# Muscle and Liver Insulin Resistance Indexes Derived From the Oral Glucose Tolerance Test

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**OBJECTIVE** — To derive indexes for muscle and hepatic insulin sensitivity from the measurement of plasma glucose and insulin concentrations during an oral glucose tolerance test (OGTT).

**RESEARCH DESIGN AND METHODS** — A total of 155 subjects of Mexican-American origin (58 male and 97 female, aged 18–70 years, BMI 20–65 kg/m$^2$) with normal glucose tolerance ($n = 100$) or impaired glucose tolerance ($n = 55$) were studied. Each subject received a 75-g OGTT and a euglycemic insulin clamp in combination with tritiated glucose. The OGTT-derived indexes of muscle and hepatic insulin sensitivity were compared with hepatic and muscle insulin sensitivity, which was directly measured with the insulin clamp, by correlation analysis.

**RESULTS** — The product of total area under curve (AUC) for glucose and insulin during the first 30 min of the OGTT (glucose$_{0-30}$[AUC] × insulin$_{0-30}$[AUC]) strongly correlated with the hepatic insulin resistance index (fasting plasma insulin × basal endogenous glucose production) ($r = 0.64$, $P < 0.0001$). The rate of decay of plasma glucose concentration from its peak value to its nadir during the OGTT divided by the mean plasma insulin concentration (dG/dt ÷ I) strongly correlated with muscle insulin sensitivity measured with the insulin clamp ($P = 0.78$, $P < 0.0001$).

**CONCLUSIONS** — Novel estimates for hepatic and muscle insulin resistance from OGTT data are presented for quantitation of insulin sensitivity in nondiabetic subjects.

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Skeletal muscle and hepatic insulin resistance are characteristic features in type 2 diabetes (1). Insulin resistance is also commonly observed in nondiabetic subjects who are overweight and is associated with a cluster of metabolic and cardiovascular risk factors (dyslipidemia, hypertension, visceral obesity, and elevated inflammatory markers) known as the insulin resistance syndrome or dysmetabolic syndrome (2). Individuals with the insulin resistance syndrome have an approximate threefold increased risk for coronary heart disease and type 2 diabetes (3). Their risk for cardiovascular and all-cause mortality is also increased compared with insulin-sensitive individuals (3). It is estimated that in the year 2000, more than one-third of the adult population (>20 years of age) in the U.S. had the insulin resistance syndrome and therefore are at high risk for the development of type 2 diabetes and cardiovascular disease (4).

Improved insulin sensitivity with lifestyle intervention, e.g., weight reduction and increased physical activity, lowers the risk of future type 2 diabetes in insulin-resistant individuals by more than one-half (5,6), reduces the prevalence of cardiovascular risk factors (7), and decreases cardiovascular morbidity and mortality (8). Pharmacological intervention with agents that improve insulin sensitivity, including thiazolidinediones and metformin, also reduces the risk of conversion from impaired glucose tolerance (IGT) to type 2 diabetes (5,9) and decreases the risk of cardiovascular disease in individuals with established type 2 diabetes (10,11). Therefore, it is important to have easy-to-perform tests that allow quantitation of the presence/severity of insulin resistance, particularly in nondiabetic subjects, in order to identify high-risk individuals and initiate intervention programs to improve their insulin sensitivity and reduce their risk for future type 2 diabetes and cardiovascular disease.

Many tissues, including the liver, skeletal muscle, and adipocytes, manifest resistance to insulin (12). Although in many individuals the insulin resistance develops simultaneously in multiple organs, the severity of insulin resistance may differ among the various tissues. Since interventions that improve insulin resistance are organ specific (e.g., physical activity for muscle insulin resistance, metformin for hepatic insulin resistance, and weight reduction and thiazolidinediones for both), it is important to quantitate which organs are resistant to insulin, as well as the magnitude of insulin resistance in each organ.

The hyperinsulinemic-euglycemic clamp is the gold standard for measuring whole-body insulin resistance (13). When combined with radiolabeled glucose, it allows one to quantify the individual contribution of hepatic and muscle insulin resistance to the defect in whole-body insulin-mediated glucose disposal (14). However, the insulin clamp is time consuming, is difficult to perform, and cannot be applied in ordinary clinical practice or in large-scale epidemiological studies. In recent years, surrogate measures of insulin resistance have been developed from measurements of glucose

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**Abbreviations:** AUC, area under the curve; EGP, endogenous glucose production; FPI, fasting plasma insulin; HGP, hepatic glucose production; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; QUICKI, quantitative insulin sensitivity index.

