Both a Reduced Acute Insulin Response to Glucose and Lower Glucose Effectiveness Are Responsible for the Worsening of Intravenous Glucose Tolerance in Healthy Subjects Independently of the Degree of Obesity

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The effects of the acute insulin response to glucose (AIRg), insulin sensitivity (S_I), and glucose effectiveness at zero insulin (GEZI) on intravenous glucose tolerance were studied in 94 non elderly healthy subjects with a wide range of body mass index (BMI). Conrad's coefficient of glucose assimilation (K_G) was calculated between 10 and 19 minutes of an intravenous glucose tolerance test. Both S_I and GEZI were estimated using Bergman's minimal model. AIRg was calculated as the area under the insulin curve above basal between 0 and 10 minutes, and the suprabasal insulin effect was determined by the product of $S_I \times$ AIRg. Stepwise multiple regression showed that the combined effect of $S_I \times$ AIRg and GEZI explained 67% of the K_G index variance. Division of the sample into tertiles according to K_G shows that subjects with the lowest K_G ($K_G < 1.32$ min^{-1}) had the lowest AIRg (2,832 ± 1,362 *v* 6,510 ± 4,410 [pmol·L^{-1}] min, $P = .0005$), the lowest GEZI (0.092 ± 0.06 *v* 0.179 ± 0.09 min^{-1}, $P = .0004$), and the lowest $S_I \times$ AIRg (0.014 ± 0.008 *v* 0.022 ± 0.01 min^{-1}, $P = .00001$), and were the oldest (41 ± 10 *v* 31 ± 10 years, $P = .002$) compared with subjects with the highest K_G ($K_G > 1.8$ min^{-1}). However, no differences in S_I (4.86 ± 4.6 *v* 6.5 ± 3.7 min^{-1} [pmol·L^{-1}],$^{-1}$ NS) or BMI (29.6 ± 5.0 *v* 26.6 ± 5.9 kg·m^{-2}, NS) were observed. These results did not vary when lean and obese subjects were analyzed separately. Age correlated significantly only with $S_I \times$ AIRg. In conclusion, although the main factors that determine intravenous glucose tolerance are the suprabasal insulin effect and GEZI, worsening of the K_G index depends on inadequate insulin secretion for the degree of insulin sensitivity and lower non–insulin-mediated glucose uptake. Age seems to be another factor in the worsening of intravenous glucose tolerance through a lower suprabasal insulin effect.

THE VALUES FOR Conrad's coefficient of glucose assimilation (K_G) vary widely in the normal population. Intravenous glucose tolerance is mainly determined by insulin secretion, insulin sensitivity, and the ability of glucose to promote its own disposal (glucose effectiveness).[1] The importance of both insulin secretion and insulin sensitivity is universally accepted, and it has been demonstrated[2] that there is a hyperbolic relationship between these two factors. However, in the last few years, the importance of glucose effectiveness in the regulation of glucose tolerance has become evident.[1,3,4] Thus, Kahn et al[4] have recently reported that both glucose effectiveness and the combined action of insulin sensitivity and insulin secretion explained 72% of the variance of the K_G index in an apparently healthy population. Using computer simulation, Bergman[1] showed several years ago that the combined defect of some of the factors was necessary to induce an impairment of intravenous glucose tolerance (particularly insulin sensitivity and glucose effectiveness at basal insulin), whereas a defect of one of the factors alone hardly modified the K_G index. On the other hand, Taniguchi et al[5,6] demonstrated that both lean and obese subjects with impaired glucose tolerance (IGT) showed a decrease in glucose effectiveness and a lower K_G index compared with their respective control groups, despite having comparable insulin sensitivity. Despite the large number of reports published on these topics, to the best of our knowledge, it still is not known exactly what the reason is for the enormous variability in the K_G index in a healthy population with normal oral glucose tolerance. The aim of this study was to establish how insulin secretion, insulin sensitivity, and glucose effectiveness determine the variability of the K_G index in a wide sample of subjects with normal oral glucose tolerance, and in what way both age and degree of adiposity influence these factors.

SUBJECTS AND METHODS

Subjects

One hundred eight healthy subjects with a variable degree of adiposity and normal glucose tolerance according to World Health Organization criteria[7] were studied. Of these subjects, 37 were controls from previous studies.[8,9] All of the subjects were less than 55 years old, and none had a family history of diabetes mellitus or hypertension or were under treatment with drugs that could affect glucose metabolism. Women were studied during the follicular phase of the menstrual cycle.[10] The study protocol was approved by the Santiago University Hospital research ethics committee, and informed consent was obtained from each participant.

