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Original Article

# Glutamic acid decarboxylase auto-antibodies prevalence among patients with type 2 diabetes mellitus and their clinical characteristics in a sample of the Egyptian population

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## Abstract

**Background**

Patients with latent autoimmune diabetes in adults may develop early loss of β-cell mass. They are often misdiagnosed as having type 2 diabetes mellitus (T2DM). This is because latent autoimmune diabetes in adults condition does share characteristics of both type 1 and T2DM.

**Aim**

To estimate the prevalence of unrecognized cases with glutamic acid decarboxylase auto-antibodies (GADA) among patients with T2DM in a sample of the Egyptian population, describing their clinical and laboratory features, and investigating the relationship with chronic complications of diabetes.

**Settings and design**

A total of 1515 Egyptian patients previously diagnosed as having T2DM were divided into two groups based on presence versus absence of GADA. Demographic and clinical characteristics were compared.

**Patients and methods**

Patients were selectively admitted according to clear criteria after informed consent and approval of the Ethics Committee. Patients underwent comprehensive history taking and examination. Laboratory investigations included blood chemistry, C-peptide, and GADA.

**Statistical analysis**

Data were analyzed using SPSS.

**Results**

Overall, 12.8% of patients with T2DM were GADA positive, showing lower C-peptide levels ($P < 0.001$). GADA-positive patients with T2DM demonstrated a positive correlation of GADA levels with central obesity ($r = 0.175$; $P = 0.015$) and systolic blood pressure ($r = 0.171$; $P = 0.018$). Moreover, a negative correlation with cardiovascular diseases ($r = -0.0175$; $P = 0.015$) was observed.

**Conclusion**

Prevalence of GADA among patients with T2DM in the analyzed sample was 12.8%, which agrees with the findings in other populations. These patients had lower C-peptide levels. GADA measurements are recommended in patients with T2DM with low C-peptide levels, especially in newly diagnosed patients, to help identify positive cases and initiate early insulin treatment to help preserve β-cell function and decrease the risk of long-term complications.

**Keywords:** Glutamic acid decarboxylase auto-antibodies, latent autoimmune diabetes in adults, type 2 diabetes mellitus

## Introduction

Diabetes is one of the most common metabolic disorders in many developing countries and in most developed

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countries [1]. The International Diabetes Federation has identified Egypt as the ninth leading country in the world for the number of patients with type 2 diabetes mellitus (T2DM). Its prevalence in Egypt has almost tripled over the past two decades [2].

Diabetes is a complex disease, and type 1 and type 2 clinical classification does not capture the range of diseases included in the diagnosis [3]. The common form of T2DM is a combination of insulin resistance and progressive loss of β-cell function. On the contrary, type 1 diabetes mellitus (T1DM) is usually the result of complete or near-complete destruction of β-cells mediated by autoimmunity. Latent autoimmune diabetes in adults (LADA), a less recognized and underdiagnosed manifestation of diabetes mellitus (DM), appears to affect adults with many T2DM characteristics but with a high risk of progression of insulin dependence [4]. Although the American Diabetes Association and WHO do not recognize LADA as a separate entity, it is included within T1DM classification [5,6]. LADA-affected patients are often misdiagnosed and treated as patients with T2DM [7].

Three main diagnostic criteria for LADA that have been established by the Immunology of Diabetes Society, include the following: (a) adult age of onset (>30 years), (b) any autoantibody islet cell presence, and (c) no insulin requirement for at least 6 months after the diagnosis [8]. Currently, glutamic acid decarboxylase auto-antibodies (GADA) is thought to be the most sensitive and specific biomarker in the diagnosis of LADA [9]. Being the most frequent islet autoantibody, many studies recommended that detection of GADA alone is sufficient when screening for patients with LADA, and that measurement of other islet auto-antibodies are not advisable [10]. Multicenter studies in Europe, North America, and Asia showed that 4–14% of patients with T2DM were positive for islet cell auto-antibodies that were diagnosed with LADA [11]. Furthermore, the prevalence of GADA-positive subgroup of adult patients initially diagnosed with T2DM together with additional criteria of no exogenous insulin during the first 6–12 months was 25% in patients under 35 years and between 4 and 13% in patients over 35 years at the diagnosis in populations of European origin [12].

