

# Prevalence and clinical significance of glutamic acid decarboxylase antibodies among young diabetic patients in Faisalabad, Punjab

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**Abstract:** Glutamic acid decarboxylase (GAD) antibodies are markers of pancreatic beta-cell autoimmunity and play a critical role in understanding the autoimmune component of diabetes mellitus. Despite its importance for distinguishing autoimmune diabetes, limited data exists on GAD antibody among young patients. This study determined the prevalence and clinical significance of GAD antibodies among young diabetic patients in Faisalabad, Punjab, Pakistan. This cross-sectional study recruited diabetic patients aged  $\leq 40$  years from tertiary care hospitals of Faisalabad. Data were collected using a validated questionnaire, and GAD antibodies were measured using the chemiluminescence immunoassay. Among 506 patients (253 T1DM, 253 T2DM), GAD prevalence was 18.2%, significantly higher in T1DM (28.9%) versus T2DM (7.5%;  $p < 0.001$ ). Age at onset demonstrated good predictive value (AUC=0.714) with an optimal cutoff at 20 years (sensitivity=69.6%, specificity=69.3%). BMI showed predictive utility (AUC=0.702) with a cutoff at  $< 23 \text{ kg/m}^2$ . Multivariate analysis also revealed younger age at onset (OR=3.2, 95% CI: 1.8-5.6) and lower BMI (OR=2.8, 95% CI: 1.6-4.9) significantly associated with GAD positivity. GAD antibodies are prevalent among young diabetic patients in Faisalabad, with significantly higher prevalence in T1DM. Younger onset age and lower BMI were significant predictors of GAD positivity but should be interpreted along with other clinical and biochemical factors.

**Keywords:** Diabetes mellitus, autoantibody, glutamic acid decarboxylase

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## INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders characterized by chronic hyperglycemia, resulting from complex interactions of genetic, behavioral, and environmental factors (Alsafi *et al.*, 2024). DM affects 537 million adults worldwide, with an expected increase to 643 million in 2030 and 783 million in 2045 (Kumar *et al.*, 2024). Pakistan has a high prevalence rate of diabetes at 30.8% (Amin *et al.*, 2024). Particularly, the disease is increasingly affecting younger populations, representing a significant public health concern with serious implications for human health (Dong *et al.*, 2023).

Historians have long recognized two major forms of DM, namely, type 1 diabetes (T1D) and type 2 diabetes (T2D). Diabetes classification, as well as diagnosis criteria and procedures, has evolved over the years (Wright Jr and McIntyre, 2022). T1D, or juvenile diabetes, is an autoimmune or idiopathic loss of cells that causes severe insulin deficiency. T2D, on the other hand, is characterized by insulin resistance. Furthermore, T1D has long been considered as a disorder that mostly affects children and adolescents (Cano-Cano *et al.*, 2022), and as a result, diagnosis, clinical management, and advocacy have usually focused on younger populations (Iqbal *et al.*, 2024).

In T1DM, the autoimmune destruction of pancreatic beta cells is mediated by circulating autoantibodies. These target  $\beta$ -cell components, such as glutamic acid decarboxylase 65 (GAD65), insulinoma Antigen-2 (IA-2), and islet Cell Antigen (ICA), often appearing early in the disease course. The pattern and combination of these antibodies can reflect different autoimmune pathways and levels of beta cell destruction (Khan *et al.*, 2021). Recent advances in the understanding of autoimmune mechanisms have highlighted the importance of autoantibodies as biomarkers for distinguishing between autoimmune and non-autoimmune forms of diabetes (ElSayed *et al.*, 2023).

Glutamic acid decarboxylase (GAD) is an enzyme responsible for the synthesis of gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter in the central nervous system. Autoantibodies targeting GAD (GADA) are significant predictors of the risk and progression of autoimmune diabetes and are commonly used as diagnostic markers for T1DM. GAD antibodies can often be detected before the clinical onset of symptoms, making it a valuable biomarker for the early identification of individuals at risk (Beunen *et al.*, 2022). Several studies conducted in Western populations have reported GADA positivity among adults who do not present with classical T1D (Aschner *et al.*, 2021). In such cases, particularly among individuals initially diagnosed with T2DM, the presence of GAD antibodies suggests ongoing autoimmune destruction

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of pancreatic beta cells, raising the possibility of Latent Autoimmune Diabetes in Adults (LADA), a slowly progressive form of autoimmune diabetes that may eventually lead to insulin dependence (Fagbemi *et al.*, 2017).

Pakistan is currently facing a substantial burden of diabetes, particularly affecting younger populations. While the prevalence and risk factors of DM have been extensively studied, data on the distribution of GAD antibodies among young diabetic patients in Pakistan, particularly in Faisalabad, are limited. Therefore, the current study aims to determine the prevalence and clinical significance of GAD antibodies in young diabetic individuals in Faisalabad.

