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RELATIONSHIP BETWEEN AGE AT DIAGNOSIS AND GLUTAMIC ACID DECARBOXYLASE ANTIBODY IN NON-OVERWEIGHT/OBESE DIABETIC PATIENTS: A CROSS-SECTIONAL COHORT STUDY

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ABSTRACT

To evaluate the association between age at diagnosis, duration of diabetes, and the positivity of glutamic acid decarboxylase antibody (GADA) in non-overweight/obese diabetic individuals. A cross-sectional study including 284 non-overweight/obese diabetic patients at Hue Central Hospital was carried out from August 2017 to August 2019. All patients underwent a blood test to measure the level of GADA. GADA positivity was determined when GADA concentration was higher than 5 IU/mL. Clinical data included age, sex, weight, and height. Age at diagnosis was obtained from the patients. Data were analyzed using SPSS version 16.0. Non-overweight/obese diabetic patients with positive GADA (n=22, 7.7%) were younger at the onset of diabetes (52.4±14.1 versus 59.8±12.8 years, p=0.0103) and had a similar disease duration (8.0±6.9 versus 7.1±6.0 years, p=0.5048), as compared with negative GADA patients. The cut-off of age at diagnosis for detecting the risk of GADA positivity in non-overweight/obese diabetic individuals was 57. The rate of GADA positivity was 2.7 times higher in the age group of under 57 years at diagnosis compared to that in the older group. GADA measurement is a useful tool in the diagnosis of diabetes in non-overweight/obese diabetic individuals.

1. Introduction

The International Diabetes Federation released new figures that highlight the alarming growth in the prevalence of diabetes around the world; that if there is no effective measure to prevent disease progression, by 2040, the number of people with diabetes worldwide will reach 642 million (1,2).
The age at diagnosis of diabetes is also a predictor factor for the presence of GADA. We found that the recommended age as a cut-off point for detection/diagnosis of type 2 diabetes with positive autoantibodies depends on the proportion of type 1 diabetes in the general population. For the white race, the rate of autoimmune diabetes with positive autoantibodies is higher than for other races, so the cut-off point for type 2 diabetes screening has lower autoantibodies. The rate of autoimmune diabetes with positive autoantibodies among Asians is assessed to be lower than the white race, so an age dependent cut-off point at diagnosis of diabetes is recommended to be higher (3-5).
Therefore, we aim to evaluate the association between age at diagnosis and the level of GADA in non-overweight/obese diabetic individuals.

2. Material and methods

Study population

We consecutively enrolled in a cross-sectional study of 284 non-overweight/obese diabetic patients admitted to Hue Central Hospital from August 2017 to August 2019. This study was approved by the ethics committee of Hue Central Hospital. Informed consent was obtained from all patients.
Inclusion criteria were:
1) Patients were diagnosed with diabetes according to The American Diabetes Association (6).

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2) Body mass index (BMI) < 23 (non-overweight and non-obesity).
3) Age at diagnosis of ≥ 35 years.
The patients with a history of gestational diabetes mellitus were excluded.

Data collection

The clinical data included: age at diagnosis of diabetes, duration of the disease, sex, weight and height of the patients. The BMI was calculated and classified according to the World Health Organization in 2000 for Asian people (Table 1).

The quantified variable GADA was investigated by the ELISA analyzer at the Department of Biochemistry, Hue Central Hospital with the reference value shown in Table 2.

Classification	BMI
Underweight	< 18.5
Normal	18.5- 22.9
At-risk of obesity	23- 24.9
Obese 1	25-29.9
Obese 2	≥ 30

Table 1. BMI classification by the World Health Organization in 2000, as it applies to Asia (7).

GADA value (IU/mL)	Result
<5.0	Negative
≥5.0	Positive

Table 2. GADA reference value (each laboratory should establish its reference values).

Statistical analysis

Data were analyzed using SPSS version 16.0 and Medcalc. Continuous variables were presented as a mean and standard deviation and compared by the ANOVA test. Categorical variables were expressed as numbers and percentages and compared using the Chi-square test.