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

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and insulin concentrations during the oral glucose tolerance test (OGTT) (15–18). These indexes correlate reasonably well with whole-body insulin sensitivity measured with the insulin clamp. Although they provide a simple measure for whole-body insulin sensitivity, they do not provide information about the relative contributions of the liver versus skeletal muscle to the observed reduction in whole-body insulin sensitivity.

In this study, we use measurement of plasma glucose and insulin concentrations during the OGTT to derive indexes that can selectively quantitate hepatic and muscle insulin resistance. These indexes are validated by comparison with measures of hepatic and muscle insulin resistance obtained directly with the hyperinsulinemic-euglycemic clamp.

## RESEARCH DESIGN AND METHODS

The study included 155 Mexican-American subjects who received a euglycemic-hyperinsulinemic clamp and a 75-g OGTT. Subjects were recruited from advertisements placed in the local newspaper and were consecutively recruited. Subjects were divided into two groups: 100 with normal glucose tolerance (NGT) and 55 with IGT based on American Diabetes Association criteria. The subjects had a wide range of obesity (BMI 19.9–64.2 kg/m$^2$ [mean 30.4 ± 6.1]). A total of 38 of the NGT and 7 of the IGT subjects had a BMI <27 kg/m$^2$. Mean age was 40 ± 12 years, and there were 97 female (41 IGT) and 58 male (14 IGT) subjects. All subjects had normal liver, cardiopulmonary, and kidney function as determined by medical history, physical examination, screening blood tests, electrocardiogram, and urinalysis. No NGT or IGT subject was taking any medication known to affect glucose tolerance. Body weight was stable (±1.5 kg) for at least 3 months before the study in all subjects. No subject participated in any excessively heavy exercise program. The study protocol was approved by the institutional review board of the University of Texas Health Science Center, San Antonio, and informed written consent was obtained from all subjects before their participation.

All studies were performed at the General Clinical Research Center of the University of Texas Health Science Center at 0800 following a 10–12 h overnight fast.

### OGTT

Before the OGTT, a small polyethylene catheter was placed into an anticubital vein and blood samples collected at −30, −15, 0, 30, 60, 90, and 120 min for the measurement of plasma glucose and insulin concentrations.

### Euglycemic insulin clamp

Before the start of the insulin clamp, a catheter was placed into an anticubital vein for the infusion of all test substances. A second catheter was inserted retrogradely into a vein on the dorsum of the hand and the hand placed into a thermoregulated box heated to 70°C. At 0800, all subjects received a primed (25 μCi)-continuous (0.25 μCi/min) infusion of 3-[$^3$H]glucose (DuPont NEN Life Science Products, Boston, MA), which was continued for 4 h. After the 2-h basal tracer equilibration period, subjects received a primed-continuous insulin infusion at a rate of 240 pmol (40 mU) · min$^{-1}$ · m$^{-2}$ for 120 min. During the last 30 min of the basal equilibration period, plasma samples were taken at 5- to 10-min intervals for the determination of plasma glucose and insulin concentrations and tritiated glucose radioactivity. During the insulin infusion, plasma glucose concentration was measured every 5 min, and a variable infusion of 20% glucose was adjusted, based on the negative feedback principle, to maintain the plasma glucose concentration at each subject's fasting plasma glucose level with a coefficient of variation <5%. Plasma samples were collected every 15 min from 0 to 90 min and every 5–10 min from 90 to 120 min for the determination of plasma glucose and insulin concentrations and tritiated glucose specific activity.

### Analytical techniques

Plasma glucose was measured by the glucose oxidase reaction (Glucose Oxidase Analyzer; Beckman, Fullerton, CA). Plasma insulin concentration was measured by radioimmunoassay (Coat A Coat; Diagnostic Products, Los Angeles, CA). Plasma 3-[$^3$H]glucose radioactivity was measured in Somogyi precipitates.

### Calculations

The measurement of the hepatic insulin sensitivity is based on the following logic: in the postabsorptive state, the higher the rate of endogenous glucose production (EGP) and the higher the fasting plasma insulin (FPI) concentration, the greater the severity of hepatic insulin resistance. Because 80–85% of EGP originates in the liver (19), basal EGP primarily reflects hepatic glucose production (HGP), and we use EGP and HGP interchangeably. The product of EGP and FPI, therefore, provides a measure of hepatic insulin resistance under postabsorptive conditions, and validation of this measure has been provided (15).