Protocol

Eighty-eight subjects underwent a standard frequently sampled intravenous glucose tolerance (FSIGT) test,[11] and the other 20 subjects underwent a FSIGT test modified with tolbutamide.[12]

The subjects were consuming a diet containing at least 300 carbohydrate per day for 3 days before the study, and they were recommended not to engage in extra exercise for 1 week before the study and not to smoke the day before. Each subject came to the Hospital at 8:30 AM after a 10- to 12-hour overnight fast. With the subject recumbent, the antecubital veins of both arms were cannulated with a 20-gauge catheter (Abbocath-T 20G; Abbott, Dublin, Ireland). One of the catheters was used for blood sampling and the other for glucose and, when necessary, tolbutamide injection. The patency of the catheters was maintained with isotonic saline 0.9% NaCl infusion. Basal glucose and insulin values were obtained from blood samples taken 20, 15, 10, 5, and 1 minute before injection of glucose. At time zero, injection of 0.3 g/kg 50% (wt/vol) dextrose (Glucosmon R/50; Leo, Madrid, Spain) was initiated; it was completed in less than 2 minutes, and further blood samples were

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taken 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 100, 120, 140, 160, and 180 minutes after the start of injection. When used, tolbutamide 4.3 mg/kg (Dolipol; Hoechst, Barcelona, Spain) was injected at time 20 minutes; for these subjects, additional blood samples were taken at 23, 24, and 27 minutes. Blood samples were collected in precooled glass tubes containing lithium heparin and 4 mg NaF. All samples were kept on ice until centrifugation. Later, the aliquots were centrifuged and stored at −20°C pending determination of glucose and insulin.

Insulin Sensitivity and Glucose Effectiveness Calculations

Bergman's minimal model was used to calculate both insulin sensitivity (S_I) and glucose effectiveness at basal insulin (S_G) indices.[11,13] Briefly, the minimal model of glucose kinetics (MMg) is a mathematical representation of the kinetics of glucose during a FSIGT test. The model is represented by two nonlinear, first-degree differential equations. The parameters of the model were estimated using a nonlinear least-squares technique with a personal program (STELLUM-MMg).[8,14] Once the model parameters are estimated, it is possible to calculate both S_I and S_G indices. The basal insulin component of S_G is BIE and is calculated as the product of basal insulin (Ib) and the S_I index. Glucose effectiveness at zero insulin (GEZI) is the difference between S_G and BIE: GEZI = $S_G - (S_I \cdot Ib)$.[15] For the accuracy of minimal model indices, the fractional standard deviation (FSD) was calculated.[16] When the FSD of S_I was higher than 6% or the FSD of S_G was higher than 15%, the coefficient of variation (CV) of these indices was calculated using the Monte Carlo technique and only coefficients less than 34% were accepted as valid.[17]

Minimal Model of Insulin Kinetics

This model is the mathematical representation of plasma insulin when plasma glucose during a FSIGT is provided.[18] The estimation of MMi parameters was performed in the same way as for MMg, using another personal program (STELLUM-MMi). MMi parameters enable calculation of both Φ_1 and Φ_2 indices, which represent the relative responsiveness of first- and second-phase posthepatic insulin release to glucose, respectively.

Numerical Methods

Differential equations were integrated using a fourth-order Runge-Kutta numerical method.[19] For parameter estimation, a nonlinear least-squares method based on Marquardt's algorithm was used.[20] The mathematical-statistical implementation was performed with a personal program (STELLUM-MM) written in C language and running on a computer with a 486 DX2 processor.

Calculations

An intravenous glucose tolerance index, K_G, was calculated as the slope of the least-squares regression line relating to the natural logarithm of glucose concentration to time between 10 and 19 minutes.

The acute insulin response to glucose (AIRg) was expressed as the area under the insulin curve above basal between 0 and 10 minutes. This variable was calculated using the trapezoidal method.

The product, $S_I \times$ AIRg, represents insulin-mediated glucose uptake, due to the hyperbolic relationship that exists between insulin sensitivity and β-cell function.[2] To maintain the same units, in this calculation the value of AIRg was divided by 10.

Assays

The plasma glucose level was measured in triplicate using a Hitachi (Barcelona, Spain) 737 autoanalyzer with a glucose oxidase method (intraassay and interassay CVs, 0.5% and 1.6%, respectively). The immunoreactive plasma insulin level was measured by radioimmunoassay using a commercial kit (ICN Pharmaceuticals, Costa Mesa, CA). Intraassay and interassay CVs were 7% and 11%, respectively.

Statistical Analysis

Data are shown as the mean ± SD. Normality was checked using the Shapiro-Wilk test. For comparisons, the nonpaired Student *t* test or the Mann-Whitney test were used as appropriate. For comparisons among subgroups, ANOVA or Kruskal-Wallis tests were used. The posthoc Bonferroni test was used for pair comparisons. Pearson's correlation coefficient and partial correlation coefficients were estimated. The influence on the K_G index of the variables studied was estimated using stepwise multiple correlation analysis. *P* less than .05 was taken to indicate statistical significance. Statistical analysis was performed with the software package SPSS (SPSS Inc, Chicago, IL).

