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Relationship between insulin sensitivity and insulin secretion rate: not necessarily hyperbolic

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Abstract

Aims—There is general acceptance that the physiological relationship between insulin sensitivity and insulin secretion is hyperbolic. This conclusion has evolved from studies in which one test assessed both variables, and changes in plasma insulin concentration were used as a surrogate measure for insulin secretion rate. The aim of this study was to see if a hyperbolic relationship would also emerge when separate and direct measures were used to quantify both insulin sensitivity and insulin secretion rate.

Methods—Steady-state plasma glucose (SSPG) was determined in 146 individuals without diabetes using the insulin suppression test, with $1/SSPG$ used to quantify insulin sensitivity. The graded-glucose infusion test was used to quantify insulin secretion rate. Plasma glucose and insulin concentrations obtained during an oral glucose tolerance test (OGTT) were used to calculate surrogate estimates of insulin action and insulin secretion rate. A hyperbolic relationship was assumed if the β coefficient was near -1 using the following model: $\log(\text{insulin secretion measure}) = \text{constant} + \beta \times \log(\text{insulin sensitivity measure})$.

Results—OGTT calculations of insulin sensitivity (Matsuda) and plasma insulin response [ratio of insulin/glucose area-under-the-curve (AUC), insulin total AUC provided the expected hyperbolic relationship [$\beta = -0.95$, 95% CI ($-1.09, -0.82$); -1.06 ($-1.14, -0.98$)]. Direct measurements of insulin sensitivity and insulin secretion rate did not yield the same curvilinear relationship [$\beta = -1.97$ ($-3.19, -1.36$)].

Conclusions—These findings demonstrate that the physiological relationship between insulin sensitivity and insulin secretion rate is not necessarily hyperbolic, but will vary with the method(s) by which it is determined.

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Competing interests

None declared.

Author contributions

SHK conceived the study and wrote the manuscript. AS and JV completed the statistical analyses. GMR critically reviewed and edited the manuscript. SHK is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility of the integrity of the data and the accuracy of the data analysis.

Introduction

Peripheral insulin sensitivity can vary by sixfold in individuals without diabetes [1]. Insulin-resistant individuals can generally maintain normal or near normoglycaemia by increasing insulin secretion rate [2]. As a corollary, hyperglycaemia develops in those insulin-resistant individuals who fail to compensate for the degree of insulin resistance. Although this concept is well accepted, the exact relationship between insulin resistance and insulin secretion has been debated [3–5]. The hyperbolic model proposed by Bergman suggests that the relationship between insulin sensitivity and insulin secretion is best represented as a hyperbola with the product of the two variables (disposition index) equalling a constant [6]. The hyperbolic curve was initially demonstrated in studies using the frequently sampled intravenous glucose tolerance test [6–8], and subsequently demonstrated with data from an oral glucose tolerance test (OGTT) [9]. Although a widely accepted model, limitations of the hyperbolic concept have been raised. First, although the hyperbolic relationship has been demonstrated using either the frequently sampled intravenous glucose tolerance test [6–8] or OGTT [9], in these studies both insulin sensitivity and insulin secretion rate have been calculated using the same test. Using a single test to calculate both insulin sensitivity and insulin secretion raises questions about the intrinsic interrelationships between the variables, particularly because both variables include plasma insulin concentration in the calculation [10]. Second, although the hyperbolic function is intended to show the relationship between insulin sensitivity and insulin secretion rate, past studies have predominately substituted insulin concentrations for insulin secretion rates, and DeFronzo *et al.* [11] recently reported that the curvilinear relationship between insulin sensitivity and plasma insulin response during the OGTT is lost when insulin secretion rate, not insulin concentration, is used.

The current study was initiated to provide for the first time a description of the relationship between insulin sensitivity and insulin secretion rate when separate and independent measurements were made of each variable in a substantial number of people without diabetes. Consequently, the insulin suppression test was used to quantify insulin sensitivity, and the graded-glucose infusion test (GGIT) was used to measure insulin secretion rate, by deconvolution of peripheral plasma C-peptide concentrations. The values from these tests were used to see if a hyperbolic relationship existed between the two.

Methods

Subjects

The subjects included 146 individuals without diabetes who had all signed informed consents to participate in studies of insulin resistance. They all responded to newspaper or radio advertisements describing studies of glucose and insulin metabolism. Non-diabetic status was confirmed by OGTT (fasting glucose < 7 mmol/l, 2-h glucose < 11 mmol/l). All individuals also had no coronary artery, kidney or liver disease. They were all required to have an OGTT and measurement of insulin sensitivity using the insulin suppression test and insulin secretion rate using the GGIT.

