Analysis of the Relationship Between Body Mass Index, Insulin Resistance, and Beta-Cell Function: A Cross-Sectional Study Using the Minimal Model

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The objective of our research was to identify the mathematical model that would best define the relationship between obesity, insulin resistance (IR), and β-cell function. Eighty-seven healthy subjects with a wide range of body mass index (BMI) were studied. Insulin sensitivity (IS) was calculated using Bergman's minimal model. Acute insulin response (AIRg) was calculated as the secretion of insulin during the first 10 minutes following a glucose bolus. IS × AIRg was used as an index of insulin-mediated glucose uptake (IMGU). The relationships among BMI, IS, fasting plasma insulin (FPI), and AIRg were studied in linear relationship terms and in terms of the hyperbolic function. Where the best fit was linear, the Jones and Molitoris method was used to investigate whether the 2-line fit was significantly better. The division of the population into BMI quartiles shows that from the third quartile, IS (12.4 ± 6.0 *v* 11.0 ± 6.4 *v* 4.8 ± 1.8 *v* 3.2 ± 2.0 E-5 $min^{-1}[pmol/L]^{-1}$, $P <$ .01) diminishes. Nevertheless, a plateau was established between the last 3 quartiles for IS × AIRg. AIRg related to BMI via a breakpoint of 29.3 kg · m^{-2}. The best fits for both the BMI/IS and BMI/FPI relationships were hyperbolic. Our data indicate that obesity represents a continuum of IR, with severity increasing as BMI increases. Nevertheless, above a value of 29 kg · m^{-2} and despite great increases in adiposity, IS tends to descend slowly. Moreover, there seems to be an IMGU threshold at a BMI value of approximately 27 kg · m^{-2}, above which an increase in adiposity leads to a greater fall in IS × AIRg. Furthermore, this threshold also appears to affect pancreatic response to a glucose stimulus.

OBESITY, a syndrome characterized by insulin resistance (IR) and hyperinsulinemia (in the fasting and glucose-stimulated state) has reached epidemic proportions in Westernized societies.[1-5] Clinical and epidemiologic interest is mainly focused on its association with different metabolic abnormalities that increase the risk of cardiovascular disease (type 2 diabetes mellitus, arterial hypertension, dyslipidemias, etc), with hyperinsulinemia, or underlying IR, postulated as the common link in these risk factors.[6] Moreover, epidemiologic studies relate obesity to cardiovascular mortality by means of a J-curve, with an inflection point at 26.5 kg · m^{-2} of the body mass index (BMI),[7] and the same relation is expected to be uncovered in cases of obesity and IR.[8]

In the last decade, more attention has been focused on the pattern of body fat distribution than on overall adiposity as the principal factor associated with the metabolic complications of obesity. However, as far as abdominal obesity is concerned, there is no agreement as to which component (subcutaneous or visceral adipose tissue) is more directly implicated in reduced IMGU in obese patients.[9,10] More recently, attention has been focused on the important role that intramuscular lipid deposits appear to play in the pathogenesis of obesity IR. It is as powerful a predictor as abdominal adipose tissue in explaining IR variations in the population at large.[11,12] These data would explain why the link between obesity and insulin sensitivity (IS) has not been completely clarified, with evidence in the literature for a linear relationship[13-17] and the existence of an obesity threshold beyond which IR manifests.[8] Moreover, it has been suggested that IS decreases progressively in line with obesity to a limit value beyond which greater levels of adiposity do not lead to significant increases in IR.[18-20] Thus, knowing how obesity is related to insulin resistance and the pancreatic β-cell function would help us to study and understand the physiopathologic mechanisms underlying the deterioration of glucose tolerance that usually accompanies the development of obesity.

The aim of our study was to characterize the relationship existing between obesity, IS, and β-cell function in a large population of subjects with normal oral glucose tolerance and a wide range of BMI.

