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Locating the source of hyperglycemia: Liver versus muscle

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Abstract

Background—Glucose homeostasis relies on insulin to suppress hepatic glucose production and to stimulate glucose uptake by peripheral tissues (primarily skeletal muscle) during and after a meal or glucose load. Glucose metabolism impairments in the liver and/or muscle attenuate these insulin actions, causing hyperglycemia. Thus, identifying the loci of the impairments can improve the understanding of hyperglycemia and enable organ-targeted interventions.

Methods—Studies were performed to identify such loci using modified oral glucose tolerance test (OGTT) techniques in individuals with type 2 diabetes (T2D) and overweight/obese individuals.

Results—Individuals with severe T2D were found to have significantly impaired glucose metabolism in both the liver and muscle. In contrast, impairments in glucose metabolism in individuals with non-severe T2D were predominantly localized in the liver or muscle, but not both. Similarly, milder impairments in overweight or obese individuals were clearly localized in either the liver or muscle, but not both. All these impairments are quantifiable.

Conclusion—Impairments in glucose metabolism in the liver and muscle can be differentiated and quantified in a clinical setting.

Keywords

hyperglycemia; localization; organ impairment; type 2 diabetes

Introduction

Hyperglycemia is the hallmark of diabetes. Hyperglycemia is a result of imbalanced appearance and disappearance of glucose. In the postabsorptive state, the rate of appearance of glucose (R_a) reflects endogenous glucose production (EGP), mainly by the liver and, to a

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Disclosure

None declared.

lesser extent, by the kidney. Conversely, the rate of disappearance of glucose (R_d) represents the uptake and utilization of glucose by the organs and tissues for which glucose is an obligate fuel (brain, red blood cells etc.). The postabsorptive state is a steady state where R_a equals R_d and thus euglycemia is maintained. Because hepatic glucose production (HGP) comprises the bulk of EGP ($HGP \approx EGP$), fasting blood glucose levels are mainly dictated by the balance between HGP and glucose uptake.¹ Therefore, an increase in HGP and a decrease in glucose uptake can independently or jointly lead to increases in fasting glucose (impaired fasting glucose or IFG).

In the postprandial state, this steady state of glucose is broken and glucose kinetics enter a dynamic phase. In this state, the appearance of the ingested glucose in the general circulation dominates glucose R_a . Under normal circumstances, the rapidly increased insulin secretion in response to the glucose influx suppresses much of the HGP. Meanwhile, glucose uptake increases under insulin action. Now, the insulin-sensitive tissues are responsible for the rapid uptake of glucose, including skeletal muscle, adipose tissue and the liver. Of these, the skeletal muscle accounts for >80% of the total glucose uptake and is thus largely responsible for postprandial glucose disposal.² The coordinated suppression of HGP and increased uptake by muscle prevent a large excursion of blood glucose levels so that 2 h after a glucose load blood glucose returns to baseline (i.e. the level immediately before the load). Impairments in HGP suppression and glucose uptake can independently or jointly cause hyperglycemia. For example, blood glucose remains elevated beyond the second hour after the glucose load (impaired glucose tolerance or IGT) as routinely determined by the oral glucose tolerance test (OGTT).

The conventional OGTT measures blood glucose levels only and thus does not seek to differentiate the location of the impairment of glucose metabolism, namely impaired HGP suppression versus impaired glucose uptake. It is sometimes assumed that IGT is caused by impaired glucose uptake. This is not always true because impaired HGP suppression also contributes to IGT.³ For a better understanding of hyperglycemia, the localization of glucose metabolism impairments is desirable.

The present study was designed to explore the possibility of differentiating liver from muscle as the location of impairments in glucose metabolism that cause or contribute to hyperglycemia. The liver and muscle are the focus of the present study because they directly handle glucose and are thus the functional units immediately relevant to blood glucose levels.

Methods

Study subjects

Twenty-one subjects participated in the present study. Of these, five were lean and non-diabetic (four men, one woman), six were overweight or obese (all men) and 10 had T2D (nine men, one woman). All participants were free of other major medical conditions. Table 1 shows the anthropometric information for all subjects and the results of blood chemistry measurements. Informed consent was obtained from all participants. The study protocol was

approved by the Institutional Research Board (IRB) of Shanghai Jiao-tong University Affiliated Sixth People's Hospital, Shanghai, China.