RESULTS

Of 108 subjects, only 94 were included in the study. The other 14 were excluded either because their parameters did not meet the accuracy criteria previously established or because some of their parameters were negative. General characteristics of the 94 subjects are shown in Table 1. Table 2 shows the whole and sex-divided results for the intravenous glucose tolerance index, minimal model indices, and the insulin response to glucose during first-phase secretion. No significant differences were found between males and females in any variable studied or when comparing the standard FSIGT and the FSIGT modified with tolbutamide (8.42 ± 6.7 *v* $9.08 \pm 6.1 \times 10^{-5}$ min^{-1} $[pmol \cdot L^{-1}]^{-1}$, NS). When lean (body mass index [BMI] < 27 $kg \cdot m^{-2}$) and obese (BMI ≥ 27 $kg \cdot m^{-2}$) subjects were compared, obese subjects showed higher fasting plasma glucose and insulin levels and a higher AIRg than lean subjects, as well as a 42.2% reduction in S_I. However, no differences were found for intravenous glucose tolerance, GEZI, $S_I \times$ AIRg, or β-cell responsiveness to glucose (Table 3).

The next step was to divide the whole sample into tertiles according to the K_G index. Plasma glucose levels during the FSIGT test are illustrated in Fig 1. There is a stepped gradation in the age of the subjects studied, so those with the highest K_G were the youngest (Fig 2). No significant differences were found in basal glucose, basal insulin (100 ± 72 *v* 100 ± 70 *v* 79 ± 50 $pmol \cdot L^{-1}$, NS), S_I, or BMI. Nevertheless, as the K_G index decreased, a significant reduction in glucose effectiveness, AIRg, and $S_I \times$ AIRg was observed. These results persisted even when the division by tertiles according to K_G was made in lean and obese subjects separately (although in the case of age, these differences did not increase statistical significance in the lean group) (Table 4).

Table 1. General Characteristics of the Subjects (N = 94)

Characteristic	Mean ± SD	Range
Age (yr)	35.1 ± 11.2	19-55
Sex (M/F)	45/49	
Height (cm)	163 ± 0.09	147-180
Weight (kg)	79.8 ± 16.3	51-120
BMI ($kg \cdot m^{-2}$)	28.3 ± 5.7	18.3-41.3
Basal glucose ($mmol \cdot L^{-1}$)	5.06 ± 0.44	4.2-6.3
2-h plasma glucose ($mmol \cdot L^{-1}$)*	5.9 ± 0.8	4.3-7.7
Basal insulin ($pmol \cdot L^{-1}$)	93 ± 65	14-366

*Plasma glucose at 120 minutes after 75-g oral glucose tolerance test.

Table 2. Metabolic Variables of the Subjects

Variable	Males		Females		All	
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range
No. of subjects	45		49		94	
Basal glucose (mmol · L^{-1})	5.07 ± 0.5	4.3-6.3	5.06 ± 0.4	4.2-6.2	5.06 ± 0.44	4.2-6.3
Basal insulin (pmol · L^{-1})	94 ± 79	14-366	92 ± 56	19-251	93 ± 65	14-366
K_G index (min^{-1})	1.77 ± 0.8	0.62-4.43	1.60 ± 0.55	0.44-3.04	1.68 ± 0.68	0.44-4.43
S_I index ($\times 10^{-5}$ min^{-1} [pmol · L^{-1}]$^{-1}$)	9.05 ± 6.17	0.51-28.8	8.43 ± 6.57	1.46-38.5	8.75 ± 6.35	0.51-38.5
S_G index ($\times 10^{-2}$ min^{-1})	0.197 ± 0.08	0.05-0.41	0.177 ± 0.07	0.08-0.41	0.190 ± 0.07	0.05-0.410
GEZI ($\times 10^{-2}$ min^{-1})	0.144 ± 0.08	0.04-0.39	0.13 ± 0.08	0.03-0.35	0.14 ± 0.01	0.03-0.39
AIRg (pmol · L^{-1} · min)	4,918 ± 4,324	932-17,918	4,567 ± 2,925	774-13,207	4,754 ± 3,650	774-17,918
$S_I \times$ AIRGg (min^{-1})	0.033 ± 0.026	0.006-0.14	0.030 ± 0.017	0.005-0.068	0.031 ± 0.022	0.005-0.14
Φ_1 index ([pmol · L^{-1}]min^{-1}[mmol · L^{-1}])*	949 ± 584	131-3,285	832 ± 461	141-3,137	891 ± 525	131-3,285
Φ_2 index ([pmol · L^{-1}]min^{-2}[mmol · L^{-1}])*	4,923 ± 3,752	420-16,179	4,289 ± 2,963	733-13,178	4,608 ± 3,358	420-16,179

*n = 74.