As the prevalence of diabetes in Egypt has been observed to be remarkably high, the prevalence of LADA in this population is expected to be high, and very little work has been done in the context of LADA in the Egyptian population. The primary aim of this study was to estimate the prevalence of GADA positivity in Egyptian patients with T2DM and to describe their clinical and laboratory features and its relationship with chronic complications of diabetes.

## Patients and methods

This study was carried out between 2016 and 2018 comprising 1515 Egyptian patients previously diagnosed as having T2DM. They comprised 1304 females and 211 males. They were divided into two groups based on presence versus absence of GADA. The study was approved by the responsible ethics committee. In addition, written informed consent was obtained from each participant, before their inclusion in the study.

### Inclusion criteria

Inclusion criteria included patients with T2DM aged between 35 and 70 years old diagnosed according to the criteria of the American Diabetes Association [5]. They were receiving insulin treatment after an initial period of at least 6 months following the diagnosis of T2DM, during which noninsulin modalities of treatment had been sufficient to achieve adequate glycemic control.

### Exclusion criteria

Exclusion criteria were patients with T1DM, known history of thyroid disease, pregnancy, unstable cardiac disease, renal impairment, liver cirrhosis, and malignancies.

All patients were subjected to proper history taking, including duration of DM, current treatment, family history of DM, and other comorbidities. Anthropometric measurements, included BMI, calculated as weight in kilograms/height in square meters, and waist circumference, a validated simple noninvasive central adiposity surrogate, which was measured as the midpoint between the lowest rib and the iliac crest.

They were all subjected to standard physical examination for chronic complications of diabetes and cardiovascular risk factors and diseases. The prevalence of hypertension was defined as systolic blood pressure (BP) of at least 140 mmHg and/or diastolic BP of at least 90 mmHg and/or current treatment with BP-lowering drug (s) prescribed for treating high BP. Peripheral neuropathy was achieved as positive when vibration sense by a 128-Hz vibration fork at both hallux was absent, combined with a disturbed 10 g Semmes–Weinstein monofilament test and absent ankle reflexes. The retinopathy diagnosis was based on fundoscopy by an ophthalmologist after pharmacological mydriasis. Nephropathy was diagnosed by moderately albumin excretion in urine (>30 mg albumin/24 h) by albumin/creatinine ratio estimation. Regarding macroangiopathy, coronary artery disease has been concluded retrospectively from medical history (myocardial infarction, angioplasty, stenting, revascularization and/or substantial angiographically confirmed coronary stenosis) and systematic evaluation of all procedures, screening (exercise testing, echocardiography), or subclinical disease imaging data in the patient's documentation. Peripheral artery disease has been identified in Doppler ultrasonography and/or angiography through a well-recorded medical history of lower-limb claudication and/or clinical or imaging evidence of ischemic diabetic foot, angioplasty, stenting, revascularization, and/or significant lower-limb artery stenosis. Stroke was defined according to the criteria of the UK Prospective Diabetes Study, that is, any neurological deficiency with symptoms or signs lasting for at least 1 month, with no diffidence made among ischemic, embolic, and hemorrhagic strokes.