Procedures

During the night prior to the study, the subjects had no food after supper and only water or soft drink was allowed. The next morning, subjects reported to the Shanghai Clinical Center for Diabetes. A typical OGTT⁴ was performed in each subject in combination with the use of deuterated glucose, a non-radioactive stable isotopic tracer (Sigma Chemical, St Louis, MO, USA). This was followed by repeated blood sampling from an antecubital vein immediately before the glucose drink (0 min) and then 15, 30, 45, 60, 90, 120, 150, and 180 min after the glucose drink. Once blood sampling had been completed, participants were free to leave the hospital. The blood was processed to separate plasma for glucose, insulin, and blood chemistry measurements.

Quantification of HGP and glucose uptake

Hepatic glucose production and glucose uptake during the OGTT were quantified for each subject based on the plasma glucose and deuterated glucose concentrations determined by gas chromatography–mass spectrometry. There were no assumptions or modeling involved or used in the calculations (assumption free and model independent). Group averages were calculated for HGP and glucose uptake in the control group and were used to quantify the degree of impairments in HGP and glucose uptake in the obese and T2D subjects. Hepatic glucose production is proportional to the degree of impairment in HGP suppression and glucose uptake is inversely proportional to the degree of impairment in glucose uptake (glucose accumulation due to slow uptake). To facilitate comparisons, the results of HGP and glucose uptake were processed to derive the so-called glucose impairment ratio (GIR):

$$x_i/X_{\text{control}} \quad (1)$$

where x_i represents HGP or glucose uptake in each subject and X_{control} is the group average of the control group. This resulted in an average GIR of 1.0 for the control group and usually higher GIR values for subjects in the other two groups. Values of GIR >1.0 mean that the subject had higher HGP (impaired HGP suppression) or reduced glucose uptake compared with the control group. Thus, the portion of GIR above 1.0 (i.e. GIR – 1.0) represents the degree of increase in HGP or reduction in glucose uptake. For example, a ratio of 1.5 means that that individual's HGP is 50% greater than control due to impaired HGP suppression during OGTT, or that the individual's ability to take up glucose is 50% lower than control (i.e. 50% more glucose had accumulated in the circulation due to reduced glucose uptake).

Cut-off values for impairment in HGP and glucose uptake

Whether a subject has impaired HGP suppression or impaired glucose uptake is judged based on the cut-off value. The cut-off value for having impaired HGP or impaired glucose uptake is calculated from the respective SD, as presented in the first paragraph of the Results.

Statistics

Data are presented in mean $\pm$ SE unless as indicated otherwise. Statistical analyses were performed using unpaired Student's *t*-test for comparisons between two groups or anova for comparisons of three groups. An α value of 0.05 was set as the level of significance, although in some cases actual *P*-values >0.05 are also given.

Results

Variabilities and detection limit for impairment

The variabilities of GIR for HGP and glucose uptake in the control group are given in Table 2. The variability (SD) for HGP GIR and glucose uptake GIR were 0.23 and 0.12, respectively. Based on these values, the cut-off values for impaired HGP suppression and impaired glucose uptake were calculated to be 0.68 and 0.36 ($3 \times \text{SD}$), respectively, for T2D subjects. These cut-off values were used to designate a T2D subject to one of three subtypes of localized glucose intolerance: liver type, muscle type, and mixed type. If a subject's HGP GIR is >1.68 , he or she is designated as liver type (impaired HGP suppression); if glucose uptake GIR is >1.36 , the subject is designated as muscle type (impaired glucose uptake). "Mixed type" refers to those subjects who met both these criteria, namely impairments in both the liver and muscle.

The obese subjects who participated in the present study had lower HGP GIR and glucose uptake GIR values that did not reach the levels of the cut-off values set for T2D subjects. Therefore, the cut-off values for obese subjects were calculated as $2 \times \text{SD}$ (using the same SD values from the lean control group) and were used to classify subjects into the same three subtypes. Because these cut-off values are lower than those used for T2D subjects ($3 \times \text{SD}$), the subtypes thus identified had milder impairment of HGP suppression or glucose uptake than the corresponding T2D subtypes. The resulting subtypes are discussed in greater detail below.

It is noted that such data treatment for the control group is somewhat arbitrary because it assumed that there were no impairments in glucose metabolism in the control group. This is not entirely true. One individual in this group had IGT and the analysis showed that it was due to increased HGP (GIR = 1.49). Therefore, this individual was excluded from calculations of control group averages. This individual was enrolled in the control group based on normal fasting glucose, medical history, and being lean. All other individuals in the control group were normoglycemic (no IFG or IGT).