When the whole sample was divided into tertiles according to age, there was a worsening of intravenous glucose tolerance accompanied by a lower AIRg and $S_I \times$ AIRg, with no appreciable difference in S_I and BMI as age increased (Table 5).

There was significant correlation between the K_G index and age ($r = -.42$, $P = .0001$), GEZI ($r = .52$, $P = .0001$), AIRg ($r = .40$, $P = .01$), and the suprabasal insulin effect ($r = .75$, $P = .00001$). The partial correlation study of different interrelated variables displayed similar correlation coefficients except for age, because the relationships observed with K_G disappeared due to the association of age with $S_I \times$ AIRg (Fig 3).

Afterward, stepwise multiple correlation analysis was performed using the K_G index as the dependent variable and age, GEZI, AIRg, and $S_I \times$ AIRg as independent variables. Only $S_I \times$ AIRg and GEZI exercised an effect on K_G index variation (multiple $r = .88$, $r^2 = .67$, $P < .01$; model, $K_G = 0.63 + 0.00025 \cdot [S_I \times AIRg] + 2.9 \cdot GEZ\ I$), $S_I \times$ AIRg being the first variable selected that alone explained 55% of K_G index variance, whereas combined with GEZI it explained 67% of K_G index variance. From the partial correlation study, the S_I index correlated negative and significantly with the BMI ($r = .45$, $P < .0001$). Also after analyzing the partial correlation coefficients, age correlated significantly only with the suprabasal insulin effect ($r = .48$, $P < .0001$).

Table 3. Comparison Between Lean (BMI < 27 kg · m^{-2}) and Obese (BMI ≥ 27 kg · m^{-2}) Subjects

Variable	Lean (n = 44)	Obese (n = 50)
Age (yr)	33 ± 11	38 ± 13
Sex (M/F)	25/19	20/30
BMI (kg · m^{-2})	23.3 ± 2.4	32.7 ± 3.8*
Basal glucose (mmol · L^{-1})	4.9 ± 0.4	5.2 ± 0.4†
Basal insulin (pmol · L^{-1})	57.4 ± 28.7	129.1 ± 71.7*
K_G index (min^{-1})	1.79 ± 0.7	1.58 ± 0.67
S_I index ($\times 10^{-5}$ min^{-1}[pmol · L^{-1}]$^{-1}$)	12.5 ± 7.0	5.3 ± 3.2†
S_G index ($\times 10^{-2}$ min^{-1})	0.184 ± 0.07	0.189 ± 0.07
GEZI ($\times 10^{-2}$ min^{-1})	0.133 ± 0.09	0.137 ± 0.08
AIRg (pmol · L^{-1} · min)	3,205 ± 1,922	6,037 ± 4,245*
$S_I \times$ AIRg (min^{-1})	0.036 ± 0.023	0.027 ± 0.020
Φ_1 index ([pmol · L^{-1}]min [mmol · L^{-1}])‡	758 ± 621	993 ± 584
Φ_2 index ([pmol · L^{-1}]min^{-2} [mmol · L^{-1}])‡	4,328 ± 3,911	5,815 ± 4,048

*$P < .0001$.
†$P < .01$.
‡n = 74.

DISCUSSION

The present study shows that the main factors that determine the worsening of intravenous glucose tolerance in nonelderly healthy subjects are a decrease in both the suprabasal insulin effect and GEZI. Moreover, the lowest suprabasal insulin effect observed in the group of subjects with worse glucose tolerance was the consequence of a lower AIRg. Our results also show that the impairment of insulin sensitivity alone, as observed in obese subjects, will not lead to glucose intolerance unless it is accompanied by inadequate insulin secretion for the degree of insulin resistance, and probably by a decrease in glucose effectiveness. Our findings suggest that one of the causes of worsening intravenous glucose tolerance could be age, via its influence on the suprabasal insulin effect.