Measurements

All tests were performed in the Stanford Clinical and Translational Research Unit after fasting for 12 h.

OGTT—Glucose and insulin concentrations were measured at fasting and after 30, 60, 120 and 180 min after 75-g glucose challenge. Individuals were subdivided based on their fasting and 120-min glucose as having normal glucose tolerance (NGT, fasting < 5.6 mmol/l, 120-min < 7.8 mmol/l), impaired fasting glucose (IFG, fasting 5.6–6.9 mmol/l, 120-min < 7.8 mmol/l), impaired glucose tolerance (IGT, fasting < 5.6 mmol/l, 120-min 7.8–11 mmol/l), or combined IFG/IGT (fasting 5.6–6.9 mmol/l, 120-min 7.8–11 mmol/l). The Matsuda Index was used as a surrogate of insulin sensitivity [12]. All time points, including 180 min, were used [13]. Insulin secretion was estimated by the ratio of insulin to glucose area-under-the-curve (Insulin/Glucose AUC_{OGTT}), as well as insulin AUC (Insulin AUC_{OGTT}). Matsuda Index and total Insulin/Glucose AUC_{OGTT} were chosen as they have been previously shown to have a hyperbolic relationship with one another [9].

Insulin suppression test—Peripheral insulin sensitivity was measured using a modified version of the insulin suppression test. The values for insulin sensitivity obtained with this approach are highly correlated ($r = 0.87$) with the hyperinsulinaemic euglycaemic clamp [14–15]. Briefly, after an overnight fast, an intravenous catheter was placed in each of the subject's arms. One arm was used for the administration of a 180-min infusion of octreotide (0.27 $\mu\text{g}/\text{m}^2/\text{min}$), insulin (32 $\text{mU}/\text{m}^2/\text{min}$) and glucose (267 $\text{mg}/\text{m}^2/\text{min}$); the other was used for collecting blood samples. Blood was drawn at 10-min intervals between 150 and 180 min to calculate the steady-state plasma glucose (SSPG). The reciprocal of SSPG ($1/\text{SSPG}$) was used as the measure of insulin sensitivity (so that higher values represent higher degree of insulin sensitivity).

Graded-glucose infusion test—To measure insulin secretion rate, subjects received graded intravenous infusions of glucose at progressively increasing rates (1, 2, 3, 4, 6 and 8 $\text{mg}/\text{kg}/\text{min}$), as described previously [16–17]. Each glucose infusion rate was administered for a total of 40 min. Glucose, insulin and C-peptide concentrations were measured at fasting and then 30 and 40 min into each glucose infusion period. The last two values at the end of each infusion period were averaged and used as the mean for that infusion. Insulin secretion rates were derived by deconvolution of peripheral plasma C-peptide concentrations, using a two-compartment model of C-peptide kinetics and standard parameters for C-peptide clearance estimated for each subject based on body surface area and age [18]. For each subject, insulin secretion rate was plotted against plasma glucose concentration. The AUC of insulin secretion rate from 5 to 10 mmol/l of glucose [ISR AUC (5–10 mmol/l)_{GGIT}] was used as the measure for insulin secretion rate [17]. We also calculated insulin AUC (Insulin AUC_{GGIT}) and the ratio of insulin AUC to glucose AUC during the GGIT (Insulin/Glucose AUC_{GGIT}).

The GGIT was conducted within one month of the insulin suppression test. The median number of days between tests was 2 days with an interquartile range of [–7, 14].

Statistical analysis

Relationship between insulin sensitivity and insulin secretion rate—Under the Bergman hypothesis [6], $y = c(1/x)$ described a rectangular hyperbola, where y and x represent the respective measures of insulin secretion and insulin sensitivity. This can be re-expressed through a log transformation to yield a linear model: $\log(y) = \text{constant} + \beta \log(x)$, where β must equal -1 if the hyperbolic relationship holds. This was tested, using properly weighted perpendicular least squares regression, which takes into account the inherent underestimation of β , when measurement error is present in both the dependent and independent variables [9,19]. This methodology adjusts for the downward estimation bias in β through a correction factor λ , based on the ratio of the y to x error variances.

