

# Antibodies against glutamic acid decarboxylase and indices of insulin resistance and insulin secretion in nondiabetic adults: a cross-sectional study

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**Background:** Autoimmunity against insulin-producing beta cells from pancreatic islets is a common phenomenon in type 1 diabetes and latent autoimmune diabetes in adults. Some reports have also related beta-cell autoimmunity to insulin resistance (IR) in type 2 diabetes. However, the extent to which autoimmunity against components of beta cells is present and relates to IR and insulin secretion in nondiabetic adults is uncertain.

**Aim:** To explore the association between antibodies against glutamic acid decarboxylase (GADA), a major antigen from beta cells, and indices of whole-body IR and beta-cell capacity/insulin secretion in adults who do not have diabetes.

**Methods:** We studied 81 adults of both sexes aged 30–70, without known diabetes or any autoimmune disease. Participants underwent an oral glucose tolerance test (OGTT) with determination of plasma glucose and insulin at 0, 30, 60, 90, and 120 minutes. From these results we calculated indices of insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR] and incremental area under the insulin curve [iAUCins]) and insulin secretion (corrected insulin response at 30 minutes and HOMA beta-cell%). GADAs were measured in fasting plasma using immunoenzymatic methods.

**Results:** We found an overall prevalence of GADA positivity of 21.3%, without differences by sex and no correlation with age. GADA titers did not change monotonically across quartiles of any of the IR or insulin secretion indices studies. GADA did not correlate linearly with fasting IR expressed as HOMA-IR (Spearman's  $r=-0.18$ ,  $p=0.10$ ) or postabsorptive IR expressed as iAUCins ( $r=-0.15$ ,  $p=0.18$ ), but did show a trend toward a negative correlation with insulin secretory capacity expressed by the HOMA-beta cell% index ( $r=-0.20$ ,  $p=0.07$ ). Hemoglobin A1c, body mass index, and waist circumference were not associated with GADA titers.

**Conclusion:** GADA positivity is frequent and likely related to impaired beta-cell function among adults without known diabetes.

**Keywords:** insulin resistance, autoimmunity, glutamate decarboxylase, latent autoimmune diabetes in adults, beta cell

## Introduction

Latent autoimmune diabetes in adults (LADA) is a distinct but heterogeneous clinical entity, characterized by the production of antibodies against insulin-producing pancreatic beta cells by the immune system, in a quantity sufficient to induce secretory dysfunction but insufficient to produce full-blown type 1 diabetes (DM1).<sup>1,2</sup> LADA patients are usually diagnosed at the initial stages of their disease as having type 2 diabetes, but their treatment rapidly progresses to become insulin-requiring.

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Additionally, their phenotype when compared to that of patients with type 2 diabetes (DM2) is characterized by a predilection for the female sex and Caucasian race, younger age, and less overweight.<sup>3</sup>

Islet autoimmunity is a complex and poorly understood process, in which the immune system ends up attacking components of the beta-cell membrane and cytoplasm. Autoimmunity may be due to molecular mimicry with viral antigens, or to impairment of regulatory mechanisms led by specific lymphocyte subpopulations that normally prevent self-reactive lymphocytes from unleashing an inflammatory reaction at the islet.<sup>4,5</sup> This process is very likely to start many years before the clinical onset of DM1 or LADA, and it is not known to what extent it is present in individuals who do not have explicit hyperglycemia and who do not have any manifestations of autoimmunity in other bodily systems. On the other hand, the involvement of beta-cell autoimmunity in the pathogenesis of diabetes may occur not only through impaired insulin secretion but also through insulin resistance (IR). Patients with LADA are more insulin resistant than DM2 patients,<sup>6</sup> and plasma titers of beta-cell autoantibodies are correlated with IR in first-degree relatives of patients with DM1.<sup>7</sup> Adolescents with DM1 had significantly decreased insulin sensitivity when compared to age-matched nondiabetic controls.<sup>8</sup> Nonetheless, the extent to which IR is associated with subclinical beta-cell autoimmunity in nondiabetic adults is basically unknown.

Given that IR and beta-cell autoimmunity share some common biological underpinnings (abnormal activation of the immune system and the inflammatory response), the exploration of autoimmunity against components of pancreatic islets among nondiabetic persons with different degrees of IR may reveal interesting phenomena related to the natural history of diabetes.<sup>9</sup> With this background, we measured a sensitive and specific marker of beta-cell autoimmunity (anti-glutamic acid decarboxylase antibodies [GADAs])<sup>10</sup> and explored the association of these titers with indices of IR and insulin secretion derived from an OGTT with insulin measurements in free-living adults with different degrees of body adiposity, who did not have a formal diagnosis of diabetes, and did not have any known autoimmune disease or process.