These results concur with what has been published so far. In 1981, Bergman et al[21] found that subjects with low glucose tolerance ($K_G < 1.5$ min^{-1}) had a lower glucose effectiveness at basal insulin and a lower disposition factor ($S_I \times \Phi_2$) than subjects with high glucose tolerance ($K_G > 1.5$ min^{-1}). However, due to the small size of some subgroups of subjects studied (n = 3), the results were not absolutely conclusive. Later, using computer simulation, Bergman[1] raised the hypothesis that impairment of at least two of the above-mentioned factors was necessary to yield a decrease in the K_G index, placing great stress on the association of a decrease in both S_I and S_G indices. More recently, Kahn et al.[4] reported that the combined action of the suprabasal insulin effect and glucose effectiveness explained 72% of the K_G index variance, a figure similar to the 67% observed in our study. Although their study and ours are similar, there are some differences. Firstly, not all subjects included in their study exhibited normal oral glucose tolerance.[13] Secondly, because of the characteristics of stepwise multiple correlation analysis, their study cannot reveal the importance of β-cell impairment in the worsening of glucose tolerance, given that the correlation coefficient of the K_G index with AIRg was considerably lower than that found between K_G and $S_I \times$ AIRg. In our study, besides corroborating the findings of the above-mentioned studies, we stated, by division into

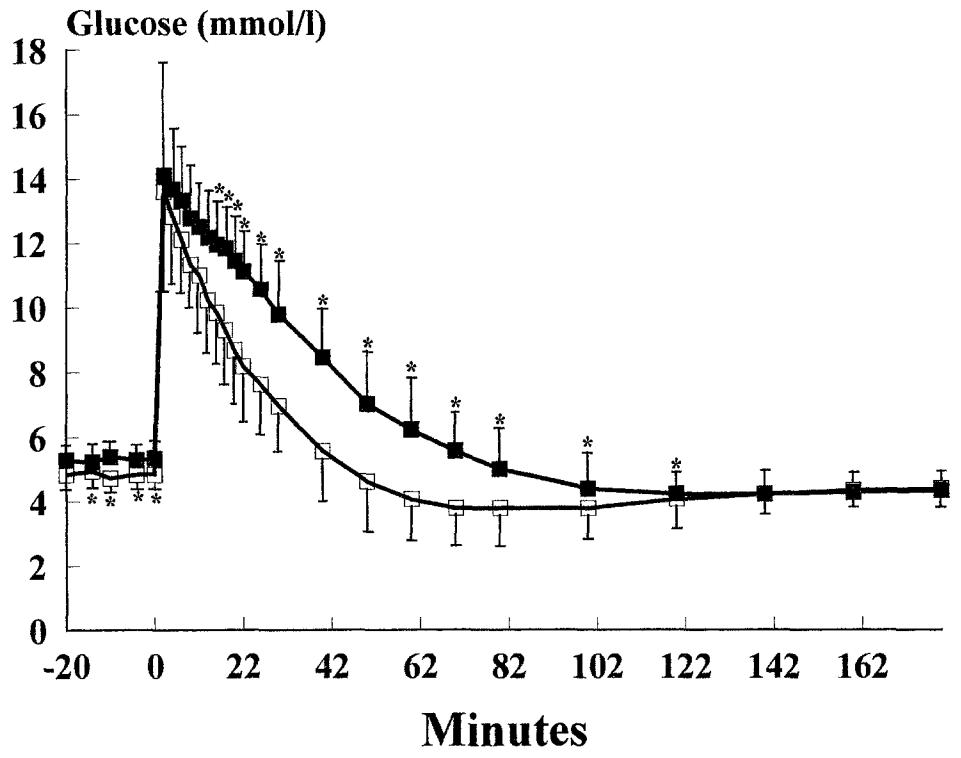

Fig 1. Glucose response during a FSIGT test in subjects with a K_G index > 1.82 min^{-1} [□] and <1.3 min^{-1} [■]. *$P < .05$. Values are the mean ± SD.

tertiles, that the main factor responsible for the decrease in the suprabasal insulin effect was lower insulin secretion, while insulin sensitivity did not change in the subgroups studied.

Our results confirm and expand those obtained by Kahn et al.[4] So, on one hand, they show that intravenous glucose tolerance depends fundamentally on the suprabasal insulin effect and GEZI but, on the other hand, that the worsening of glucose tolerance will be determined by an absolute or relative impairment in insulin secretion and by lower non–insulin-mediated glucose uptake. This means that given the hyperbolic relationship between insulin secretion and insulin sensitivity,[2] a subject with low first-phase insulin secretion can have a normal or high K_G index if their insulin sensitivity is high. For instance, during physical exercise,[22] improvement has been reported in glucose tolerance despite lower insulin secretion compared with an "at-rest" situation, due to an increase in both insulin