Type 2 diabetes

All T2D subjects had impaired HGP suppression and reduced glucose uptake to varying degrees (Table 3). The individual HGP values were as high as 569% of the control group (GIR = 5.69), indicating severely impaired HGP suppression. Glucose uptake values were up to 260% of the control group (GIR = 2.60).

Subtyping—In the T2D group, although two subjects were found to have recovered following the use of medications in combination with dietary management (no IFG or IGT),

they continued to exhibit mild to modest impairments in HGP suppression ($\text{GIR} = 1.31$ and 1.79) with normal glucose uptake. The remaining eight subjects were classified into liver type ($n = 2$), muscle type ($n = 4$) or mixed type ($n = 2$). The two individuals classified as liver type had impaired HGP suppression ($\text{GIR} = 2.48$ and 3.93) but nearly normal glucose uptake ($\text{GIR} = 1.28$ and 1.29 , respectively). In contrast, the four individuals classified as muscle type had significant impairment in glucose uptake ($\text{GIR} = 2.46 \pm 0.12$; $P < 0.01$) but modest impairment in HGP suppression ($\text{GIR} = 1.68 \pm 0.07$; $P > 0.05$). The two individuals classified as mixed type had severely impaired HGP ($\text{GIR} = 5.69$ and 4.12) and glucose uptake ($\text{GIR} = 1.91$ and 2.41 , respectively). The results are detailed in Table 4.

Obese subjects

In most cases, obese individuals had lower GIR values than did T2D subjects. Four obese individuals had normoglycemia (no IGT or IFG) although one of them had mild impairment of HGP suppression ($\text{GIR} = 1.42$). The other two obese individuals were found to have IGT. Both had mildly decreased glucose uptake ($\text{GIR} = 1.26$ and 1.37 ; Table 4). An important and clear distinction from T2D subjects was that these obese subjects only exhibited simple impairment (i.e. they were either liver or muscle type and none exhibited the mixed type, as seen in the T2D group).

Insulin factor

Figure 1 shows the relationship between impairments in HGP and glucose uptake and plasma insulin, which is expressed as the area under curve (AUC) of the plasma insulin concentration during the course of the OGTT (0–180 min). There was a negative logarithmic relationship between glucose uptake GIR and insulin ($r = -0.52$; $P = 0.01$). The data points of HGP GIR were more scattered and the correlation with insulin was weak and failed to reach statistical significance ($r = -0.19$; $P = 0.12$).

In Fig. 1, the relativity and magnitude of the impairment in HGP versus glucose uptake in the affected subjects are apparent. Three of the T2D patients had very high HGP (outliers), implying severe HGP impairment. In contrast, the glucose uptake in these individuals was less impaired. In addition, there were other T2D and obese subjects in whom the degree of HGP impairment was greater than that of glucose uptake. Conversely, there were subjects in whom the impairment in glucose uptake was greater than that in HGP.

Discussion

The present study was designed to differentiate liver from skeletal muscle as the locus of impairments in glucose metabolism. The results of the study indicate that impairments in the liver and skeletal muscle (including adipose tissue) likely do not contribute to hyperglycemia equally. The difference in the degree of impairment in HGP versus glucose uptake can be substantial in magnitude and reciprocal in relativity (liver > muscle versus muscle > liver). Based on the results from the non-severe T2D subjects (in whom GIR was not very high) in the present study, the predominance of impairment can be localized in the liver, with the muscle being normal or only mildly affected (liver type). The reverse is true for muscle type. As such, liver or muscle may be the main source of glucose intolerance, and

thus hyperglycemia, and it differs from person to person depending on the subtypes. In contrast, subjects with severe T2D (very high GIR) had impairments in the liver and muscle (mixed type) and thus both organs could contribute substantially to hyperglycemia. These impairments are most likely due to insulin resistance.⁵ Therefore, the present study is about the identification of the loci of insulin resistance with a focus on the liver and skeletal muscle.