### Sample collection and laboratory analysis

From each patient, 8 ml of venous blood was withdrawn and divided into three sample tubes after (12–14 h) overnight fasting. First 4 ml was put in a serum separator tube for blood chemistry and was left to clot. Serum was rapidly separated by centrifugation at 3000 rpm for 10 min. It was tested for fasting blood glucose and lipid profile [total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-c), and low density lipoprotein cholesterol] by using BT 3500, Clinical Chemistry, Turbidimetric and ISE analyzer (Rome, Italy; Alfa Diagnostic (Biotecnica Instruments, Rome, Italy). The second 2 ml was put in a separate EDTA vacutainer for glycated hemoglobin (HbA1c) analysis by HPLC technique using D-10 HPLC ion exchange chromatography (BioRad, Hercules, California USA); Afak el Mostakbal Company, Cairo, Egypt). The last 2 ml was put in a serum separator tube and was left to clot. Serum was separated after centrifugation for 15 min at 3000 rpm. Serum was stored at –80°C until analysis of GADA and C-peptide levels by commercially available enzyme-linked immunosorbent assay (ELISA) technique according to manufacturer's instructions. GADA levels were determined with a ELISA assay based on microplate wells coated with human recombinant glutamic acid decarboxylase isoform (DRG International Inc., Springfield, New Jersey USA); *http://www.drg-international.com*). GADA value were read as follows: negative less than 1.00 U/ml, positive more than 1.050 U/ml, and indeterminate 1.00–1.050 U/ml (borderline). Borderline samples were retested, and they still had borderline values, another sample was taken for reanalysis. The DRG C-peptide ELISA kit is a solid-phase ELISA, based on the principle of competitive binding for quantitative assay. A random urine sample was collected in a sterile cup for measurement of micro-albumin and creatinine (A/C) in urine and calculation of micro-A/C ratio by using ARCHI TECT 8000 chemistry analyzer (Abbott, USA; Al-Kamal Company, Cairo, Egypt).

### Statistical analysis

Data were analyzed using the IBM program SPSS 20.0 Package (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± SD and compared using *t*-test when normally distributed, and as median and range using Mann–Whitney *U*-test when not normally distributed. Categorical data were represented as frequencies (%). The differences in frequencies of categorical parameters were analyzed by $\chi^2$-test. Correlations were done using Pearson's correlation coefficient test (*r*) or Spearman's coefficient. *P* values less than 0.05 were considered statistically significant.

## Results

This study was conducted on 1515 Egyptian patients with T2DM, with an age range of 35–70 years, attending the outpatient clinic during the study period; they included 1304 (86%) females and 211 (14%) males. Of these patients, 1321 were GADA negative, representing 87.2%, and 194 were GADA positive, representing 12.8%.

Demographic and laboratory characteristics of the GADA negative in comparison with GADA positive patients with T2DM are mentioned in Table 1. Regarding age, duration of diabetes, BMI, waist circumference, and diastolic BP, no statistically significant differences were observed between the two groups ($P = 0.409$, 0.235, 0.072, and 0.763, respectively). The systolic BP in the GADA-negative group was significantly higher than in the GADA-positive group ($P = 0.022$). Regarding fasting blood glucose, HbA1c, total cholesterol, TG, low-density lipoprotein, HDL, and A/C ratio, there was no statistical significant difference ($P > 0.05$), but a highly statistical significant difference between the two groups in C-peptide level was noted ($P < 0.001$).

Furthermore, according to sex, there was no statistically significant difference between females and males in

**Table 1: Demographic and laboratory characteristics of the glutamic acid decarboxylase auto-antibodies negative in comparison with glutamic acid decarboxylase auto-antibodies positive among type 2 diabetes mellitus patients**

| Parameters | GADA Negative [*n*=1321 (87.2%)] (mean±SD) | GADA Positive [*n*=194 (12.8%)] (mean±SD) | *P* |
|---|---|---|---|
| Age (years) | 48.8±7.3 | 49.3±8.6 | 0.409 |
| Duration (years) | 13.4±8.2 | 12.7±6.5 | 0.235 |
| BMI (kg/m$^2$) | 32.2±6.0 | 33.0±6.0 | 0.072 |
| Waist (cm) | 109.6±12.8 | 109.9±12.0 | 0.763 |
| Systolic BP (mmHg) | 130.9±15.2 | 128.3±13.6 | 0.022* |
| Diastolic BP (mmHg) | 80.2±8.2 | 79.1±7.7 | 0.093 |
| FBS (mg/dl) | 243.2±95 | 252.8±101.4 | 0.271 |
| HbA1c (%) | 9.6±1.9 | 9.7±1.9 | 0.749 |
| Cholesterol (mg/dl) | 219.8±39.4 | 223.3±39.7 | 0.289 |
| TG (mg/dl) | 177.6±95.9 | 161.4±82.2 | 0.071 |
| LDL-c (mg/dl) | 134.8±37.7 | 135.7±38.5 | 0.621 |
| HDL-c (mg/dl) | 45.0±10.2 | 44.5±10.2 | 0.512 |
| A/C | 96.3±212.9 | 101.7±234.0 | 0.691 |
| C-peptide (ng/ml) | 2.0±1.7 | 1.3±1.9 | <0.001* |

A/C, albumin/creatinine ratio; BP, blood pressure; FBS, fasting blood sugar; GADA, glutamic acid decarboxylase auto-antibodies; HbA1c, glycated hemoglobin; HDL, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; TG, triglycerides. *Statistically significant.