To find the cut-off age between the two groups of GADA (positive and negative group), the receiver operating characteristic (ROC) curves were analyzed. Then, we divided the patients into two groups according to the age dependent cut-off value, as mentioned above, and compared the rate of GADA positivity between those two groups. It was considered significant in all statistical tests at the 5% level of significance if the *p*-value was less than 0.05.

3. Results

In our cohort, the GADA was positive in 22 out of the 284 cases. The mean of age at diagnosis in the GADA-negative group was significantly higher than that in the positive group (59.8 ± 12.8 years vs. 52.4 ± 14.1 years, p = 0.0103); while the duration of diabetes was not different between the two groups (as shown in Table 3). The age of 57 years was found to be the cut-off point compatible with negative GADA. It resulted in a sensitivity of 64.5% and a specificity of 63.6% (Figure 1). The rate of GADA positivity was 2.7 times higher in the group aged under 57 years compared to that in the older group (Table 4).

	Positive GADA (n=22)	Negative GADA (n=262)	p-value
Age at diagnosis (years)	52.4±14.1	59.8±12.8	0.0103
Duration of diabetes (years)	8.0±6.9	7.1±6.0	0.5048

Table 3. Comparison of age at diagnosis between two groups of diabetic patients with positive and negative GADA.

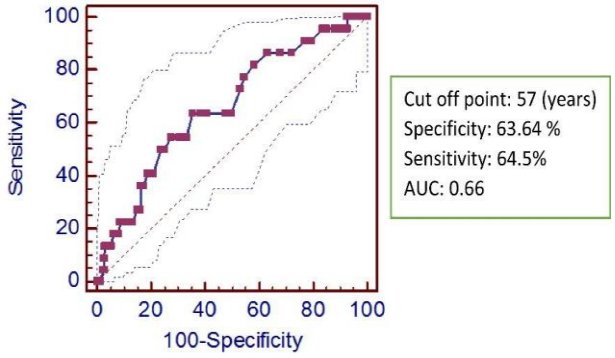

Figure 1. The receiver operating characteristic curve of age at diagnosis with the area under curve (95% confidence interval) AUC = 0.66. 57 years of age was found to be the cut-off point compatible with negative GADA where the Youden index was maximum (Youden index = 1).

Age group	Positive GADA (n=22)	Negative GADA (n=262)	Odd ratio/ p-value
< 57 years (n=53)	8 (15.1%)	45 (84.9%)	OR=2.7 (CI 95%:1.09-6.95= p=<0.05
≥ 57 years (n=231)	14 (6.1%)	217 (93.9%)	

Table 4. The rate of GADA positivity for the age diagnosis under 57 years old.

4. Discussion

The age during detection of diabetes is also a predictor factor of the presence of GADA. In our study (Table 1), the average age at diagnosis of diabetes in positive GADA patient groups was lower than for patients with negative GADA, the difference was statistically significant (p <0.05). In a study in Vietnam, the average age at diagnosis of diabetes with positive GADA (51.6 ± 12.6 years) was higher than that of patients with negative GADA (51.2 ± 11.4 years), the difference was not statistically significant (p> 0.05) (8).

The age at diagnosis of diabetes in the group of patients with positive GADA earlier than the negative group was 7.39 years. This result was larger than that in another study in Vietnam where patients with positive GADA started the disease earlier than the negative group with 4.04 years, but this difference was not statistically significant (9).

Meanwhile, Khanh's study noted that the difference in age of disease detection between two groups was insignificant and not statistically significant (8).

There was no consensus on the age at which autoantibodies should be screened in the population of diabetic patients. Zimmet suggested the age of 25 to detect type 2 diabetes with a positive autoantibody (10).

Many other authors had proposed the cut-off point for the detection of type 2 diabetes with positive autoantibodies was over 35 years old because it overlaps with the detection of classic type 1 diabetes between 25-35 years of age (11-13). The Immunology of Diabetes Society had estimated that the minimum cut-off point for the age of detecting type 2 diabetes with positive autoantibodies varies between 25-40 years old and suggests 30 years old was the average age in detecting type 2 diabetes with positive autoantibodies (14).