## Methods

### Study design

This is a cross-sectional study whose primary aim was to explore the association of autoimmunity against pancreatic beta cells (manifested as plasma titers of GADA) and various

indices that quantitatively assess IR. Secondary objectives were to explore the absolute frequency of detectable GADAs among individuals not known to have diabetes or any autoimmune disease and to correlate patient characteristics like sex, body adiposity, and chronic glycemic levels to levels of GADA.

### Patients

We included adults of both sexes aged 30–70 years, who were not known to have diabetes and who had no prior clinical or laboratory evidence of autoimmune conditions. The same applies to body mass index (BMI) and waist circumference. Exclusion criteria were known diabetes or autoimmune conditions, a prior diagnosis of cancer, chronic obstructive pulmonary disease or other major comorbidity, and use of antidiabetic drugs (e.g., metformin for the treatment of IR or polycystic ovary syndrome). As one of the secondary aims of the study was to explore the correlation between beta-cell autoimmunity and chronic glycemic levels, we had no exclusion criteria based on fasting glycemia or hemoglobin A1c (HbA1c).

### Sample size

For this exploratory study, we employed a convenience sample of 81 adults, while intentionally trying to include subjects of both sexes and diverse degrees of body adiposity. The purpose was to explore the association of beta-cell autoimmunity and IR in apparently healthy subjects of different characteristics, more than to extrapolate these findings to the general population.

### Participant evaluation

We evaluated all study participants after an overnight fast for weight, height, waist circumference, tetrapolar impedance (percent body fat, abdominal fat, lean body mass, and estimated bone mass), blood pressure, and heart rate. We inquired about medical conditions and concurrent medications, and performed a 5-point oral glucose tolerance test (OGTT). For the OGTT, participants were instructed to keep their normal diet and physical activity habits during the 3 days prior. Subjects arrived after a 8–14-hour fast and received 75 g of glucose dissolved in 300 mL water, which they had to drink in <5 minutes. Blood samples were collected in ethylenediaminetetraacetic acid-anticoagulated tubes at time points 0, 30, 60, 90, and 120 minutes, during which participants remained seated and did not smoke or ingest food or drinks. After separation of a small aliquot for HbA1c measurement, plasma was immediately separated,

aliquoted, a cocktail of protease inhibitors was added, and frozen at  $-80^{\circ}\text{C}$  for later analysis.

## Laboratory measurements

Blood glucose from the OGTT time points, creatinine, and a lipid panel were determined using standard colorimetric procedures (Biosystems, Spain). Anti-glutamic acid decarboxylase (anti-GAD65) antibodies were measured using a biotin-coupled sandwich ELISA (Kronus, ID, USA, CAT# KR7710), with an analytical sensitivity of 0.18 U/mL and functional sensitivity (the lowest level yielding an interassay coefficient of variation not  $>20\%$ ) of 4 U/mL. Absorbance was read at a wavelength of 450 nm according to the manufacturer's instructions. We measured plasma insulin at times 0, 30, 60, and 120 of the OGTT using a sandwich ELISA (Abcam, CAT# ab100578) with a functional sensitivity of 4  $\mu\text{UI/mL}$ . Absorbance for the insulin ELISA was also read at a wavelength of 450 nm according to the manufacturer's instructions. HbA1c was measured by the boronate affinity method,<sup>11</sup> using the NycoCard II<sup>®</sup> reader. This technique and manufacturer have been certified by the United States National Glycohemoglobin Standardization Program as traceable to the Diabetes Control and Complications Trial standard. All ELISA plates were read in a BioTek Synergy HT Reader<sup>®</sup>. All measurements were performed in duplicate, and positive and negative controls were ran within each batch. We executed all procedures at the Diabetes, Lipids and Metabolism laboratory of Universidad de los Andes.