## MATERIALS AND METHODS

### *Ethical consideration*

The study was conducted in accordance with the Declaration of Helsinki (Association, 2025) and was approved by the Ethical Review Committee of Government College University (Ref No. GCUF/ERC/493-A) and Faisalabad Medical University (FMU), Faisalabad (No. 48-ERC/FMU/2024-25/368). Written informed consent was obtained from all participants.

### *Study design, setting, duration and sample size*

This cross-sectional study was conducted in Faisalabad, Punjab, over a period of six-months from 25 October 2024 to 25 April 2025. The study population comprised individuals aged  $\leq 40$  years of both sexes with a confirmed diagnosis of T1DM or T2DM based on the American Diabetes Association (ADA) criteria. Patients were classified into T1DM and T2DM by experienced endocrinologists based on clinical presentation at diagnosis, including age of onset, BMI, presence or absence of ketosis, family history, insulin requirement, and response to initial therapy. Participants were recruited from selected diabetic clinics and three tertiary care hospitals affiliated with FMU (Allied-1, Allied-2, and Faisalabad Teaching Hospital) that serve diverse socioeconomic backgrounds from both urban and rural areas of Faisalabad district. The sample size was calculated using an overall prevalence of diabetes as 26.7% (Azeem *et al.*, 2022), a 3.8% precision level and a 95% confidence level; the calculated sample size was 506 individuals. Patients having a familial history of neonatal DM, infant hypoglycemia, hyperinsulinemia, and maternally inherited diabetes and deafness were excluded.

A structured, validated, and pretested questionnaire was used for data collection. The questionnaire consisted of socio-demographic and behavioral factors, disease history, physical measurements, and family history of DM. Internal

consistency was later assessed using the full study data ( $n=506$ ), with a Cronbach's alpha of 0.691.

The data collectors were trained at each clinic/hospital to ensure the data quality and consistency. Approximately 3-5 ml of venous blood samples were collected in gel tubes and properly labeled. Serum was separated by centrifugation and stored at  $-20^{\circ}\text{C}$  for further analysis. The anti-GAD antibodies testing was done using MAGLUMI-X3, a fully automated chemiluminescence immunoassay analyzer by Snibe Diagnostic, as per the manufacturer's instructions.

## STATISTICAL ANALYSIS

Data was entered and analyzed using SPSS version 26. Median and interquartile range (IQR) were calculated for continuous variables, with group comparisons made using the Mann-Whitney U test. ROC curve analysis assessed the predictive ability of continuous variables, with AUC values interpreted as poor (0.5-0.6), fair (0.6-0.7), good (0.7-0.8), and excellent ( $\geq 0.8$ ). Categorical variables were compared using the chi-square test. Unadjusted and adjusted odd ratios (ORs) with 95% confidence intervals were estimated by  $2 \times 2$  tables and binary logistic regression, respectively. A p-value  $< 0.05$  was considered statistically significant.