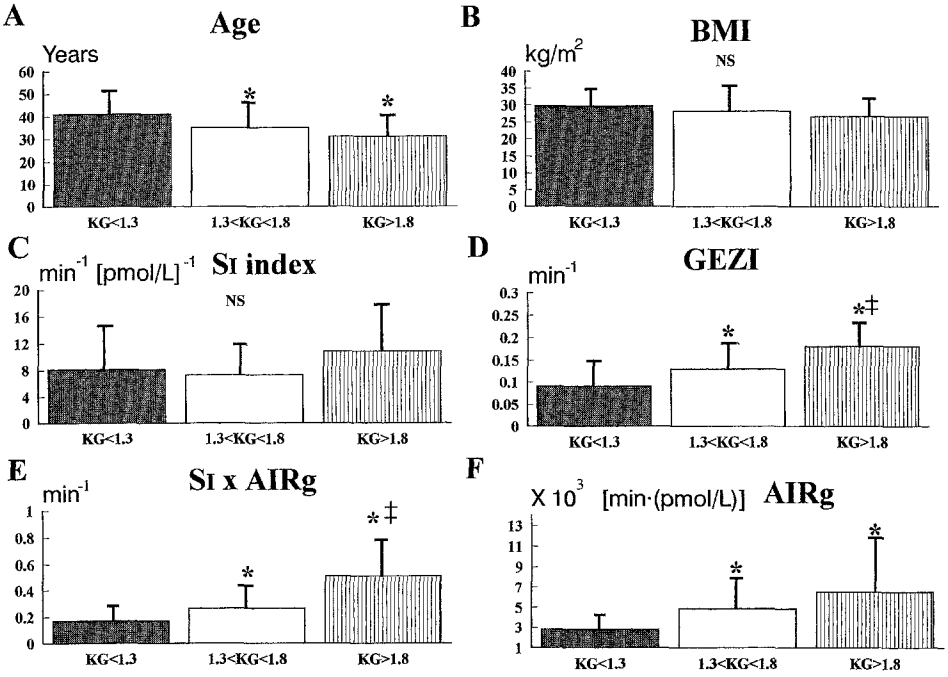

Fig 2. Age (A), BMI (B), S_I index (C), GEZI (D), S_I × AIRg (E), and AIRg (F) in the whole sample subdivided into tertiles according to the K_G index. Values are the mean ± SD. *$P < .05$ *v* K_G < 1.3 min^{-1}, ‡$P < .05$ *v* K_G 1.3 to 1.8 min^{-1}.

Table 4. Metabolic Variables for Lean and Obese Subjects Divided by Tertiles According to the K_G Index

Variable	Lean Subjects		Obese Subjects	
	Low Tertile	High Tertile	Low Tertile	High Tertile
No. of subjects	15	13	16	18
Age (yr)	37 ± 12	29 ± 10	46 ± 4	31 ± 9*
BMI ($kg \cdot m^{-2}$)	24.3 ± 2.4	22.4 ± 2.4	32.2 ± 3.9	33.4 ± 4.3
Basal glucose ($mmol \cdot L^{-1}$)	5.0 ± 0.4	4.7 ± 0.3	5.4 ± 0.5	5.0 ± 0.3
Basal insulin ($pmol \cdot L^{-1}$)	65 ± 36	50 ± 22	115 ± 73	130 ± 44
K_G index (min^{-1})	1.19 ± 0.1	2.5 ± 0.8*	0.94 ± 0.2	2.3 ± 0.6*
S_I index ($\times 10^{-5}\ min^{-1}[pmol \cdot L^{-1}]^{-1}$)	13.3 ± 9.3	14.3 ± 5.8	5.0 ± 3.3	6.4 ± 3.7
GEZI ($\times 10^{-2}\ min^{-1}$)	0.077 ± 0.007	0.20 ± 0.09*	0.098 ± 0.005	0.171 ± 0.06*
AIRg ($pmol \cdot L^{-1} \cdot min$)	2,194 ± 1,018	4,603 ± 2,588*	2,989 ± 1,205	8,919 ± 4,589*
$S_I \times$ AIRg (min^{-1})	0.023 ± 0.009	0.058 ± 0.029*	0.012 ± 0.005	0.045 ± 0.017*

*$P < .05$ *v* low tertile.

sensitivity and GEZI. In a similar way, a subject with marked insulin resistance will maintain normal glucose tolerance if the AIRg is high enough, as can be seen in our study (comparison between lean and obese subjects) and others.[6,21] However, it follows from the tertile division of the sample studied and from the comparison between lean and obese subjects that when an impairment of intravenous glucose tolerance exists, this will be secondary to inadequate insulin secretion for the degree of insulin sensitivity. Thus, for example, in obese subjects divided into tertiles according to K_G, the three subgroups had a similar degree of insulin resistance; however, the subjects with worse glucose tolerance had a significantly lower AIRg than those with the highest K_G. An identical pattern was observed in lean subjects, with the difference in this case being that as these subjects had higher insulin sensitivity than the obese subjects, the absolute AIRg values were lower than observed in the obese group. Others have obtained similar results. Taniguchi et al[6] found that obese subjects with IGT had similar insulin resistance but significantly lower insulin secretion than obese subjects with normal glucose tolerance, and an AIRg similar to that of lean control subjects (ie, inadequate insulin secretion for the degree of insulin resistance). The same group[5] reported that a subgroup of lean IGT subjects with a S_I index similar to that of lean controls with normal glucose tolerance exhibited a clear decrease in first-phase insulin secretion. The significant role of impaired first-phase insulin secretion in the development of IGT or diabetes mellitus is widely acknowledged.[8,23-27] In a recent study, Davies et al[27] observed that only subjects with persistent IGT had deficient insulin secretion compared with normal controls and subjects with transitory IGT. On the other hand, Haffner et al[28] have recently reported that both decreased insulin secretion and increased insulin resistance predict the development of IGT.