## Variables

Using results from the OGTT, we calculated various indices of IR and insulin secretion,<sup>12</sup> namely:

1. Homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR): (fasting insulin [ $\mu\text{U/mL}$ ]  $\times$  fasting glucose [ $\text{mmol/L}$ ])/22.5): Higher values indicate higher IR, especially in the fasting state.
2. Incremental area under the insulin curve (iAUCins), calculated by the trapezoid method<sup>13</sup>: Higher values indicate higher IR, especially in the postabsorptive state.
3. HOMA of beta-cell function: (HOMA beta-cell%: (20 $\times$  fasting insulin)/(glucose [ $\text{mmol/L}$ ]  $-3.5$ ): Higher values indicate better overall insulin secretory capacity.
4. Corrected insulin response (CIR): 100 $\times$ 30 minutes insulin/(30 minutes glucose [ $\text{mg/dL}$ ]  $\times$  (30 minutes glucose [ $\text{mg/dL}$ ]  $-70$ ): Higher values indicate better early insulin secretion and beta-cell function.

## Statistical analyses

We analyzed the association between GADA titer and IR and secretion, expressed as the trend of mean GADA concentrations across quartiles of each IR or insulin secretion index. We also explored the correlations between GADA titer and predictors like sex, BMI, waist circumference, and HbA1c. We compared means of continuous variables between two independent groups using independent samples t-tests or Mann–Whitney *U*-tests for dependent variables that did not follow a normal distribution. Mean levels of GADAs across categories of HOMA-IR, iAUCins, CIR, and HOMA beta-cell% were compared using analysis of variance. We also performed a trend test to evaluate dose–response relationship between categories of each IR/secretion index and GADA. Linear correlations were estimated using Spearman's rank correlation coefficient. Categorical variables were compared between groups analyzed using Chi-square tests for independence.

## Ethical aspects

The protocol was approved by the Human Ethics Committee of Universidad de los Andes Committee. All research activities were conducted according to the principles expressed in the Declaration of Helsinki. All participants provided written informed consent.

## Results

### Characteristics of the study population

The study sample consisted of 81 mostly middle-aged adults (age  $51.4\pm 10.1$ ) and was well balanced by sex (56.7% female, 43.3% male). Average BMI was  $26.7\pm 4.1$ , without marked differences by sex. Percent body fat was much higher among women than men, while lean body mass and abdominal adiposity were higher among men than women (Table 1). According to HbA1c and OGTT criteria, 58% (47 individuals) of study participants were completely normoglycemic, while 42% had fasting plasma glucose  $\geq 100$  mg/dL, 2-hour plasma glucose  $\geq 140$  mg/dL, or HbA1c  $\geq 5.7\%$ .

### Anti-GAD antibodies

GADA titers ranged between  $<0.18$  and 8.07 U/mL. The overall prevalence of positive GADA ( $\geq 5$  U/mL) was 21.3%, without differences by sex (women 20.0%, men 22.9%;  $p=0.72$ ). Among participants positive for GADA, the mean titer was 6.03 U/mL, with no significant differences by sex (women  $6.32\pm 1.1$ , men  $5.70\pm 0.67$ ;  $p=0.18$ ). Age was not correlated with GADA (Spearman's  $r=0.02$ ,  $p=0.82$ ).

**Table 1** Characteristics of the study population

	Women (n=46)	Men (n=35)	Total (n=81)
Age (years)	52.2±8.6	50.4±11.7	51.4±10.1
Weight (kg)	64±10.4	78.7±13.2	70.4±13.8
Height (cm)	156.9±5.9	168.6±7.8	161.9±8.9
Body mass index (kg/m <sup>2</sup> )	26±4.1	27.6±4	26.7±4.1
Percent body fat (%)	34.7±5.8	26.4±6.2	31.1±7.3
Waist circumference (cm)	82.3±10.5	95.1±11.6	88.2±12.7
Systolic blood pressure (mmHg)	115.2±14.1	121.7±16.6	118±15.4
Diastolic blood pressure (mmHg)	70±18.2	73.2±16.2	71.4±17.3
Fasting plasma glucose (mg/dL)	94.3±11.5	98.1±6.6	95.9±9.8
Glycated hemoglobin A1c (%)	5.5±1.6	5.6±1.1	5.5±1.4
Serum creatinine (mg/dL)	0.73±0.12	0.92±0.17	0.81±0.17
Total cholesterol (mg/dL)	211±52.5	182.8±38.1	198.8±48.7
Triglycerides (mg/dL)	153.2±84	156.4±68.2	154.6±77.1
High-density lipoprotein cholesterol (mg/dL)	47.8±11.3	39±11.9	44±12.3
Low-density lipoprotein cholesterol (mg/dL)	134.8±46.4	112.6±41	125.2±45.2
Anti-glutamic acid decarboxylase antibodies (U/mL)	4.39±1.15	4.31±0.88	4.36±1.04