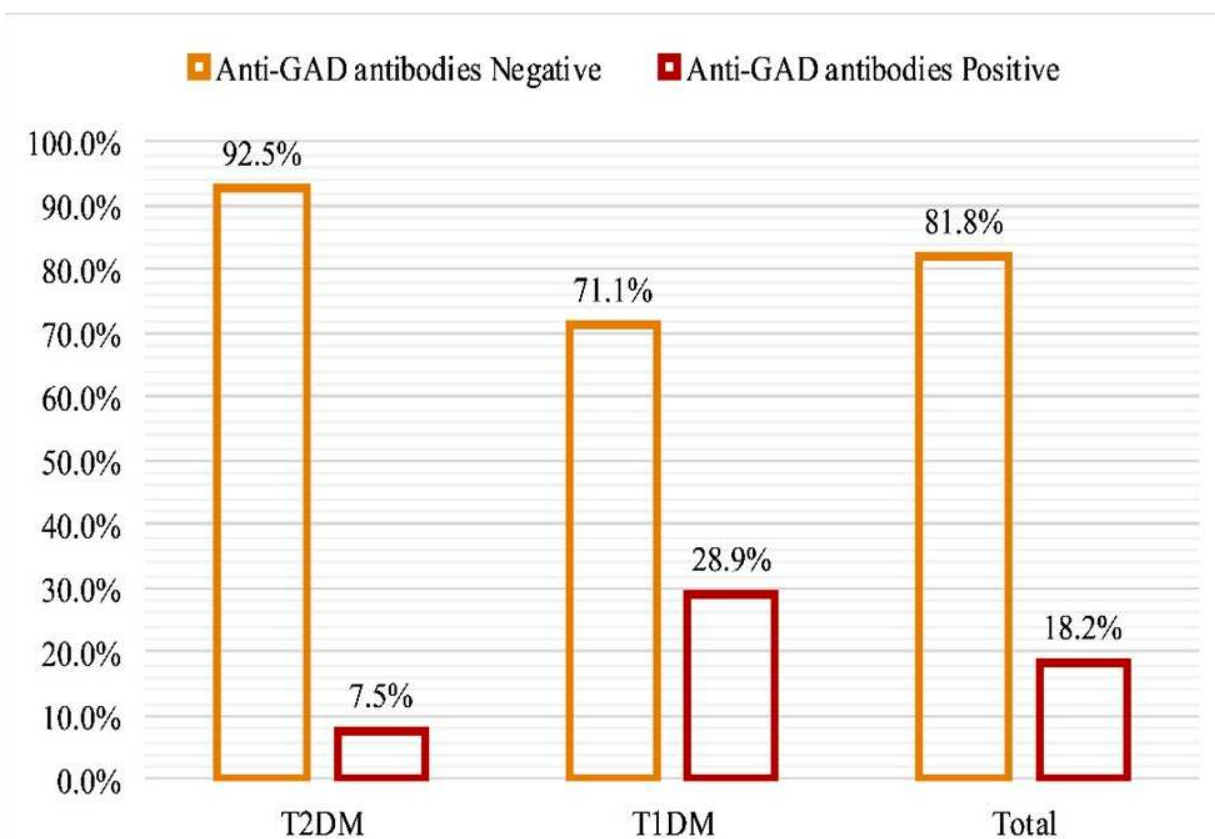
## RESULTS

Table 1 describes the baseline demographic characteristics of the subjects. An overall significant difference was observed in terms of age [median age 38 (IQR 5) vs. 18 (IQR 15)], onset age of diabetes [33 (6) vs. 12 (13)], gender distribution [32.0% vs. 44.7% males and 68.0% vs. 55.3% females], and BMI [28.0 (7.9) vs. 22.2 (8.4)]. and generational involvement [one generation: 21.7% vs. 41.9%, two generations: 59.3% vs. 41.9%, and three generations: 19.0% vs. 16.2%] between T2DM and T1DM, respectively. These differences suggest that T2DM was more prevalent among older individuals with stronger familial aggregation, whereas T1DM was more commonly associated with younger age. Most T2DM participants had been diagnosed for less than 5 years (64.4%), whereas a greater proportion of T1DM patients had diabetes for more than 10 years (20.9%). Treatment modalities varied between the two groups ( $p < 0.001$ ). The majority of T1DM patients (84.2%) were on insulin.

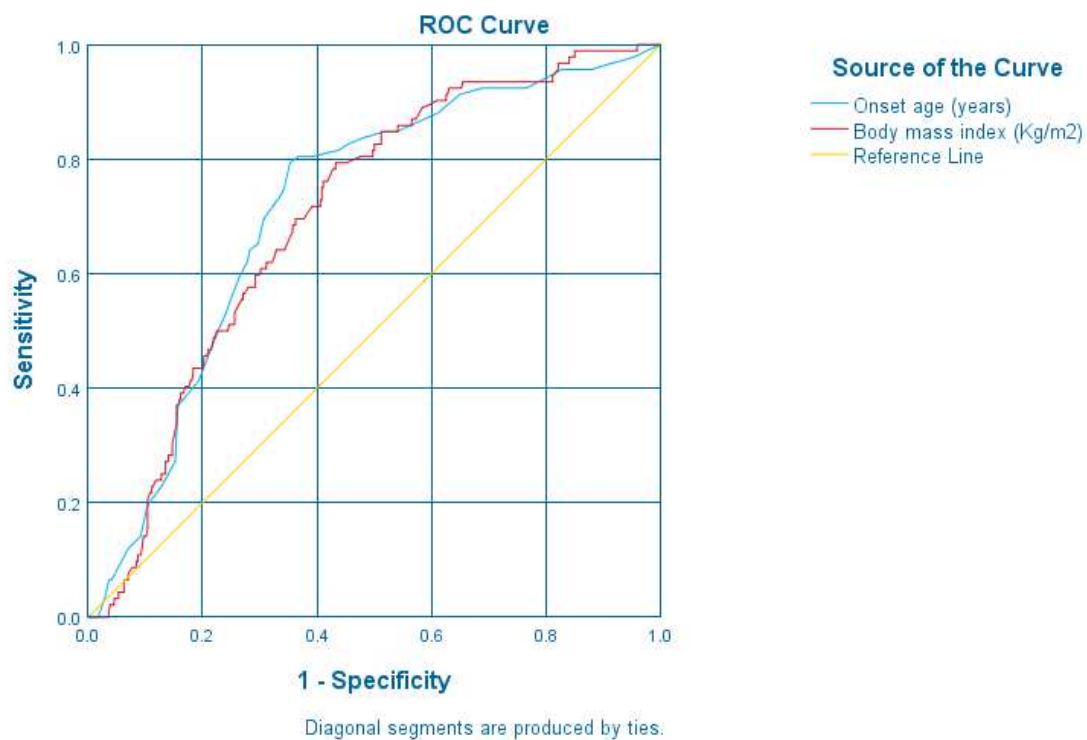
Overall, 92 (18.2%) patients were GAD positive, while 414 (81.8%) were GAD negative. Among patients with T1DM, 73 (28.9%) were GAD positive compared to 19 (7.5%) in T2DM, showing a statistically significant difference ( $p < 0.001$ ) (fig. 1). As shown in fig. 2, the ROC curve analysis was performed using the onset age of diabetes (in years) and BMI as predictor variables on the x-axis, with GAD antibody positivity as the outcome variable on the y-axis.