The results showed that it is possible to identify the relativity of impairments and to quantify the magnitude of the impairment in glucose metabolism in these organs clinically. The ability to localize and quantify organ-specific impairments may improve our understanding of the mechanism and dynamics of hyperglycemia. In theory, knowledge of localized impairments may enable informed selection of appropriate medications to target the affected organ(s) to improve glycemic control. It is realized that doing so would rely on the availability of medications that are directed at specific organs. For example, metformin seems to be a medication that reportedly acts on the liver to reduce HGP primarily by suppressing gluconeogenesis.^{6–12} In contrast, thiazolidinediones seem to improve glycemia primarily by increasing peripheral insulin sensitivity and glucose uptake.^{13–17} However, whether these compounds can indeed deliver organ-specific actions is not very clear at present. Therefore, the ability to identify organ(s) with impaired glucose metabolism raises the question whether pharmaceutical companies are able to develop more organ- or pathway-specific medications. It is clear that such efforts are consistent with the trend for individualization of glycemic control, as indicated by the experts:

The identification of subtypes of diabetes within T2DM, whether by specific genetic markers or other clinical features, remains a challenge. For example, whether an accurate separation of patients with T2DM into those with predominant insulin resistance versus those with predominant insulin deficiency would aid the selection of the most effective therapies is unknown. Nor is it known whether further subtyping based on the locus of resistance (e.g. muscle versus liver) would improve outcomes. These are all testable hypotheses that have been largely unexplored.¹⁸

Meanwhile, by differentiating between the liver and peripheral tissues as the (main) source of insulin resistance, proper remedies can be used to prevent the development of hyperglycemia in populations with greater risk of developing T2D. From the results of the present study, it appears that it is possible to identify organs with milder impairments in obesity, and presumably in other high-risk populations. In fact, it appears possible to do so in “healthy” individuals who have normoglycemia but with mild or early stage deteriorations in the liver or muscle. These observations suggest that interventions could be initiated as soon as possible in these populations so that organ deterioration is impeded and hyperglycemia prevented. Another useful feature of the procedure is its ability to quantify the degree of organ-specific impairment. As such, titration of medications becomes possible so that treatment-related hypoglycemia may be reduced or avoided altogether.

It is noted that some blood chemistry measurements in the T2D subjects (e.g. aspartate aminotransferase, blood pressures) were even more favorable than in the obese or lean control group. This is probably the result of the antidiabetic medications used in these

patients. However, this does not affect the objectives of the present study, which were to identify and quantify organ-specific impairments in glucose metabolism. Unfortunately, not knowing the pretreatment liver or muscle impairments in these patients precludes the evaluation of the effects of the medications on insulin resistance in these organs because all the subjects were only studied once.

A limitation of the present study is its small sample size, especially in the control group. Therefore, the results are considered preliminary and caution should be exercised in interpreting the findings. For example, the small sample size affects the reliability of using the average values of the control group as the criteria for subtyping. Larger studies are needed to confirm the observations made in the present study. The results indicate that the variability in HGP GIR is greater than that for glucose uptake and this is true for all three groups, albeit to different degrees. Therefore, the cut-off values were greater for the detection of HGP impairment. Whether this is a characteristic of HGP requires further investigation. In contrast, the variability of glucose uptake is in the range typical for human studies and thus milder impairments can be detected. Whether this implies that glucose uptake is a more reliable predictor of postprandial glycemia remains to be determined. Nonetheless, it seems clear that “liver type” and “muscle type” are distinct. In obese subjects, only one subtype could be present and mild in severity. In contrast, in T2D subjects often both subtypes are present in the same individual, with one subtype being predominant. The simple localization of glucose impairment in obesity could be good news for diabetes prevention because this may suggest that relatively simple medications are needed to target a single organ with mild impairment. None of the T2D subjects had a truly single site of impairment, except for the two who recovered from T2D. Therefore, for most T2D individuals, subtypes seem to be only relative terms. However, the predominance of one site seems firm, except for the mixed type.

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References

1. Féry F. Role of hepatic glucose production and glucose uptake in the pathogenesis of fasting hyperglycemia in type 2 diabetes: Normalization of glucose kinetics by short-term fasting. *J Clin Endocrinol Metab.* 1994; 78:536–42. [PubMed: 8126123]
2. Bonadonna RC, Del Prato S, Saccomani MP, et al. Transmembrane glucose transport in skeletal muscle of patients with non-insulin-dependent diabetes. *J Clin Invest.* 1993; 92:486–94. [PubMed: 8326013]
3. Gerich JE. Control of glycaemia. *Baillieres Clin Endocrinol Metab.* 1993; 7:551–86. [PubMed: 8379904]
4. Heine RJ, Hanning I, Morgan L, Alberti KG. The oral glucose tolerance test (OGTT): Effect of rate of ingestion of carbohydrate and different carbohydrate preparations. *Diabetes Care.* 1983; 6:441–5. [PubMed: 6400703]

