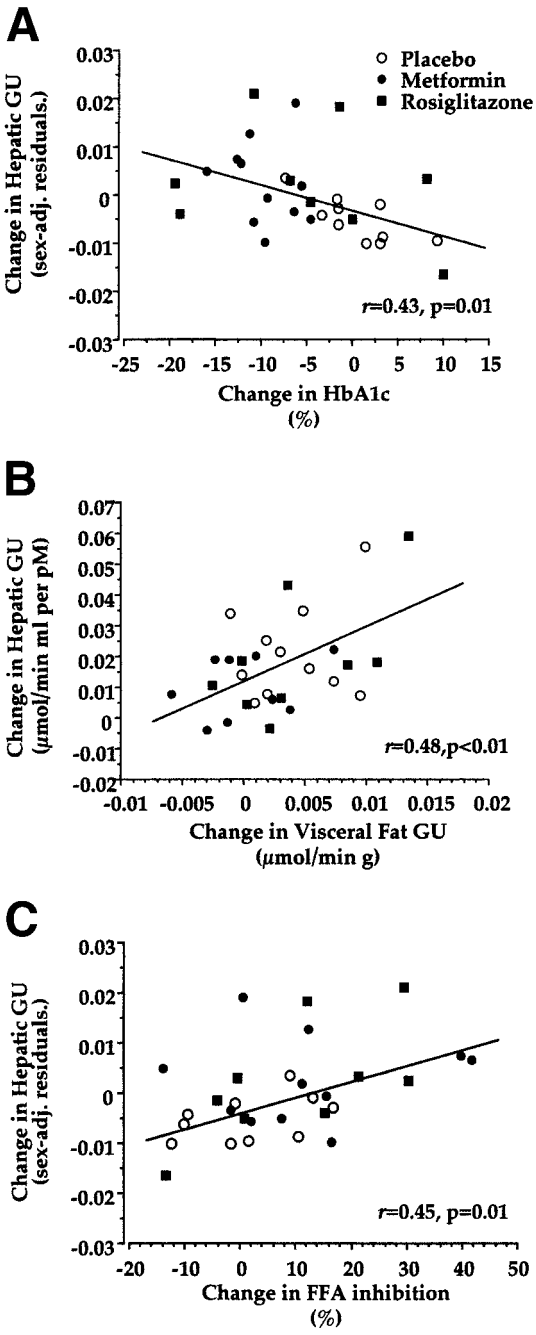

Figure 2—*Relationship between changes in hepatic glucose uptake and changes in HbA_{1c}* (A)*, changes in VFGU* (B)*, or changes in FFA inhibition* (C) *after 26 weeks of treatment. GU, glucose uptake.*

than the latter in enhancing insulin-mediated whole-body glucose disposal. This suggests that an overall improvement in insulin resistance may extend to HGU, but the contribution of changes in peripheral insulin sensitivity may have a small impact in comparison with the nonspecific effect of improved glycemic control.

Metformin acts on the liver to suppress gluconeogenesis—either by potentiating the effect of insulin or by reducing hepatic extraction of substrates—and glycogenolysis, and it decreases the activity of glucose-6-phosphatase (8,9). Additionally, metformin enhances insulin binding to hepatocytes of insulin-resistant mice, and it stimulates tyrosine kinase activity (8). Glucose transport and glycogen synthesis represent postreceptor targets of this drug (8). Recent data indicate that metformin modulated these enzymatic activities by upregulating AMP kinase, a key regulator of fuel sensing (22). Decreased hepatic gluconeogenesis and glycogenolysis and augmented glucose uptake have been attributed to thiazolidinediones (10,23). Thiazolidinediones have been suggested to affect the insulin signaling cascade and the activity of glycogen synthase. The evidence that PPAR-γ–responsive elements have been found in glucokinase-encoding genes is most intriguing (10). Thus, it is conceivable that the stimulatory effect on HGU seen in our patients taking either metformin or rosiglitazone represents direct, if different, actions of the two agents on liver metabolism.

The possibility that the observed effect of metformin or rosiglitazone on HGU were mediated by other metabolic changes is also plausible, as suggested by the data on adipose tissue glucose uptake. In our patients, treatment with either drug resulted in a significant enhancement of glucose uptake in visceral adipose tissue, whereas the corresponding changes in subcutaneous fat depots were smaller (and statistically not significant, likely due to the limited sample size). Increased glucose uptake in adipose tissue translates into increased reesterification of FFAs through augmented generation of glycerolphosphate from glycolysis. Increased FFA reesterification reduces net lipolysis and FFA delivery to the circulation; in turn, a reduced supply of FFA to the liver may be coupled with increased glucose uptake. Hepatic FFA oxidation promotes gluconeogenesis, thereby feeding indirect glycogen synthesis, and it might also directly regulate glycogen turnover, whereas circulating glucose provides the substrate for direct glycogen formation. Furthermore, a more pronounced effect of treatment on VF rather than subcutaneous fat is especially compatible with an improved HGU because of the preferential drainage of viscerally derived FFAs into the liver. This metabolic sequence may explain the direct association between changes in HGU and changes in VFGU on the one hand and suppression of lipolysis on the other (Fig. 2). The in vivo studies described herein lack the numerousness and measurement accuracy that would be required to provide conclusive evidence for the hypothetical sequence of events outlined above. The observed pattern of relationships is nevertheless strongly suggestive of a causal link between fat glucose metabolism, particularly in the visceral area, and hepatic glucose metabolism. In previous studies, increasing peripheral FFA

levels with the use of intralipid infusion has led to contrasting findings on hepatic/splanchnic glucose uptake (24,25). The relationship between insulin resistance and VF mass is well established; removal of VF is followed by improved whole-body insulin sensitivity and decreased hepatic glucose production (26,27). Taken together with these experimental data, the current results may help explain why small weight changes, first involving VF mass, have unexpectedly profound metabolic consequences (26).

In conclusion, metformin or rosiglitazone monotherapy significantly increased HGU, thus providing evidence that improved HGU contributes to the therapeutic efficacy of these drugs in patients with type 2 diabetes. Direct drug effects together with improved glycemic control were likely determinants of the heightened HGU. Our data draw attention to the concept that VF insulin sensitivity may be a determinant of liver glucose metabolism in human type 2 diabetes.

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