The error variance for each study variable was estimated from the corresponding intrasubject coefficient of variation (CV) based on two replicates, using special purpose sample of 13 obese subjects. The demographic profile of the sample mirrored that of our study participants (mean age 54 ± 10 years, BMI 33 ± 3 kg/m², 69% female, and 54% non-Hispanic white). The CVs for insulin sensitivity, as assessed by Matsuda Index and 1/SSPG, were 18.1% and 13.6%, respectively. The CVs for Insulin/Glucose AUC_{OGTT} and Insulin AUC_{OGTT} from the OGTT were 23.4% and 23%. Finally, measures of insulin secretion derived from the GGIT yielded the following CVs: ISR AUC_{GGIT} (12.8%), Insulin AUC_{GGIT} (20.3%) and Insulin/Glucose AUC_{GGIT} (17.3%). All AUCs represented total AUC calculated by the trapezoidal method.

Incremental AUCs were also calculated by taking the positive area above the insulin or glucose baseline, derived from the respective OGTT and GGIT curves. The corresponding CVs for the incremental Insulin/Glucose AUC_{OGTT} and Insulin AUC_{OGTT} were 37.1% and 23.0%. Similarly, the CVs for the incremental Insulin AUC_{GGIT} and Insulin/Glucose AUC_{GGIT} were 28.2% and 43.0%, respectively.

The suite of regression models corresponding to the four levels of glucose impairment were fitted to the log transformed data, via the Methcomp package in R [20]. The 95% confidence limits of β were calculated by the bootstrap with 1000 replications. A hyperbolic relationship was assumed if β was near -1 , and the 95% confidence interval (95% CI) excluded 0 [21].

Results

The clinical characteristics of the population are shown in Table 1. The study population was mostly overweight or obese. One-fifth had normal glucose tolerance and the remainder had prediabetes (IFG, IGT or IFG/IGT).

Figure 1 shows the relationship between insulin sensitivity and insulin secretion rate when estimated with values obtained during the OGTT (A) and when directly measured using the insulin suppression test and GGIT (B). Using plasma glucose and insulin concentrations obtained during the OGTT, the relationship between the Matsuda Index (insulin sensitivity) and Insulin/Glucose AUC_{OGTT} (insulin secretion) appeared curvilinear (Fig. 1A). As seen in Table 2, the regression coefficient, β , was near -1 , confirming previous findings of a hyperbolic relationship between the two variables calculated from the OGTT. Matsuda Index

and insulin AUC_{OGTT} (AUC of plasma insulin during the OGTT) also had a hyperbolic relationship (Table 2).

When insulin action and secretion rate were directly and independently measured, the relationship between these variables was no longer hyperbolic (Fig. 1B), and the β coefficient was not -1 [$\beta = -1.97$, 95% CI $(-3.19, -1.36)$, Table 2]. The relationship between $1/\text{SSPG}$ and Insulin AUC_{GGIT} (AUC of plasma insulin during the GGIT) or Insulin/Glucose AUC_{GGIT} (the ratio of plasma insulin AUC and glucose AUC) was also not hyperbolic.

The bottom of Table 2 also shows the relationship between different measures of insulin sensitivity and insulin secretion stratified by glucose tolerance categories (NGT, IFG, IGT and IFG/IGT). The hyperbolic relationship was maintained in all groups when using measures from the OGTT. The only exception was the relationship between Matsuda Index and insulin AUC_{OGTT} in the isolated IFG group [$\beta = -1.16$, 95% CI $(-1.30, -1.02)$]. Note that in the other groups, β coefficients remained near -1 and ranged between -1.03 and -1.14 . By contrast, the relationship between $1/\text{SSPG}$ and measures from the GGIT was not hyperbolic in any group, and the β coefficients ranged between -1.48 and -2.62 .

Finally, we also evaluated the relationship between insulin sensitivity and insulin secretion when incremental, instead of total, AUC was used for indices derived from OGTT and GGIT (see Table S1; the incremental AUC is not applicable for ISR AUC_{GGIT}, which represents the dose-response relationship between glucose and ISR). Incremental AUC takes the area above fasting values and may represent dynamic change in insulin response to glucose challenge. As seen in Table S1, the hyperbolic relationship between $1/\text{SSPG}$ and Insulin/Glucose Incremental AUC_{OGTT} was less evident with a β of -0.73 $(-1.09, -0.37)$. The relationship between $1/\text{SSPG}$ and insulin secretion measures from the GGIT continued not to be hyperbolic.