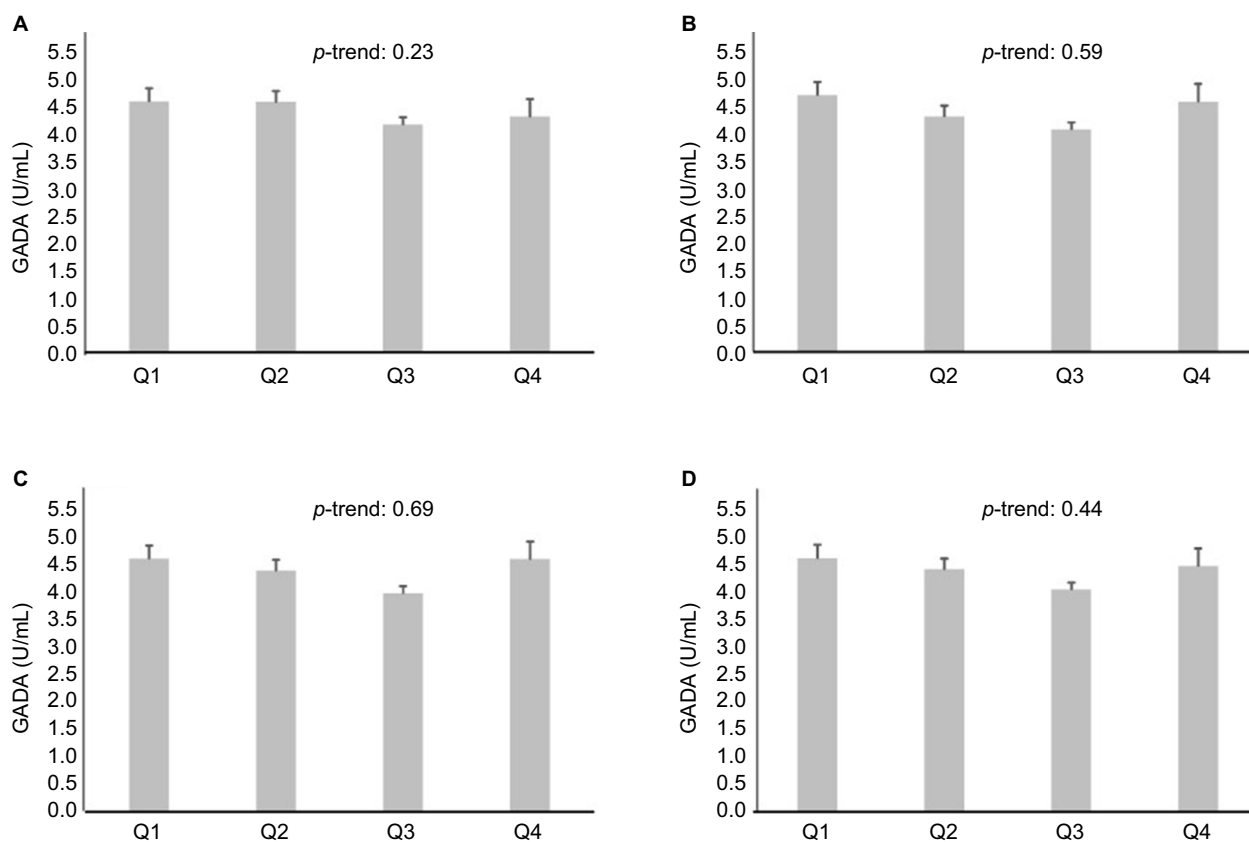
**Note:** Data are mean±SD unless indicated otherwise.

## Association between GADA and IR/secretion

GADA titers did not change monotonically across quartiles of any of the IR or insulin secretion indices studies (Figure 1). GADA titers did not correlate linearly with IR expressed as iAUCins (Spearman's  $r: -0.15, p=0.18$ ) or HOMA-IR ( $r=-0.18, p=0.10$ ). GADA titers were not linearly associated with early insulin secretion expressed as the CIR ( $r=-0.18, p=0.12$ ), but did show a trend toward a negative correlation with insulin secretory capacity expressed by the HOMA-beta cell% index ( $r=-0.20, p=0.07$ ).