GADA-negative and GADA-positive groups ($P$ = 0.377). Moreover, regarding age (≥50 and <50 years), BMI (underweight, normal and overweight groups), and central obesity (normal and central obesity), there was no statistically significant differences between the two groups ($P$ = 0.409, 0.539, and 0.371, respectively), as shown in Table 2.

Moreover, Table 3 showed no statistically significant differences between both groups regarding clinical presentations of diabetic microvascular and macrovascular complications [nephropathy, retinopathy, peripheral neuropathy, cardiovascular diseases (CVD), peripheral vascular diseases, and stroke ($P$ > 0.05)].

Considering the correlation between GADA and demographic and laboratory data in GADA-positive patients with T2DM, no statistically significant correlation was observed between GADA and age, sex, duration of diabetes, BMI, and diastolic BP ($P$ > 0.05), but a positive correlation was noted with central obesity ($r$ = 0.175; $P$ = 0.015) and systolic BP ($r$ = 0.171; $P$ = 0.018). Regarding laboratory results, no statistically significant correlation was observed ($P$ > 0.05; Table 4).

More interesting, the correlation between GADA-positive patients with T2DM and the clinical presentations of diabetic microvascular and macrovascular complications revealed a negative correlation with CVD ($r$=−0.0175; $P$ = 0.015; Table 5).

## Discussion

Although sufficient data are available on the prevalence of diabetes in the Middle East, little is known about the characteristics of autoimmune diabetes in this area [13]. Knowledge of pathophysiology and the characteristics of the disease is extremely important to implement general preventive strategies and to treat diabetes-affected patients correctly, so that safe and effective therapies are possible [14]. Data from randomized clinical trials demonstrated the importance of an early initiation of insulin therapy in LADA avoiding the use of secretagogues [15].

The main finding of this study is the prevalence of GADA-positive patients, representing 12.8% (194 of 1515 Egyptian patients with T2DM) of the patients enrolled in the study. This is within the range cited in similar studies in European countries, where ~4–14% of patients classified with T2DM have diabetes-associated auto-antibodies, and the GADA frequency is high in northern European studies (7–14% with decreasing prevalence as patient age increases) [16]. Results from the Norwegian Nord-Trondelag Health (HUNT) study showed that of 1049 patients with T2DM, 106 (10.1%) were positive for GADA [17]. Moreover, this prevalence was found to be comparable with other studies. In the UK Prospective Diabetes Study group (25), which measured GADA and ICA at the diagnosis of diabetes in a representative population of 3672 White patients with T2DM (aged between 25 and 65 years), 361 (9.8%) were positive [18]. In BOTNIA study in Finland, of 1122 patients with T2DM, only 104 (9.3%) were found to have those auto-antibodies [19]. In action LADA 7, they consecutively studied 6156 European diabetic patients attending clinics within 5 years of diagnosis (age range: 30–70 years), and 541 (8.8%) had GADA [11].