Discussion

Although insulin resistance is a risk factor for Type 2 diabetes, most insulin-resistant individuals can maintain glucose homeostasis through an increase in insulin secretion rate [2]. To determine the adequacy of this compensation, or β -cell function, many prior studies have calculated the product of insulin sensitivity and insulin secretion (disposition index) [22–26], assuming a hyperbolic relationship between any measures for these two variables. As illustrated in this study, the relationship between direct measures of insulin sensitivity and insulin secretion was not hyperbolic.

Bergman first proposed that there is a hyperbolic relationship between insulin sensitivity and acute insulin response as measured by the frequently sampled intravenous glucose tolerance test [6]. Others have confirmed this relationship using the frequently sampled intravenous glucose tolerance test [7–8] and subsequently OGTT [9]. We also show a hyperbolic relationship between the Matsuda Index and Insulin/Glucose AUC_{OGTT}, as well as Insulin AUC_{OGTT}. However, we did not find a similar relationship when using independent and direct measures of insulin sensitivity and insulin secretion rate. The reasons

for this disparity may be twofold. First, the majority of past studies [6–9] have calculated insulin sensitivity and plasma insulin response using a single test, which may create intrinsic inter-relationships between the two variables [10]. To avoid this, the current study used independent tests to individually quantify insulin sensitivity and insulin secretion rate. Second, past studies have used plasma insulin response as a surrogate for insulin secretion rate [6–9], and DeFronzo *et al.* used OGTT data to demonstrate that the hyperbolic relationship between insulin sensitivity and plasma insulin response is lost when insulin secretion, not insulin concentration, is used in the calculation [11]. In the current study, when independent studies were conducted, neither plasma insulin concentrations (Insulin AUC_{GGIT}) nor insulin secretion rate (ISR AUC_{GGIT}) had a hyperbolic relationship with insulin sensitivity. Therefore, it seems that the existence of a hyperbolic relationship between insulin sensitivity and secretion is less related to using insulin response vs. insulin secretion rate, but is more a function of determining both variables with the same test.

Our results demonstrate that the methods used to measure insulin sensitivity and insulin secretion determine whether a hyperbolic relationship exists. However, it must be made clear that our goal was not to argue that the particular methods we used to quantify insulin action and/or secretion will provide the ‘correct’ interpretation of the relationship between these two variables. Rather, the intent was simply to raise the possibility that the existence of a hyperbolic relationship between an estimate of insulin action and secretion, per se, does not prove that the pathophysiological findings and implications using that approach are correct.

For example, in terms of the goal of a given study, an oral glucose challenge, which mimics the physiology of eating, would be preferred to the use of an intravenous glucose challenge. Similarly, the insulin response to a glucose challenge involves both changes in insulin secretion and clearance and represents total compensation to insulin resistance. However, if the goal is to understand changes in insulin secretion, apart from insulin clearance, a direct measure of insulin secretion rate would be desirable. In other words, depending upon the goal of the investigation, there are a number of considerations that must be kept in mind, and whether or not the relationship between insulin action and insulin secretion is hyperbolic should not be the paramount consideration.

In conclusion, although our findings are based on only 146 individuals without diabetes, we are unaware of publication containing separate and direct measures of both insulin sensitivity and insulin secretion in this many persons. Retnakaran *et al.* did evaluate the Matsuda Index and total Insulin/Glucose AUC_{OGTT} measured on separate days, but used a single methodology to evaluate both parameters [9]. Larsson and Ahren described a hyperbolic relationship between insulin sensitivity using the euglycaemic–hyperinsulinaemic clamp and acute insulin response to arginine; although they used two independent tests, they did not report the regression coefficient (β) relating insulin sensitivity to insulin response [27]. Finally, Ferrannini and Mari also measured insulin sensitivity using the clamp and three measures of insulin response using the OGTT but found a wide range in the β coefficients (–0.7 to –1.8) [3]. Again, methodological differences may explain the disparate findings, but neither study measured insulin secretion rate. A limitation of our study is that we did not measure first phase insulin secretion, which may have a different relationship with insulin resistance. We also did not measure HbA_{1c} to better distinguish