Following the glucose load, the rise in plasma glucose concentration stimulates insulin secretion from the β-cells, and the combination of hyperglycemia and hyperinsulinemia suppress EGP. In subjects with normal hepatic insulin sensitivity, the rise in plasma glucose and insulin (20,21) concentrations is sufficient to suppress EGP and ameliorate the rise in plasma glucose concentration. On the other hand, in hepatic insulin-resistant individuals, an even greater rise in plasma glucose and insulin concentrations causes only a small to moderate suppression of EGP, and this results in a greater increase in plasma glucose concentration during the early phase (0–30 min) of the OGTT. It follows that the magnitude of the rise in plasma glucose and insulin concentrations immediately (0–30 min) following the glucose load is proportional to the magnitude of hepatic insulin resistance. We previously have shown that during the initial 20 min of insulin infusion, muscle glucose uptake is minimally increased, whereas HGP is markedly inhibited in NGT individuals (22,23). The rise in plasma glucose and insulin concentrations can be quantitated by the incremental area under the curve (AUC) for plasma glucose and insulin. Therefore, the total AUC during the OGTT reflects the combination of the fasting plasma glucose/insulin concentrations and the rise in plasma glucose/insulin concentrations, and the product of glucose AUC and insulin AUC provides an index of hepatic insulin resistance. Because the suppression of EGP during the OGTT reaches its nadir 45–60 min following ingestion of a glucose load (22), we calculated the product of the glucose and insulin AUCs during the first 30 min during the OGTT as the hepatic insulin sensitivity index. We compared this index against hepatic insulin sensitivity directly measured with EGP × FPI.

The rise in plasma glucose concentration during the OGTT stimulates glucose disposal into peripheral tissues, primarily skeletal muscle. Because there is no significant change in the rate of EGP production during the 60- to 120-min time

period of the OGTT (see Fig. 4 in ref. 22), the decline in plasma glucose concentration after 60 min primarily reflects glucose uptake by peripheral tissues, skeletal muscle. Therefore, the decline from the peak plasma glucose concentration during the OGTT is determined by the combination of two factors: *1*) skeletal muscle insulin resistance and *2*) plasma insulin concentration. The greater the muscle insulin resistance and the lower the plasma insulin concentration, the slower is the decline in plasma glucose concentration. Thus, skeletal muscle insulin sensitivity can be calculated as the rate of decline in plasma glucose concentration divided by plasma insulin concentration, as follows. Muscle insulin sensitivity index = dG/dt ÷ mean plasma insulin concentration (*I*), where dG/dt is the rate of decline in plasma glucose concentration and is calculated as the slope of the least square fit to the decline in plasma glucose concentration from peak to nadir. It should be noted that in some cases plasma glucose concentration has rebounded after it reached its nadir. In such instances, the rebound glucose concentration was not included in the regression. *I* represents the mean plasma insulin concentration during the OGTT.

During the last 30 min of the hyperinsulinemic-euglycemic clamp, HGP is suppressed by >85–90% in NGT and IGT subjects and glucose disposal mainly reflects insulin sensitivity of the skeletal muscle. Therefore, we validated the proposed skeletal muscle insulin sensitivity index during the OGTT against the rate of whole-body insulin-mediated glucose disposal measured with the euglycemic insulin clamp.

All data are expressed as means ± SD. Correlation analyses were performed with JNC software package version 5.1.

## RESULTS

### Muscle insulin resistance

Insulin-stimulated total-body glucose disposal, i.e., insulin sensitivity, measured with the euglycemic-hyperinsulinemic clamp (total glucose disposal/steady state plasma insulin), correlated strongly with the OGTT-derived muscle insulin sensitivity index (dG/dt ÷ I) ($r$ = 0.78, $P < 0.0001$) (Fig. 1*A*, Table 1). This correlation was equally strong in subjects with NGT ($r$ = 0.78, $P < 0.0001$) and in subjects with IGT ($r$ = 0.76, $P < 0.0001$), as well as in overweight/obese (BMI ≥27 kg/m$^2$) subjects ($r$ = 0.76, $P < 0.0001$) and in lean (BMI <27 kg/m$^2$) subjects ($r$ = 0.81, $P < 0.0001$). Other OGTT-derived indexes of insulin sensitivity had a lower correlation coefficient with total-body insulin sensitivity (Table 1). The skeletal muscle insulin sensitivity index