**Table 2: Comparison between glutamic acid decarboxylase auto-antibodies negative and glutamic acid decarboxylase auto-antibodies positive among type 2 diabetes mellitus patients as regards different categories of demographic characteristics**

| Parameters | GADA negative ($n$=1321) [$n$ (%)] | GADA positive ($n$=194) [$n$ (%)] | $P$ |
|---|---|---|---|
| Sex | | | |
| Female | 1141 (86.4) | 163 (84.0) | 0.377 |
| Male | 180 (13.6) | 31 (16.0) | |
| Age (years) | | | |
| ≥50 | 769 (58.2) | 119 (61.3) | 0.409 |
| <50 | 552 (41.8) | 75 (38.7) | |
| BMI | | | |
| Underweight | 8 (0.6) | 0 | 0.539 |
| Normal | 115 (8.8) | 18 (9.3) | |
| Overweight | 1198 (90.6) | 174 (90.7) | |
| Central obesity | | | |
| Normal | 98 (7.5) | 19 (9.7) | 0.371 |
| Central obesity | 1223 (92.5) | 175 (90.3) | |

GADA, glutamic acid decarboxylase auto-antibodies.

**Table 3: Comparison between glutamic acid decarboxylase auto-antibodies negative and glutamic acid decarboxylase auto-antibodies positive among type 2 diabetes mellitus patients as regards clinical presentation of diabetic complications**

| Parameters | GADA negative ($n$=1321) [$n$ (%)] | GADA positive ($n$=194) [$n$ (%)] | $P$ |
|---|---|---|---|
| Nephropathy | | | |
| No | 1097 (83.0) | 163 (84.0) | 0.200 |
| Yes | 224 (17.0) | 31 (16.0) | |
| Retinopathy | | | |
| No | 1191 (90.1) | 177 (91.1) | 0.657 |
| Yes | 130 (9.9) | 17 (8.9) | |
| PN | | | |
| No | 164 (12.4) | 25 (13.0) | 0.824 |
| Yes | 1157 (87.6) | 167 (87.0) | |
| CVD | | | |
| No | 1074 (81.4) | 164 (84.5) | 0.159 |
| Yes | 247 (18.6) | 30 (15.5) | |
| PVD | | | |
| No | 1281 (97.0) | 189 (97.5) | 0.251 |
| Yes | 40 (3.0) | 5 (2.5) | |
| Stroke | | | |
| No | 1302 (98.6) | 191 (98.5) | 0.896 |
| Yes | 19 (1.4) | 3 (1.5) | |

CVD, cardiovascular diseases; GADA, glutamic acid decarboxylase auto-antibodies; PN, peripheral neuropathy; PVD, peripheral vascular diseases.

**Table 4: Correlation between glutamic acid decarboxylase auto-antibodies with demographic and laboratory characteristics among glutamic acid decarboxylase auto-antibodies positive type 2 diabetes mellitus patients**

| Parameters | GADA positive T2DM | |
|---|---|---|
| | *R* | *P* |
| Age (years) | 0.067 | 0.354 |
| Sex | −0.135 | 0.060 |
| Duration (years) | 0.50 | 0.495 |
| BMI (kg/m$^2$) | 0.014 | 0.851 |
| Central obesity | 0.175 | 0.015* |
| Systolic BP (mmHg) | 0.171 | 0.018* |
| Diastolic BP (mmHg) | 0.047 | 0.517 |
| FBS (mg/dl) | −0.011 | 0.879 |
| HbA1c (%) | −0.089 | 0.217 |
| Cholesterol (mg/dl) | 0.142 | 0.062 |
| TG (mg/dl) | 0.061 | 0.403 |
| LDL-c (mg/dl) | 0.100 | 0.172 |
| HDL-c (mg/dl) | 0.135 | 0.061 |
| A/C | −0.056 | 0.444 |
| C-Peptide (ng/ml) | 0.054 | 0.459 |

A/C, albumin/creatinine ratio; BP, blood pressure; FBS, fasting blood sugar; GADA, glutamic acid decarboxylase auto-antibodies; HbA1c, glycated hemoglobin; HDL, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus; TG, triglycerides. *Statistically significant.

**Table 5: Correlation analysis between glutamic acid decarboxylase auto-antibodies with clinical presentation of diabetic complications among glutamic acid decarboxylase auto-antibodies positive type 2 diabetes mellitus patients**

| Parameters | GADA positive T2DM | |
|---|---|---|
| | *R* | *P* |
| Nephropathy | −0.086 | 0.237 |
| Retinopathy | 0.009 | 0.902 |
| PN | −0.037 | 0.610 |
| CVD | −0.0175 | 0.015* |
| PVD | 0.097 | 0.181 |
| Stroke | 0.075 | 0.303 |

CVD, cardiovascular diseases; GADA, glutamic acid decarboxylase auto-antibodies; PN, peripheral neuropathy; PVD, peripheral vascular diseases; T2DM, type 2 diabetes mellitus. *Statistically significant.