5. Abdul-Ghani MA, Matsuda M, Balas B, DeFronzo RA. Muscle and liver insulin resistance indexes derived from the oral glucose tolerance test. *Diabetes Care*. 2007; 30:89–94. [PubMed: 17192339]
6. Inzucchi SE, Maggs DG, Spollett GR, et al. Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. *N Engl J Med*. 1998; 338:867–72. [PubMed: 9516221]
7. Caton PW, Nayuni NK, Kieswich J, Khan NQ, Yaqoob MM, Corder R. Metformin suppresses hepatic gluconeogenesis through induction of SIRT1 and GCN5. *J Endocrinol*. 2010; 205:97–106. [PubMed: 20093281]
8. He L, Sabet A, Djedjos S, et al. Metformin and insulin suppress hepatic gluconeogenesis through phosphorylation of CREB binding protein. *Cell*. 2009; 137:635–46. [PubMed: 19450513]
9. Kim YD, Park KG, Lee YS, et al. Metformin inhibits hepatic gluconeogenesis through AMP-activated protein kinase-dependent regulation of the orphan nuclear receptor SHP. *Diabetes*. 2008; 57:306–14. [PubMed: 17909097]
10. Radziuk J, Zhang Z, Wiernsperger N, Pye S. Effects of metformin on lactate uptake and gluconeogenesis in the perfused rat liver. *Diabetes*. 1997; 46:1406–13. [PubMed: 9287039]
11. Yu B, Pugazhenth S, Khandelwal RL. Effects of metformin on glucose and glucagon regulated gluconeogenesis in cultured normal and diabetic hepatocytes. *Biochem Pharmacol*. 1994; 48:949–54. [PubMed: 8093107]
12. Wollen N, Bailey CJ. Inhibition of hepatic gluconeogenesis by metformin. Synergism with insulin. *Biochem Pharmacol*. 1988; 37:4353–8. [PubMed: 3058129]
13. Kranebitter M, Niederwanger A, Tatarczyk T, et al. Pioglitazone has direct effects on insulin sensitivity and intracellular lipid content in L6 skeletal muscle cells. *Horm Metab Res*. 2010; 42:987–90. [PubMed: 20945270]
14. Rasouli N, Raue U, Miles LM, et al. Pioglitazone improves insulin sensitivity through reduction in muscle lipid and redistribution of lipid into adipose tissue. *Am J Physiol Endocrinol Metab*. 2005; 288:E930–4. [PubMed: 15632102]
15. Zhao Z, Lee YJ, Kim SK, et al. Rosiglitazone and fenofibrate improve insulin sensitivity of pre-diabetic OLETF rats by reducing malonyl-CoA levels in the liver and skeletal muscle. *Life Sci*. 2009; 84:688–95. [PubMed: 19250943]
16. Muurling M, Mensink RP, Pijl H, Romijn JA, Havekes LM, Voshol PJ. Rosiglitazone improves muscle insulin sensitivity, irrespective of increased triglyceride content, in *ob/ob* mice. *Metabolism*. 2003; 52:1078–83. [PubMed: 12898477]
17. Mayerson AB, Hundal RS, Dufour S, et al. The effects of rosiglitazone on insulin sensitivity, lipolysis, and hepatic and skeletal muscle triglyceride content in patients with type 2 diabetes. *Diabetes*. 2002; 51:797–802. [PubMed: 11872682]
18. Smith RJ, Nathan DM, Arslanian SA, Groop L, Rizza RA, Rotter JI. Individualizing therapies in type 2 diabetes mellitus based on patient characteristics: What we know and what we need to know. *J Clin Endocrinol Metab*. 2010; 95:1566–74. [PubMed: 20194712]

Significant findings of the study

The liver or muscle as the main source of hyperglycemia varies from person to person and can be diagnosed individually to enable personalized glycemic control.

What this study adds

An improved understanding of the mechanism underlying postprandial hyperglycemia at the organ level and the possibility of selectively targeting the liver or muscle in the intervention and prevention of type 2 diabetes.

Figure 1.

Plots of hepatic glucose production (HGP) glucose impairment ratio (GIR; open symbols) and glucose uptake GIR (filled symbols) against the insulin area under the curve (AUC) for control, overweight/obese, and type 2 diabetes (T2D) subjects ($n = 20$). The different shapes of the symbols have no special meaning and are only used to differentiate among subjects. For each subject, the two symbols for HGP and glucose uptake (in pairs of open and filled symbols, respectively, of same shape) are aligned vertically at the corresponding values on the x -axis. Thus, the relativity and magnitude of the impairments in liver versus muscle can be inspected visually. The horizontal broken line at GIR 1.0 is the group average of HPG GIR and glucose uptake GIR for the control group. The three outliers of HGP GIR, all T2D subjects, were not used to calculate the statistical values. The corresponding glucose uptake GIR for these three subjects is indicated by a larger filled circle for ease of matching within subjects.