MATERIALS AND METHODS

Our study was based on 87 healthy subjects (42 men and 45 women) with normal oral glucose tolerance[21] and no family history of type 2 diabetes mellitus, who were living a sedentary lifestyle; all were younger than 55 years of age and had a wide range of BMI (18.1 to 43.6 kg · m^{-2}). The subjects had been included as a healthy reference population in previous research by our team.[4,5,22-24] The female subjects were premenopausal and were studied during the follicular stage of the menstrual cycle. The purpose, nature, and potential risk of the study were explained before obtaining written consent from the subjects. This study was performed according to the ethical guidelines of the Declaration of Helsinki.[25]

The patients underwent a frequently sampled intravenous glucose tolerance test (FSIVGTT), with a 50% wt:vol dextrose bolus (300 mg/kg of weight) administered at time 0, with/without a subsequent tolbutamide infusion at minute 20 of the FSIVGTT (as described in previous research[4,22-24]). Insulin sensitivity (IS index, 10^{-5} · $min^{-1}(pmol \cdot L^{-1})^{-1}$) was calculated using the minimal model of glucose metabolism.[26,27] Using the trapezoidal method, glucose-stimulated insulin secretion was calculated as the area above the basal level enclosed by the insulin curve. The first secretion phase—acute insulin

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Table 1. Descriptive Statistics of the Studied Variables

	Mean ± SD	Range
Age (yr)	34 ± 1	19-54
BMI (kg/m^2)	28.7 ± 0.6	18.1-43.6
IS index ($10^{-5} \cdot min^{-1}$ [pmol · L^{-1}]$^{-1}$)	7.88 ± 6.03	0.52-31.95
Fasting insulin (pmol · L^{-1})	94 ± 62	14-328
AIRg (pmol/L · min)	3466 ± 3060	480-15,660
IS × AIRg ($10^3 \cdot min^{-1}$)	20.56 ± 17.91	1.34-94.72

response—included the first 10 minutes following the glucose stimulus (AIRg, pmol · L^{-1} · min). Insulin-mediated glucose uptake (IMGU) was identified with the insulin suprabasal effect, expressed as the product of IS and AIRg, given that both variables are related via a hyperbolic function in such a way that this product is an indicator of β-cell compensation for IR.[19]

The whole sample was divided into 2 groups (lean and obese subjects) on the basis of a BMI cut-off point of 27 kg · m^{-2}. We had chosen this cut-off for three reasons: (1) epidemiologic studies linked obesity to cardiovascular mortality about this cut-off;[7] (2) in Spain,[18] obesity could be defined by a BMI value of 27.5 kg · m^{-2}; and (3) a previous report had shown that this BMI cut-off was the threshold for the adverse effects of obesity on glucose metabolism.[8]

To study the interaction between BMI, IS, and pancreatic response to establish which model best explained the relationship between these variables, 3 models were investigated, namely, the linear relationship, the 2-line fit, and the hyperbolic function. The linear relationship was measured using the simple linear regression method. The hyperbolic function ($x \cdot y$ = constant) was defined as $\log(y) = -\log(x) + c$, since it has been suggested that a similar function determines the relationship between IS and the pancreatic β-cell response.[19] First, the 2-line fit was tested to determine whether it was an improvement on the linear relationship, and thus a breakpoint was defined, employing the Jones and Molitoris mathematical method,[29] as previously used by others.[8] Subsequently, the best linear/breakpoint relationship was compared with the hyperbolic relationship, and the generalized Wald test was applied to determine the best fit. This test gives us a tool to decide between 2 different generalized linear models. It has to be performed twice by changing the role of the null (H0) and the alternative (H1) hypothesis. Next we collected the 4 possible results (for technical details see Fahrmeir and Tutz[30]): H0 not rejected and H1 rejected, choice of H0; H0 rejected and H1 not rejected, choice of H1; H0 rejected and H1 rejected, both models rejected; and H0 not rejected and H1 not rejected, no conclusion possible.