glucose tolerance categories. Our population also included more women and non-Hispanic white people, and the results may be different in other populations. Despite these limitations, our results demonstrate that the relationship between insulin sensitivity and insulin secretion is not necessarily hyperbolic, and the assumption that the product of insulin sensitivity and insulin secretion rate (disposition index) is a constant does not apply when direct measures of insulin sensitivity and insulin secretion are used. Finally, our results strongly suggest that interpretation of studies of pancreatic β -cell function, and definition of its relationship to insulin sensitivity, is not simple, and likely to vary as a function of the methodology used to quantify these variables. There is evidently a need for studies to establish more precisely the circumstances under which the hyperbolic relationship obtains and its pathophysiological meaning. Issues that need to be better discriminated in future studies include the relative importance of insulin secretion and insulin elimination, which aspects of the β -cell insulin response are being measured and whether the research question is best served by simultaneous or independent evaluations of insulin response and insulin resistance. However, what does seem clear is that the quantitative methods used to measure insulin action and secretion should be chosen on the basis of their perceived 'pros' and 'cons' in terms of the question being addressed, not whether their relationship is hyperbolic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What's new?

- The relationship between degree of insulin sensitivity and insulin secretory response is conventionally depicted as a hyperbolic curve based on studies using one test to quantify both insulin sensitivity and insulin secretion.
- The current study used independent and direct measures of both variables to demonstrate that the relationship between insulin sensitivity and secretion is not necessarily hyperbolic.
- The results raise questions regarding current pathophysiological views of glucose-intolerant states and indicate the need for studies to establish more precisely the circumstances under which the hyperbolic relationship obtains and its pathophysiological meaning.

FIGURE 1.

Relationship between insulin sensitivity and insulin secretion using surrogate measurements from the OGTT (A) and direct measurements from the insulin suppression test and graded-glucose infusion test (B). $N = 146$. NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IFG/IGT, combined IFG/IGT.

Table 1

Clinical characteristics

	<i>N</i> = 146	Range
Age (years)	54 ± 9	29–72
Female, <i>n</i> (%)	90 (62)	
Non-Hispanic white, <i>n</i> (%)	99 (68)	
BMI (kg/m ²)	31.6 ± 3.4	24–42
Fasting glucose (mmol/l)	5.8 ± 0.5	4.5–6.9
2-h glucose (mmol/l)	7.3 ± 1.8	2.8–10.9
Glucose tolerance		
NGT	30 (20)	
Isolated IFG	58 (40)	
Isolated IGT	13 (9)	
Combined IFG/IGT	45 (31)	

Mean ± SD. NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Table 2

Relationship between different measures of insulin sensitivity and insulin secretion

	Insulin sensitivity	Insulin secretion	β	95% CI
Total study population				
Surrogate measures	Matsuda	Insulin/Glucose AUC _{OGTT}	-0.95	-1.09 -0.82
	Matsuda	Insulin AUC _{OGTT}	-1.06	-1.14 -0.98
Direct measures	1/SSPG	ISR AUC (5–10 mmol/l) _{GGIT}	-1.97	-3.19 -1.36
	1/SSPG	Insulin AUC _{GGIT}	-1.61	-1.94 -1.37
	1/SSPG	Insulin/Glucose AUC _{GGIT}	-1.49	-1.92 -1.20
By glucose tolerance categories				
	Matsuda	Insulin/Glucose AUC _{OGTT}	-1.10	-1.38 -0.88
		Isolated IFG	-1.09	-1.32 -0.86
		Isolated IGT	-1.08	-1.29 -0.92
		Combined IFG/IGT	-1.03	-1.24 -0.83
Surrogate measures	Matsuda	Insulin AUC _{OGTT}	-1.14	-1.41 -0.94
		Isolated IFG	-1.16	-1.30 -1.02
		Isolated IGT	-1.10	-1.30 -0.91
		Combined IFG/IGT	-1.03	-1.14 -0.90
	1/SSPG	ISR AUC (5–10 mmol/l) _{GGIT}	-1.48	-2.56 -0.96
		Isolated IFG	-1.34	-2.19 -0.72
		Isolated IGT	-1.92	-2.74 -1.28
		Combined IFG/IGT	-2.62	-13.48 -0.85
Direct measures	1/SSPG	Insulin AUC _{GGIT}	-1.51	-2.02 -1.21
		Isolated IFG	-1.40	-1.89 -1.06
		Isolated IGT	-2.52	-3.67 -1.07
		Combined IFG/IGT	-1.82	-3.69 -1.17
	1/SSPG	Insulin/Glucose AUC _{GGIT}	-1.53	-2.11 -1.14
		Isolated IFG	-1.47	-2.06 -1.06
		Isolated IGT	-2.28	-3.64 -1.41
		Combined IFG/IGT	-1.82	-3.95 -1.05

Estimated regression coefficient (β) and 95% CI. AUC refers to total area under the curve.