Table 5. Metabolic Variables for the Subjects Divided by Tertiles According to Age

Variable	Age (yr)		
	<25	25-44	>44
No. of subjects	30	36	28
BMI ($kg \cdot m^{-2}$)	27.3 ± 6.3	27.7 ± 6.2	28.9 ± 3.4
Basal glucose ($mmol \cdot L^{-1}$)	4.9 ± 0.4	5.1 ± 0.4	5.2 ± 0.5
Basal insulin ($pmol \cdot L^{-1}$)	100 ± 79	90 ± 57	91 ± 57
K_G index (min^{-1})	2.07 ± 0.8	1.61 ± 0.5*	1.41 ± 0.53*
S_I index ($\times 10^{-5}\ min^{-1}\ [pmol \cdot L^{-1}]^{-1}$)	5.32 ± 4.4	5.3 ± 2.9	5.32 ± 4.5
S_G index ($\times 10^{-2}\ min^{-1}$)	0.200 ± 0.07	0.200 ± 0.08	0.160 ± 0.07
GEZI ($\times 10^{-2}\ min^{-1}$)	0.150 ± 0.09	0.150 ± 0.08	0.110 ± 0.08
AIRg ($pmol \cdot L^{-1} \cdot min$)	6,639 ± 4,223	4,030 ± 3,886*	3,879 ± 2,280*
$S_I \times$ AIRg (min^{-1})	0.0037 ± 0.02	0.025 ± 0.014*	0.018 ± 0.012*

*$P < .01$ *v* the lower tertile.

Although obesity is considered a risk factor for the development of glucose intolerance, our results show that the degree of adiposity does not influence glucose tolerance, and that some defect in insulin secretion is also necessary to induce an impairment in glucose tolerance.

In our study, GEZI is the other factor for which intravenous glucose tolerance exhibits dependence, and it decreases gradually as K_G decreases. Decreased GEZI has been reported in subjects with IGT[5,6] and non–insulin-dependent diabetes mellitus (NIDDM).[29,30] A perusal of the available literature on the subject and our own results lead us to conclude that although glucose effectiveness is a factor that influences glucose tolerance in a decisive way,[4-6] its impairment is not essential in order to observe a decrease in the K_G index.[31,32] Nevertheless, it must be stressed that the association of the worsening of glucose tolerance with lower glucose effectiveness and lower insulin secretion is acknowledged in several studies.[15,33,34] Thus, administration of octreotide in normal subjects yields a decrease in the K_G index due to lower insulin secretion and GEZI with no perceptible change in insulin sensitivity.[15] On the other hand, in a study on dogs,[33] animals with transplanted autograft islets of Langerhans showed worse glucose tolerance, lower insulin secretion, and lower glucose effectiveness than control dogs, with insulin sensitivity being similar. That said, although it is generally accepted that insulin resistance is the primary defect in the genesis of NIDDM[35-37] and there are some studies reporting that subjects with a high risk to develop NIDDM did not show a decreased glucose effectiveness,[38-40] given the heterogeneity of NIDDM, it could be postulated, as suggested by Martin et al,[36] that in some groups of subjects reduced glucose effectiveness could contribute to glucose intolerance. So far, the causes of the impairment of glucose effectiveness are unknown. Even though it has been suggested that it could be related to an alteration in GLUT1,[5] expression of this glucose