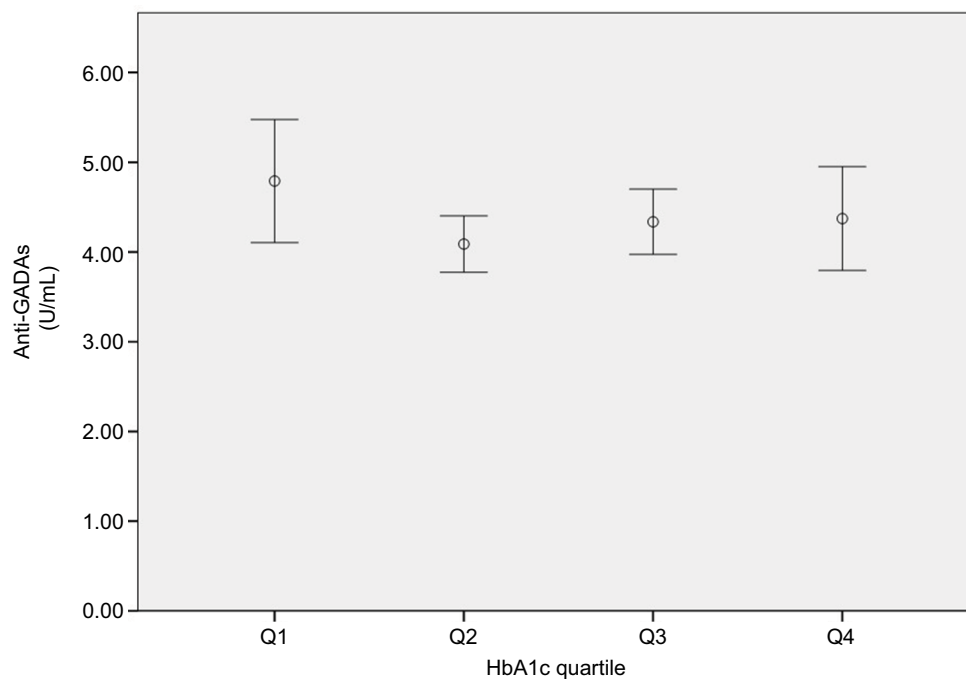
## Other predictors of GADA

We did not find an association between chronic glycemic levels expressed as quartile of HbA1c and GADA titers (Figure 2). Likewise, we found no association between BMI category (normal, overweight, or obese) and anti-GAD immunity (Figure 3). Central body fat accumulation, expressed as waist circumference, was also not significantly related to positivity for GADA (Figure 4).



**Figure 1** Mean GADA titers across quartiles of IR indices (HOMA-IR [A]) and incremental area under the insulin curve [B]) and insulin secretion indices (corrected insulin response [C] and HOMA-beta cell% [D]). Error bars represent standard deviations.

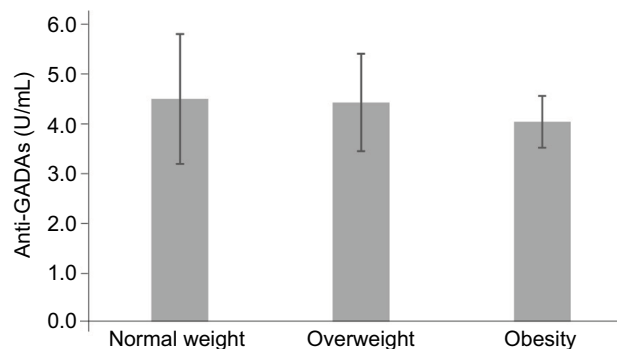
**Abbreviations:** GADA, glutamic acid decarboxylase antibody; HOMA-IR, homeostasis model assessment-insulin resistance.