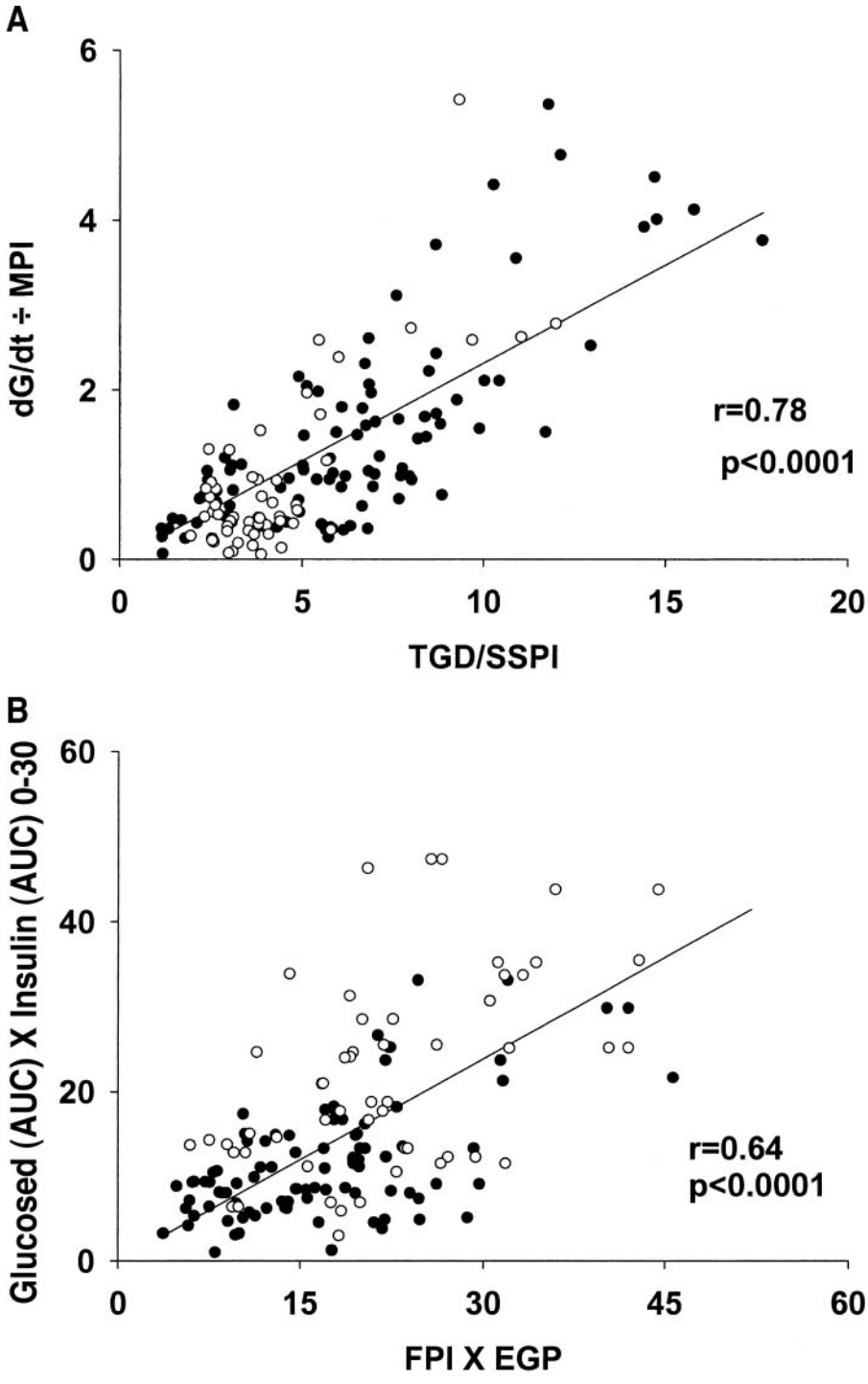


**Figure 1—**A: *Relation between OGTT-derived index of muscle insulin resistance (dG/dt ÷ I) and insulin resistance measured directly by the euglycemic insulin clamp (total glucose disposal/steady state plasma insulin). dG/dt, rate of change in plasma glucose from its peak to its nadir; MPI, mean plasma insulin concentration during OGTT; SSPI, steady-state plasma insulin concentration; TGD, total body glucose disposal.* B: *Relation between OGTT-derived index of hepatic insulin resistance and the hepatic insulin resistance index measured on the same day as the insulin clamp. EGP, basal endogenous glucose production; FPI, fasting plasma insulin concentration.* ○, *subjects with IGT;* ●, *subjects with NGT.*