The normal distribution of the variables was tested using the Kolmogorov-Smirnov test. When the variables did not follow a normal distribution the nonparametric statistic was employed. Statistical significance was considered as $P < .05$. Our data are presented as the mean ± SD. Confidence intervals were estimated using the bootstrap method. Statistical analysis was performed using the S-PLUS 2000 package (MathSoft Inc, Seattle, WA).

Table 3. Simple Correlations Between Metabolic Parameters and BMI Using a BMI Cut-Off Point of 27 kg · m^{-2}

	BMI <27 (n = 33)	BMI ≥27 (n = 54)
IS index	−0.03 (NS)	−0.51 ($P < .001$)
Fasting insulin	0.10 (NS)	0.56 ($P < .001$)
AIRg	−0.11 (NS)	0.50 ($P < .001$)
IS × AIRg	−0.15 (NS)	0.06 (NS)

RESULTS

For the metabolic variables studied, there were no significant differences between men and women, nor between the IS values calculated using the standard protocol and those modified by tolbutamide. The subjects were thus grouped into a single sample, representative of the healthy population at large.[4] Table 1 shows the distribution of subjects in respect to age, BMI, and the metabolic variables studied.

The first step in our study consisted of an examination of simple age and BMI correlations with the metabolic variables (IS index, fasting plasma insulin [FPI], AIRg, IS × AIRg). BMI correlated significantly with all of the variables. Age correlated with IS and with IS × AIRg, but after removing the influence of BMI, only the correlation with IS × AIRg was statistically significant ($r = -0.37$, $P < .01$). Once the effects of age were taken into account, BMI did not correlate significantly with IS × AIRg ($r = -0.11$, difference not significant [NS]).

The next step was to study the behavior of the metabolic variables when the population was divided into BMI quartiles ($Q_1 < 22.9$; $22.9 \le Q_2 < 29.1$; $29.1 \le Q_3 < 33.0$; $Q_4 \ge 33.0$ kg · m^{-2}). The results are described in Table 2. All were well-matched for sex. The age for the Q_1 sample was significantly lower than than that of the other quartiles. There was a significant decline in IS for Q_3, with an overall decrease of 75% from Q_1 to Q_4. Inversely, β-cell function increased in line with the degree of adiposity, to 62% for basal insulin and 52% for AIRg. Basal hyperinsulinemia and AIRg only differed significantly in Q_4 in comparison to the lower quartiles. The suprabasal insulin effect (IS × AIRg) decreased progressively as BMI increased, with a reduction of 48% for Q_2 and approximately 57% for Q_3 and Q_4.

Dividing the sample into lean and obese individuals on the basis of a BMI cut-off point of 27 kg · m^{-2}, it was observed that the 4 variables did not correlate significantly below the cut-off point, with the single exception of IS × AIRg, where there was a slight correlation above the threshold value (Table 3).

Table 2. Age and Metabolic Variable Differences Between BMI Quartiles

	BMI (kg/m^2)				
	Q1 (n = 21)	Q2 (n = 23)	Q3 (n = 21)	Q4 (n = 22)	*P*
IS index (10^{-5} min^{-1} · $pmol^{-1}$ L)	12.4 ± 6.0	11.0 ± 6.4	4.8 ± 1.8	3.2 ± 2.0	<.01
Fasting insulin (pmol · L^{-1})	63 ± 36	68 ± 46	91 ± 50	156 ± 71	<.01
AIRg (pmol · L^{-1} min)	2,707 ± 1,669	2,139 ± 1,174	3,056 ± 2,802	5,617 ± 4,272	<.05
IS × AIRg ($10^3 \cdot min^{-1}$)	33.1 ± 26.5	20.6 ± 12.3	12.6 ± 9.2	15.9 ± 13.1	<.05
Age (yr)	23 ± 1	36 ± 2	41 ± 2	36 ± 2	<.01