In contrast, in the Asian race, Zhou noted that the age at diagnosis of diabetes with positive autoantibodies in China is less than 40 years old in order to avoid overlap with the classic type 2 diabetes diagnosis (15). Similarly, Tan and Thai noted that type 2 diabetic patients with positive autoantibodies in Singapore were often found in 40 year-olds (16). Kobayashi presents the age at which detection of type 2 diabetes with positive autoantibodies in the Japanese diabetic population is over 40 (17). We found that the recommended age as a cut-off point for detection/diagnosis of type 2 diabetes with positive autoantibodies depends on the proportion of type 1 diabetes in the general population. For the white race, the rate of autoimmune diabetes with positive autoantibodies is higher than for other races, so the cut-off point for type 2 diabetes screening has lower autoantibodies. The rate of autoimmune diabetes with positive autoantibodies among Asians is assessed to be lower than that of the white race, so an age dependent cut-off point at diagnosis of diabetes is recommended to be higher.

According to our results, the rate of positive GADA was 15.1% among diabetes patient groups diagnosed under 57 years old. In non-overweight/obese diabetic patients at the time of diabetes diagnosis ≥ 57 years old, the increased relative risk of GADA is 2.7 times higher. So, these subjects do not rule out the possibility of becoming insulin-dependent in the future.

Using the ROC curve of age at diagnosis of diabetes predicts risk of positive GADA in non-overweight/obese diabetic patients was 57 years of age with an area under the curve (AUC) 0.66 (95% confidence interval: 0.602 - 0.715); sensitivity 64.5% and specificity 63.64%; $p < 0.01$

Our results were higher than other authors, and there was discussion about the association between positive autoantibodies in type 2 diabetics and the age at diagnosis of diabetes. Fourlanos S., et al. carried out a prospective study in Melbourne, Australia when comparing two groups of type 2 diabetes patients that had positive and negative GADA. They noted the age at diagnosis of type 2 diabetes that had positive GADA was less than 50 years old, and this difference was significant compared to type 2 diabetes that had negative GADA. This was a predictive factor for the presence of GADA (18). Khanh used the cut-off point of over 25 years old to screen for autoantibodies because of the unknown rate of autoimmune diabetes with positive autoantibodies in the Vietnamese population. Also, the author did not record the difference in age, the age at diagnosis of diabetes, and disease duration time between type 2 diabetes patients group with positive and negative autoantibodies (8).

In Finland, the type 2 diabetic population age at diagnosis of diabetes under 45 years had a significantly higher rate of positive GADA than the population group that was diagnosed over 45 years old in Toumi's cross-sectional study (19). Carlson suggests that age over 60 is an important risk factor for both type 2 diabetes and type 2 diabetes with positive autoantibodies (20).

Arikan believes that, in Turkey, type 2 diabetes with positive GADA were diagnosed at a younger age than patients with negative GADA significantly (45.1 years of age compared to 50.8 years old) (3). UK Prospective Diabetes Study (UKPDS) 25 observed that there was a negative correlation between the rate of positive autoantibodies and the age of disease detection. The rate of positive GADA decreases as patients were diagnosed with diabetes at an older age (21). UKPDS 70 found that type 2 diabetes patients with positive autoantibodies were usually 4 years younger than negative GADA patients (22).

In contrast, Zinman commented that there was no difference in the rate of positive GADA between ages based on data from the A Diabetes Outcome Progression Trial (23).

In Asia, Ishii's research on the Japanese diabetes population had shown that type 2 diabetes patients with positive autoantibodies who had high GADA titre were often older than type 2 diabetes patients with positive antibodies who had a medium or low antibodies titre (24).

Meanwhile, Hamaguchi did not record a difference in diagnostic age between type 2 diabetes patients with positive and negative autoantibodies (7). Wang noted that the rate of negative autoantibodies increases gradually as type 2 diabetes patients were diagnosed at an older age (25).

5. Conclusions

GADA measurement is a useful tool in the diagnosis of diabetes in non-overweight/obese diabetic individuals. The cut-off age at diagnosis of diabetes for detecting GADA positivity in non-overweight/obese diabetic individuals was 57. The rate of GADA positivity in non-overweight/obese diabetic individuals increased 2.7 times when the age at diagnosis was under 57 years old.

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