**Table 1—*Correlation coefficient between OGTT-derived insulin sensitivity indexes and muscle and hepatic insulin sensitivity measured with the euglycemic insulin clamp***

| | TGD/SSPI | FPI × EGP |
|---|---|---|
| dG/dt ÷ I | 0.78 | 0.46 |
| $Glucose_{0–30}$(AUC) × $insulin_{0–30}$(AUC) | −0.55 | 0.64 |
| QUICKI index (ref. 14) | 0.71 | −0.58 |
| HOMA-IR (ref. 15) | −0.56 | 0.59 |
| logHOMA-IR | −0.67 | 0.61 |
| Matsuda index (ref. 12) | 0.75 | −0.52 |
| Stumvoll index (ref. 13) | 0.73 | −0.54 |

HOMA-IR, HOMA of insulin resistance; SSPI, steady state plasma insulin concentration during the last 30 min of the insulin clamp; TGD, total glucose disposal during the last 30 min of the insulin clamp. FPI was measured on the day of the insulin clamp. All correlation coefficients were statistically significant at $P < 0.0001$.

during the OGTT had a significant but much weaker correlation with the liver insulin sensitivity index measured as the product of EGP and FPI (Table 1).

### Liver insulin resistance

The product of basal EGP (measured with tritiated glucose) and FPI concentration provides a direct measure of hepatic insulin resistance under postabsorptive conditions. This measure of hepatic insulin resistance correlated strongly with the proposed hepatic insulin resistance index ($glucose_{0–30}$[AUC] × $insulin_{0–30}$[AUC]) ($r = 0.64$, $P < 0.0001$) (Fig. 1*B*, Table 1). This correlation was similar in NGT ($r = 0.58$, $P < 0.0001$) and IGT ($r = 0.62$, $P < 0.0001$) subjects. The proposed hepatic insulin sensitivity index correlated better with the direct measure of hepatic insulin resistance in obese (BMI ≥27 kg/m$^2$) subjects ($r = 0.65$, $P < 0.0001$) compared with lean (BMI <27 kg/m$^2$) subjects ($r = 0.31$, $P < 0.05$). The lower correlation in the lean group most likely is explained by the rather limited range of hepatic insulin resistance (3.78–26.6, mean ± SD 14.1 ± 5.8) compared with the obese group (5.8–79.3, 22.6 ± 13.2). The proposed hepatic insulin sensitivity index was correlated with the whole-body insulin sensitivity index measured with the insulin clamp, but the correlation coefficient was lower than that of the proposed muscle insulin sensitivity index (Table 1).

**CONCLUSIONS** — Insulin resistance is a characteristic feature of type 2 diabetes (1), is present in multiple tissues (12), is evident long before the onset of overt diabetes (24), and is associated with obesity and atherosclerotic cardiovascular disease (2). Nondiabetic insulin-resistant individuals are characterized by increased inflammatory markers (C-reactive protein and plasminogen activator inhibitor 1) (25) and the aggregation of multiple cardiovascular risk factors (hypertension, dyslipidemia, and microalbuminuria), a clinical constellation that has been referred to as the insulin resistance syndrome or "dys" metabolic syndrome. Recent clinical trials have demonstrated that amelioration of insulin resistance by lifestyle intervention in subjects with IGT reduces their risk for conversion to type 2 diabetes by more than one-half (5,6) and reduces the prevalence of cardiovascular risk factors (7). Furthermore, pharmacological treatments that improve insulin sensitivity in subjects with type 2 diabetes reduce the incidence of cardiovascular events, independent of glycemic control (10,11). Because of the clinical benefit derived by treating the insulin resistance, there has been widespread interest in the development of techniques to assess insulin sensitivity in vivo. The hyperinsulinemic-euglycemic clamp technique is considered the most definitive method to quantitate whole-body insulin sensitivity (13). When combined with radiolabeled glucose, one can quantify the individual contributions of hepatic and muscle insulin sensitivity to whole-body insulin-mediated glucose disposal (14). Although the insulin clamp is the most accurate method for quantifying insulin sensitivity, it is complicated and cannot be used easily in routine clinical practice or large-scale epidemiological studies. Therefore, there has been considerable interest in developing simpler methods to quantitate insulin sensitivity from the OGTT (15–18), which is the most commonly used test to assess glucose homeostasis in clinical practice and epidemiological studies. All OGTT-derived indexes rely upon the measurement of plasma glucose and insulin concentrations, either from fasting values (e.g., quantitative insulin sensitivity index [QUICKI] and homeostasis model assessment [HOMA]) (17,18) or postload values (15,16), to provide an assessment of the whole-body insulin resistance without reference to the contribution of individual organs, e.g., liver and muscle. Since insulin resistance occurs in multiple organs and with varying degrees, and since the interventions that improve insulin resistance are organ dependent (physical activity for muscle insulin resistance, metformin for hepatic insulin resistance, and weight loss and thiazolidinediones for muscle and hepatic insulin resistance), it is important to have a simple method that can assess the contribution of each organ to the whole-body insulin resistance. In this study, we describe a very simple method to quantitate separately hepatic and muscle insulin resistance from measurements of plasma glucose and insulin concentrations during the OGTT. The proposed indexes were compared with measures of hepatic and muscle insulin resistance quantitated directly with the euglycemic insulin clamp technique.