Table 1

Anthropometric data for all study participants

	Control (n = 5)	Obese (n = 6)	T2D* (n = 10)	P-value
Age (years)	50.2 ± 4.3 ^a	39.7 ± 3.2 ^b	50.5 ± 2.3 ^a	0.04
BMI (kg/m ²)	22.7 ± 0.6 ^a	29.1 ± 0.9 ^b	26.5 ± 0.8 ^b	<0.01
SBP (mmHg)	126 ± 6	132 ± 5	123 ± 6	NS
DBP (mmHg)	78.0 ± 4.9	88.3 ± 4.0	80.0 ± 3.0	NS
HbA1c (%)	5.5 ± 0.3 ^a	5.5 ± 0.3 ^a	7.6 ± 0.6 ^b	<0.05
ALT (U/L)	19.0 ± 3.4	33.7 ± 7.0	22.8 ± 3.6	NS
AST (U/L)	20.8 ± 1.5 ^a	27.2 ± 3.7 ^b	18.1 ± 1.4 ^a	<0.05
BUA (μmol/L)	347 ± 31	355 ± 29	331 ± 20	NS
BUN (mmol/L)	5.5 ± 1.0	5.3 ± 0.4	5.4 ± 0.4	NS
Creatinine (μmol/L)	72.6 ± 3.6	73.8 ± 2.7	74.6 ± 4.3	NS
tTG (mmol/L)	1.4 ± 0.2	1.6 ± 0.3	2.3 ± 0.4	NS
tChol (mmol/L)	4.8 ± 0.5	5.0 ± 0.3	5.0 ± 0.2	NS
HDL (mmol/L)	1.4 ± 0.2	1.2 ± 0.1	1.1 ± 0.1	NS
LDL (mmol/L)	3.2 ± 0.4	3.9 ± 0.2	3.6 ± 0.3	NS

Data are the mean ± SE. Values with different superscript letters within a row differ significantly (at the *P*-value given in the last column).

* The average duration since diagnosis of type 2 diabetes was 5 years.

T2D, type 2 diabetes; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotrans-ferase; AST, aspartate aminotransferase; BUA, blood uric acid; BUN, blood urea nitrogen; tTG, total triglycerides; tChol, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2

Glucose impairment ratio and variabilities in hepatic glucose production and glucose uptake in the control group

	<i>n</i>	GIR	Range	SD
HGP	5	1.0	0.78–1.28	0.23
Glucose uptake	5	1.0	0.81–1.15	0.12

GIR, glucose impairment ratio; HGP, hepatic glucose production.

Table 3

Glucose impairment ratio and variabilities in hepatic glucose production and glucose uptake in overweight/obese and type 2 diabetes subjects

Group	<i>n</i>	HGP GIR	Glucose uptake GIR	HGP versus uptake
Obese	6	1.14 ± 0.07 [‡]	1.08 ± 0.09	NS
T2D	10	2.70 ± 0.45 ^{*‡}	1.75 ± 0.21 ^{*‡}	<i>P</i> = 0.08

Data are the mean ± SE.

^{*} *P* = 0.02 compared with the obese group;

[‡] *P* < 0.01 compared with the control group (see Table 2);

[‡] *P* = 0.1 compared with the control group (Table 2).

GIR, glucose impairment ratio; HGP, hepatic glucose production; T2D, type 2 diabetes.

Table 4

Subtypes of glucose metabolism impairments in patients with type 2 diabetes and overweight/obese subjects

GIR	Liver type	Muscle type	Mixed type
T2D subjects			
HGP GIR	2.56, 4.06	1.68 ± 0.07 (n = 4)	5.69, 4.12
Glucose uptake GIR	1.25, 1.26	2.46 ± 0.12 (n = 4)	1.91, 2.41
Obese subjects			
HGP GIR	1.42	1.14, 1.02	None
Glucose uptake GIR	0.82	1.26, 1.37	None

Where possible, data are given as the mean ± SE. Values without SE are from individual subjects, with the hepatic glucose production (HGP) and glucose uptake glucose impairment ratios (GIR) corresponding in order for each subject.

The subtypes are designated based on bolded values. The cut-off values used for type 2 diabetes (T2D) group are calculated as $3 \times \text{SD}$, whereas those for the overweight/obese group are calculated as $2 \times \text{SD}$.