**Figure 2** Mean GADA titers across quartiles of HbA1c.

**Notes:** Error bars represent standard deviations, *p*-value from analysis of variance: 0.25.

**Abbreviations:** GADA, glutamic acid decarboxylase antibody; HbA1c, hemoglobin A1c.



**Figure 3** Mean GADA titers across categories of body mass index.

**Note:** *p*-value from analysis of variance: 0.46.

**Abbreviation:** GADA, glutamic acid decarboxylase antibody.

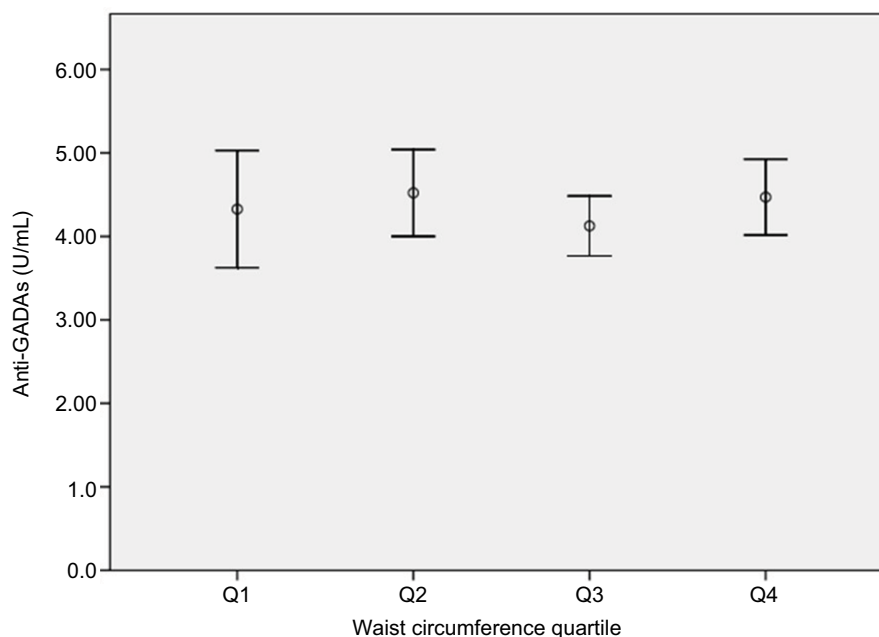
## Discussion

In this exploratory, cross-sectional study, we examined the levels of antibodies against GAD65, a major antigen in beta cells in a sample of individuals not known to have diabetes or any autoimmune disorder. The potential role of autoimmunity in the early pathogenesis of metabolic disturbances via involvement in insulin secretory dysfunction or IR is poorly understood, so an approach toward the detection of immunity before the development of frank hyperglycemia or other alterations may reveal clues in this direction.

We were surprised to find such a high prevalence of detectable GADA (21.3%), because this serological evidence has been documented mostly among patients with

autoimmune diabetes or stiff-man syndrome.<sup>14–18</sup> We must highlight, however, that all of these positive results were of a low titer (below 10 U/L), but still well above the analytical and functional sensitivities of the technique (0.18 and 4 U/L, respectively).<sup>19</sup> In the control group of a study of beta-cell autoimmunity among children with thyroiditis, the prevalence of GADA was 3.8%,<sup>20</sup> while in first-degree relatives of patients with DM1 the prevalence has been 10.1%.<sup>21</sup> Higher prevalence of GADA in nondiabetic adults (40.4%) have only been reported among workers exposed to polychlorinated biphenyl products.<sup>22</sup> Similar prevalences have only been found for Indian patients with DM2.<sup>23</sup> Whether the high prevalence of GADA among nondiabetics that we found is related to genetic or environmental exposure-related factors will need to be elucidated in further studies. Despite accumulated prior evidence showing that autoimmune diabetes and other autoimmune disorders tend to be more prevalent among females,<sup>24</sup> we found no difference in either positivity for the antibodies, or in their average levels, by sex. Similarly, age had no relationship with GADA titers.

We found no relationship between beta-cell autoimmunity and IR, measured by an index focused on the fasting state (HOMA-IR) or one focused on the postabsorptive state (iAUCins). A study in Asian patients with adult-onset diabetes found greater IR among GADA-positive patients.<sup>25</sup> Thus, it is possible that GADA positivity is related to IR



**Figure 4** Mean GADA titers across quartiles of waist circumference.

**Note:** *p*-value from analysis of variance: 0.46.

**Abbreviation:** GADA, glutamic acid decarboxylase antibody.

only in the context of overt diabetes, but not in normal or prediabetic individuals. It is remarkable that we did observe a trend toward impaired insulin secretory function expressed as HOMA beta-cell% with higher titers of GADA. Thus, it is possible that the autoimmune process leading to any sort of dysglycemia starts very early in the pathogenesis, and that beta-cell autoimmunity contributes to deterioration of beta-cell function in an important fraction of people who develop diabetes later on.

Indicators of body adiposity or regional fat distribution showed no association with beta-cell autoimmunity. This runs in accordance with our findings related to IR indices, and with the prevailing view that GAD65 autoimmunity clusters with adipose dysfunction, central obesity, and IR only in patients with overt diabetes, but not before its appearance.<sup>26</sup>

The main limitations of our study are its modest sample size, and its cross-sectional nature, which does not allow to prospectively follow the evolution of glucose metabolism among GADA-positive participants. However, the fact that GADA positivity is frequent and likely related to impaired beta-cell function in adults without diabetes suggests that autoimmunity plays a relevant role in the pathogenesis of diabetes, more so in certain populations.

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## Disclosure

The authors report no conflicts of interest in this work.

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