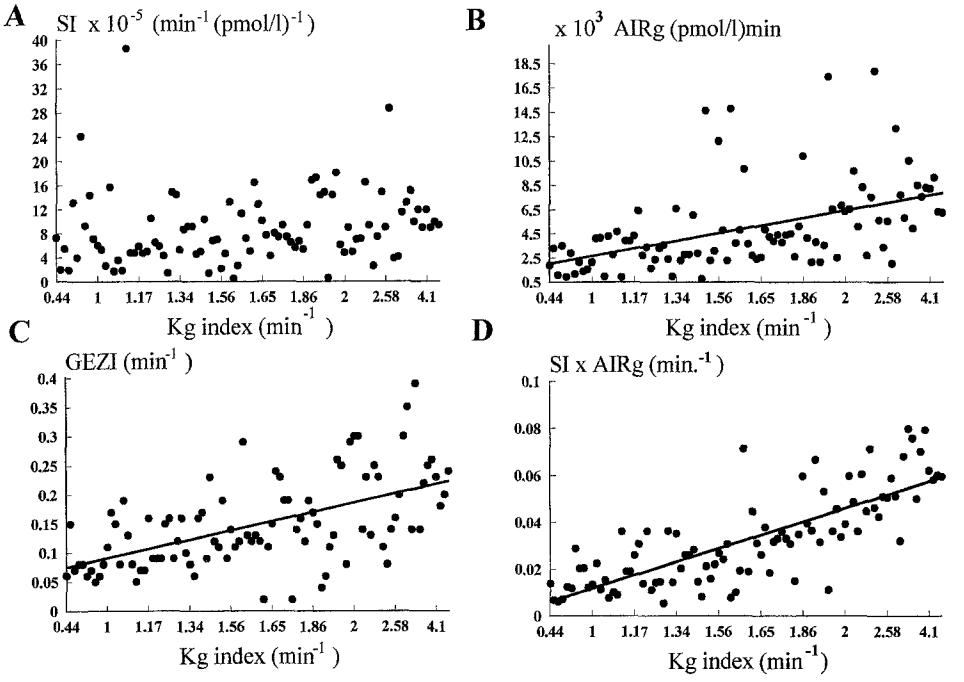

Fig 3. Relationship between the K_G index and S_I (A), AIRg (B), GEZI (C), and S_I × AIRg (D) in 94 subjects with normal oral glucose tolerance. The solid line depicts the best-fit relationship that was significant for AIRg (r = .4, P = .01), GEZI (r = .52, P = .0001), and S_I × AIRg (r = .75, P = .00001) but not S_I (r = .15, NS).

transporter in the muscle of patients with NIDDM, where glucose effectiveness is decreased, is normal.[41] Although, theoretically, GEZI also includes the effect of glucose suppression of hepatic glucose output, a recent study[42] has shown that S_G is independent of the sensitivity of the liver to suppression by glucose. Furthermore, neither does it seem related to a higher hepatic glucose output, because in subjects with IGT, where glucose effectiveness is also decreased, hepatic glucose production was found to be normal.[23] It has also been suggested that diet could influence glucose effectiveness.[43,44] Recently, Best et al[45] and Finegood and Tzur[46] have pointed out that the association of deficient insulin secretion and a reduced glucose effectiveness estimation could be due to insulin itself being a regulator of glucose effectiveness or to the glucose effectiveness estimation being distorted in subjects with a reduced insulin response. It has thereby been reported that the AIRg conditioned glucose effectiveness values, so that the minimal model overestimated S_G in normal dogs.[46] However, although caution must be exercised in the interpretation of differences in minimal model estimates of glucose effectiveness between subject groups with significantly different values for insulin secretory function, other studies in dogs[47] and humans[48] found similar values for both directly measured and minimal model–derived S_G. On the other hand, we have reported that during physical exercise, GEZI increased significantly despite a significant reduction of AIRg.[22]

In the present study, we report a negative correlation between age and intravenous glucose tolerance. This relationship is a consequence of an association between age and the suprabasal insulin effect, whereas age does not seem to have an influence on GEZI. Although the effect of aging on glucose tolerance is documented,[49,50] controversy persists about the cause of this association. It has been postulated that some changes in body composition,[51] diet,[52] or physical activity[53] associated with aging are responsible for the glucose impairment present in elderly people. Because these variables were not specifically evaluated in our study, we cannot specify their influence on the worsening of glucose tolerance with age observed in our sample. What is evident in our study is that age negatively influences glucose tolerance in nonelderly people, and this was secondary to lower insulin-mediated glucose uptake. Since we have not found any correlation between insulin sensitivity and age, it seems obvious that the cause of the lower K_G index in our oldest subgroup was insufficient insulin secretion, as others have reported.[54] The effect of age on glucose metabolism is controversial because many factors, apart from aging itself, might affect insulin sensitivity and insulin secretion. In our study, no significant differences were found among age subgroups for basal glucose, basal insulin, and BMI; however, we do not discount the possibility that other determinants that have not been specifically evaluated (body fat distribution and physical activity) might explain such differences.

In summary, intravenous glucose tolerance in healthy subjects is determined mainly by the suprabasal insulin effect and GEZI. The worsening of glucose tolerance depends on inadequate insulin secretion for the degree of insulin sensitivity and lower glucose effectiveness. Finally, age seems to influence the worsening of glucose tolerance through a lower suprabasal insulin effect, and the degree of adiposity seems not to affect carbohydrate tolerance.

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