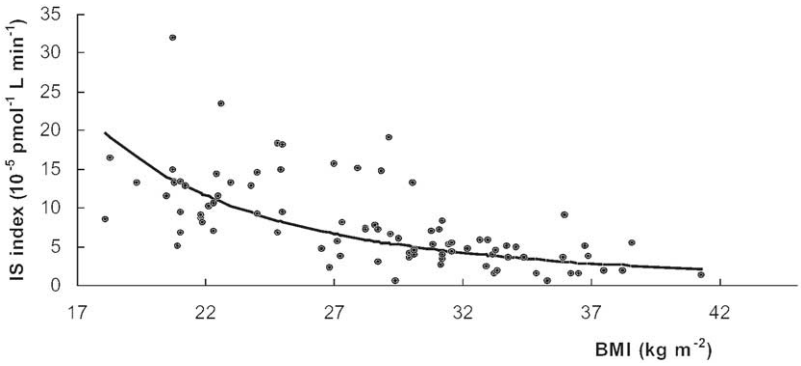

Fig 1. Hyperbolic relationships between BMI and insulin sensitivity in normal subjects with a wide BMI range. Equation: ln(IS) = −2.72 lnBMI + 10.86.

Fits

The model that best explained the relationship between BMI and IS was the hyperbolic fit defined by the equation ln (IS) = −2.72 ln(BMI) + 10.86 (Fig 1). The BMI versus fasting insulin connection was best explained by the hyperbolic function, ln(FPI) = −1.40 + 1.72 ln(BMI). Nevertheless, for the BMI versus AIRg relationship, the 2-line fit with a breakpoint at 29.3 kg · m^{-2} ($IC_{95\%}$, 24.7 to 32.7 kg · m^{-2}) (Fig 2) was significantly better than the linear or hyperbolic fits.

DISCUSSION

This work proves yet again that obesity is a state of insulin resistance with reactive hyperinsulinemia. The division of BMI into quartiles shows the IS graph to be the complementary image of the graph of the β-cell function, both basal and glucose-stimulated. The severe IR in the highest quartile (75% greater than in the first quartile) was accompanied by an increase in pancreatic response, both basal (+62%) and AIRg (+52%) but, as demonstrated via the suprabasal effect of the insulin, the increase in the β-cell response to glucose load did not reach the levels necessary to compensate for the severity of the IR. Our group has previously demonstrated that IMGU in fasting does not differ in lean control subjects and obese patients, since basal hyperinsulinemia is in fact compensatory.[5] Nevertheless, all of the obese patients included in the present study had normal oral glucose tolerance, supporting the hypothesis that a serious deterioration in a single regulatory glucose tolerance parameter (low IS in this case) is not sufficient in itself to produce glucose intolerance if the other metabolic parameters are normal or increased.[31]

Our data would suggest that obesity and IR are related by means of a hyperbolic function, given that beyond a BMI of 30 kg · m^{-2}, large increases in BMI are translated into small declines in IS. Our results show then that the relationship is not linear as suggested earlier.[13-17] Nor have we found evidence for the existence of an obesity threshold (breakpoint)—as suggested by Campbell and Gerich[8]—beyond which IR would become evident. For their IR index, Campbell and Gerich employed the insulin concentration, which produced the half-maximum glucose uptake, and not the rate of glucose disposition infused to maintain the euglucemia (M value) or the sensitivity index derived from the clamp (relationship of the M value to the insulin steady-state).[32] Therefore, we do not know how these variables respond to the level of adiposity. On the other hand, in our study the AIRg did produce a better 2-line fit, with a breakpoint at 29.3 kg · m^{-2} of BMI, and the BMI and AIRg variables were independent up to the breakpoint value and above this threshold they demonstrated a mild correlation ($r = 0.52$, $P < .001$), likewise when the classical obesity threshold of 27 kg · m^{-2} was employed.[7] Thus, although the finding of a new breakpoint has an important physiopathologic significance, we believe that the obesity threshold criterion of