Moreover, LADA and CARDS reported that out of 2425 European patients with presumed T2DM, 173 patients (7.1%) had GADA [20]. Similarly, in Bulgarian Population, the prevalence of positive diabetes-associated auto-antibodies among patients diagnosed with T2DM is 10.16%, and GADA were the main positive autoantibody [21]. Interestingly, in Saudi Arabian patients with T2DM, 8 of 99 patients were GADA positive (8%) [22].

However, in Southern Europe, Asia, and North America, it appears to be lower (4–6%). In 2007, it was found that out of 4250 consecutive patients with T2DM, 4.5% had either GADA and/or IA-2As [12]. Moreover, in a 2010 study, the screening of 5568 patients with T2DM for GADA identified 276 (5%) LADA patients [23]; another study in North America and Europe demonstrated that of 4134 patients with T2DM, 174 (4.2%) had GADA [24]. In Asia, the LADA China study revealed that of 4880 patients with T2DM, 5.9% had GADA. Furthermore, within China, the prevalence was lower in the south than the north [25]. Similarly, in Japan, it was concluded that GADA was detected in 188 (3.8%) of the 4980 diabetic patients tested [26], whereas the prevalence in the Korean population ranged from 4.4 to 5.3% [27].

The global variance in the frequency of autoantibody positivity in patients with T2DM could be primarily owing to differences in the study design, selection criteria, study entry duration, ethnicity, and sensitivity and specificity of autoantibody assay. Furthermore, increasing T2DM prevalence in some populations could affect the frequency of autoantibody positivity in these patients [28]. In fact, the three criteria that are conventionally used to define LADA are nonspecific, namely, age at diagnosis, autoantibody positivity, and insulin treatment. Adult age definitions range from 15 to 30 years, up to 70 years. Autoantibody criteria are lacking in specificity even in the best laboratories because they are based on auto-antibodies associated with T1DM in childhood that lack 100% specificity [29]. The definition of positive autoantibody is not clear, and various cutoff points have been applied in various studies. Technically, it is possible to limit false positives by setting a higher cutoff or retesting positive results. In longitudinal studies, the autoantibody status changes over time [30]; moreover, most patients are positive for only one type of autoantibody, the loss of existing auto-antibodies and the development of others may be a different scenario. The fluctuating status of the autoantibody is still not fully understood, and the clinical significance of borderline positivity remains unsettled [31].

Regarding sex, in this study, no statistically significant difference was observed between females and males, which is not consistent with other studies that reported a higher female prevalence in the GADA-positive patient group [32–34]. When comparing between GADA-negative and GADA-positive patients with T2DM regarding demographic and laboratory characteristics, only systolic BP in the GADA-positive group was significantly lower than in the GADA-negative group ($P = 0.022$). Many studies identified that patients with LADA generally have a better metabolic profile than those with T2DM, with lower BMI, waist-to-hip ratios, BP, and triglyceride and higher HDL-c levels [11,12,25,35], which is not in accordance with results of this study. Furthermore, considering the correlation between GADA and demographic and metabolic profile in GADA-positive patients with T2DM, a positive correlation was noted with central obesity and systolic BP. The study findings were consistent with the Swedish and Norwegian records of increased risk of autoimmune diabetes associated with overweight and obesity [36]. On the contrary, a negative correlation was observed in the Korean population

between GADA levels and onset age, BMI, total cholesterol, triglycerides, and C-peptide levels, whereas HbA1c and HDL-c showed a positive correlation [27].