The proposed index for muscle insulin sensitivity during the OGTT correlated strongly with insulin-stimulated total glucose disposal during the euglycemic clamp, and the correlation coefficient was greater than all other OGTT-derived indexes of insulin sensitivity (Table 1). Furthermore, it had a much weaker correlation with hepatic insulin resistance measured with tritiated glucose, suggesting that this index specifically reflected insulin sensitivity of the skeletal muscle.

Indexes derived from measurements of fasting plasma glucose and insulin concentrations (HOMA and QUICKI) primarily reflect hepatic insulin resistance. The proposed hepatic insulin resistance index derived from plasma glucose and insulin concentrations during the OGTT correlates more strongly with the HGP × FPI index than HOMA and QUICKI. The better correlation observed with the proposed hepatic insulin resistance index may be explained the fact that the HOMA and QUICKI indexes are based only on fasting plasma glucose and insulin concentrations, while the proposed index takes into consideration both the basal

measurement of HGP and the suppression of HGP during the OGTT.

Our results also shed light on the course of plasma glucose concentration during glucose load (e.g., mixed meal or OGTT). They suggest that the initial rate of rise in plasma glucose concentration is mainly determined by hepatic insulin resistance and by the suppression of HGP in response to the insulin that is secreted in response to hyperglycemia. The greater the hepatic insulin resistance, the smaller the suppression of the HGP, and the greater is the initial rise in plasma glucose concentration. Obviously, the β-cell response is an important determinant of the rate of rise in plasma glucose, but our proposed measure of hepatic insulin resistance ($glucose_{0-30}$[AUC] × $insulin_{0-30}$[AUC]) takes this into account. Thus, worsening hepatic insulin resistance or impaired β-cell function would result in a greater initial increase in plasma glucose concentration following the glucose load. Approximately 60 min after the ingestion of the glucose load, HGP is maximally suppressed and remains suppressed at a constant level for the subsequent 60–120 min (22). Therefore, the rate of decline in plasma glucose concentration from its peak value to its nadir primarily reflects glucose uptake by peripheral tissues, muscle, and the insulin secretory response to hyperglycemia. In the face of increased muscle insulin resistance, the decline in plasma glucose concentration will be reduced. In subjects with type 2 diabetes, the plasma glucose concentration often rises continuously during the last hour (60–120 min) of the OGTT. Therefore, determination of muscle insulin sensitivity using the current approach is not feasible.

In summary, the early glucose response during the OGTT ($glucose_{0-30}$[AUC] × $insulin_{0-30}$[AUC]) provides an index of hepatic resistance to insulin, while the decline in plasma glucose concentration from its peak to its nadir provides a measure of muscle resistance to insulin, and these insulin sensitivity indexes correlate well with those obtained from the euglycemic insulin clamp/3-$^3$H-glucose turnover measured in the same individual. Although the improvement in the correlation over the current indexes of insulin sensitivity is modest, the proposed indexes have greater selectivity in detecting changes in muscle and hepatic insulin sensitivity separately and are easily calculated.

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