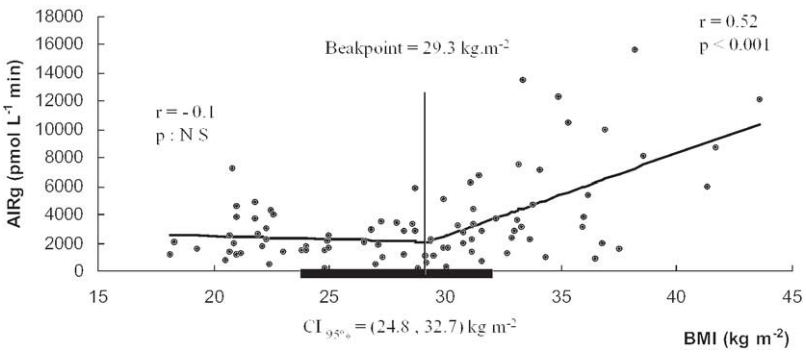

Fig 2. Two-line fit for the relationship between BMI and AIRg, with a breakpoint at 29.3 kg · m^{-2}.

BMI $\geq$ 27 kg · m^{-2} should be maintained, a belief that is reinforced by the fact that all the metabolic variables analyzed here (fasting insulin, IS index, AIRg, and IS ×AIRg) have proven themselves to be independent up to a BMI value of 27 kg · m^{-2}.

From the division of the BMI into quartiles it can be appreciated that, for IS above a value of approximately 29 kg · m^{-2}, increments in adiposity are not translated into significant decreases in IS ($Q_1 = Q_2 > Q_3 = Q_4$). This result is congruent with the existence of a breakpoint at 29.3 kg · m^{-2} for the BMI versus AIRg relationship. IMGU did not differ significantly in the 3 last quartiles ($Q_1 > Q_2 = Q_3 = Q_4$), and on dividing the population in terms of a BMI of 27 kg · m^{-2}, obesity did not correlate significantly with glucose uptake. This is hardly surprising given that intravenous glucose tolerance is 70% regulated by glucose effectiveness and the suprabasal insulin effect, without BMI contributing independently to the variation in glucose tolerance.[4,19] Moreover, the fact that IMGU does not differ significantly from the second to the fourth quartiles (average BMI of 26.4 kg · m^{-2} and 36.3 kg · m^{-2}, respectively) suggests that beyond a level of adiposity of about 27 kg · m^{-2}, increments are not associated with significant declines in IMGU.[18-20] These data are congruent with the finding of a breakpoint of 29.3 kg · m^{-2} for AIRg, in such a way that it can be inferred that the obese patient with normal glucose tolerance will increase pancreatic response in an attempt to overcome the reduced IMGU.

In our study, obesity per se explained about 40% of IR variation (r_2) but only 10% of IMGU variation. This low correlation between IMGU and BMI may be due to regional body fat distribution patterns, since it is known that android obesity is more significant than overall adiposity in the pathogenesis of IR and the metabolic complications that accompany obesity. Although our study has not measured the influence of abdominal obesity on the pathogenesis of IR, the relevance of our data is supported by other studies that show that intramuscular lipid deposits increase with obesity and are correlated negatively with IS,[11,12] with BMI as the anthropometrical variable that best correlates with the intramuscular triglyceride content.[12] Whatever the case, in studies that determine the content of abdominal fat via computed tomography, subcutaneous abdominal tissue only explains about 40% and visceral adiposity about 30% of the variation in IMGU.[9,10]

In conclusion, our data show the following: (1) obesity is a continuum of resistance to the action of insulin, with IR severity increasing in line with the BMI; nonetheless, above a BMI value of 29 to 30 kg · m^{-2} and despite significant increases in adiposity, IS tends to drop slowly; (2) there seems to exist an IMGU threshold, located at a BMI value of approximately 27 kg · m^{-2} and beyond which an increase in the level of adiposity does not lead to a greater fall in IMGU, at least when it is expressed as IS × AIRg; and (3) a pancreatic hyper-response to the glucose stimulus occurs beyond a BMI threshold located at about 29 kg · m^{-2}.

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