Regarding HbA1c, patients with autoimmune diabetes tend to have worse glycemic control despite increased use of insulin than patients with T2DM HbA1c (>6.9%) [20,37]. The study results showed no statistically significant difference between HbA1c mean levels in GADA-positive and GADA-negative groups of patients. In agreement, the LADA China study reported that this difference was not evident [25]. Another study found that early insulin therapy does not appear to improve control [38]. This study regarding C-peptide level showed that it was significantly lower in the GADA-positive T2DM ($P < 0.01$). Similarly, in the HUNT study, GADA positivity was found to be associated with decreased C-peptide fasting in adult patients with noninsulin-requiring diabetes [17]. In Italian patients, an inverse relationship was reported between GADA and C-peptide levels [39]. The fact that patients with autoimmune diabetes require insulin treatment more frequently and earlier after diagnosis than those with GADA-negative T2DM may be explained by that the low-grade inflammation and typical of visceral adiposity in obese patients with genetic susceptibility to T2DM, could trigger a low-grade autoimmune process marked by auto-antibodies positivity, resulting in loss of function of β-cell and impairment of insulin secretion [25]. On the contrary, in two large studies, insulin secretion was similar in recently diagnosed patients with autoimmune diabetes and T2DM [24,40]. However, data from studies with the available new, second-line antidiabetic drugs suggested that the loss of B-cell function could be postponed [41,42].

Concerning chronic microvascular complications of diabetes, there was no difference in the prevalence of nephropathy, retinopathy, and neuropathy between GADA-positive and GADA-negative patients with T2DM in this study. Similar to these results, there were no differences in the prevalence of microvascular complications in South Korea [27]. The Fremantle Diabetes Study's analysis of longitudinal data showed less frequency of albumin excretion in urine in newly diagnosed patients with LADA than in patients with T2DM. In addition, a reduced risk of developing albumin excretion in urine during the follow-up period (<5 years) was associated with GADA positivity [43]. Another cross-sectional study confirmed that in Chinese patients with LADA, nephropathy and retinopathy rates were lower than in patients with T2DM [44]. This observation, however, was only evident for people with a disease duration of less than 5 years [45]. Accordingly, studies evaluating patients with T2DM with a duration of disease more than 5 years who were positive for GADA had equal or even higher rates of microvascular complications than those who were negative for GADA [20]. Furthermore, studies investigating diabetic neuropathy have shown that neuropathy is generally more prevalent in LADA than in T2DM [27,45], except for a study by Baum *et al*. [46]. These findings, however, could be explained by the fact that chronic exposure to hyperglycemia with late diagnosis can ultimately lead to microvascular complications in patients with T2DM.

Finally, regarding macrovascular complications, no difference in the prevalence of coronary heart disease, peripheral artery disease, and stroke was observed between the two groups in this study. A negative correlation between GADA and CVD was also revealed in this results. Most studies have found that patients with LADA have lower central adiposity, a healthier lipid profile, and lower BP than patients with T2DM [11,35]. In such patients, these factors collectively suggest a lower risk of macrovascular complications. This results matched those of the BOTNIA study that did not identify statistically significant differences between LADA and T2DM in coronary heart disease, stroke, overall cardiovascular morbidity, and mortality [47], similar results have been achieved by other independent studies [43], whereas the HUNT2 study showed that GADA-positive patients had a similar risk of cardiovascular disease and ischemic heart disease as GADA-negative patients with T2DM [48]. However, this is not fully explained by hyperglycemia, suggesting that the development of cardiovascular disease is based on a different pathophysiological mechanism. This hypothesis warrants further investigation of the potential pathways of autoimmune diabetes atherogenesis irrespective of the metabolic profile [49].

## Conclusion

This study showed 12.8% prevalence of positive diabetes-associated auto-antibodies namely GADA among patients with T2DM in the analyzed sample of the Egyptian population, which agrees with the already revealed findings concerning some other populations. In daily practice, this means that we can measure GADA in patients with early T2DM, and in the case of positive antibodies, an earlier start of insulin treatment is often needed. Future large-scale studies, including all types of auto-antibodies, will bring more light into the field of autoimmune diabetes. A personalized approach to medicine is most likely required to achieve optimal metabolic control and preserve β-cell function. This is associated with a lower risk of long-term diabetic complications and helps improve these patients' quality of life.

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### Conflicts of interest

There are no conflicts of interest.

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