**Table 1:** Characteristics of study population

		T2DM (n=253)		T1DM (n=253)		Total (n=506)		p Value
Current age (years)	Median (IQR)	38 (5)		18 (15)		34 (21)		< 0.001
	≥25.0	249	98.4%	88	34.8%	337	66.6%	<0.001
	<25.0	4	1.6%	165	65.2%	169	33.4%	
Sex	Male	81	32.0%	113	44.7%	194	38.3%	0.007
	Female	172	68.0%	140	55.3%	312	61.7%	
Education status	No formal schooling	73	28.9%	51	20.2%	124	24.5%	0.15
	Primary	57	22.5%	72	28.5%	129	25.5%	
	Matric	33	13.0%	52	20.6%	85	16.8%	
	Intermediate	74	29.2%	61	24.1%	135	26.7%	
	Graduate	16	6.3%	17	6.7%	33	6.5%	
Employment status	Student	1	0.4%	117	46.2%	118	23.3%	
	Unemployed	39	15.4%	54	21.3%	93	18.4%	<0.001
	Govt. employee	10	4.0%	1	0.4%	11	2.2%	
	Pvt. Employee	20	7.9%	14	5.5%	34	6.7%	
	Businessman	13	5.1%	8	3.2%	21	4.2%	
Cigarette smoking	Others	170	67.2%	59	23.3%	229	45.3%	
	No	248	98.0%	249	98.4%	497	98.2%	1.000
	Yes	5	2.0%	4	1.6%	9	1.8%	
Onset age of Diabetes	Median (IQR)	33 (6)		12 (13)		25 (22)		< 0.001
	≥20	245	96.8%	70	27.7%	315	62.3%	< 0.001
	<20	8	3.2%	183	72.3%	191	37.7%	
BMI (kg/m <sup>2</sup> )	Median (IQR)	28.0 (7.9)		22.2 (8.4)		25.5 (9.5)		< 0.001
	≥23	205	81.0%	115	45.5%	320	63.2%	<0.001
	<23	48	19.0%	138	54.5%	186	36.8%	
Generations involved	One generation	55	21.7%	106	41.9%	161	31.8%	
	Two generations	150	59.3%	106	41.9%	256	50.6%	0.004
	Three generations	48	19.0%	41	16.2%	89	17.6%	
Duration of DM	<5 years	163	64.4%	121	47.8%	284	56.1%	
	6-10 years	72	28.5%	79	31.2%	151	29.8%	< 0.001
	>10 years	18	7.1%	53	20.9%	71	14.0%	
Treatment	Insulin	112	44.3%	213	84.2%	325	64.2%	
	Tablets	86	34.0%	23	9.1%	109	21.5%	< 0.001
	Both	18	7.1%	6	2.4%	2	4.7%	
	No treatment	37	14.6%	11	4.3%	48	9.5%	



**Fig. 1:** Anti-GAD antibodies status distribution between diabetes types



**Fig. 2:** Predictors of anti-GAD antibodies positivity

**Table 2:** Unadjusted odds of Anti-GAD antibodies positivity.

		Anti-GAD antibodies		OR (95% CI)	p-value
		Negative (n=414)	Positive (n=92)		
Onset age of diabetes (years)	≥20	287 (91.1%)	28 (8.9%)	Ref	<0.001
	<20	127 (66.5%)	64 (33.5%)	5.165(3.162-8.438)	
Sex	Male	159 (82.0%)	35 (18.0%)	Ref	0.948
	Female	255 (81.7%)	57 (18.3%)	1.015(0.638-1.617)	
BMI (Kg/m <sup>2</sup> )	≥23	285 (89.1%)	35 (10.9%)	Ref	<0.001
	<23	129 (69.4%)	57 (30.6%)	3.598(2.250-5.754)	
Family history of diabetes	1 generation	122 (75.8%)	39 (24.2%)	Ref	0.053*
	2 generations	215 (84.0%)	41 (16.0%)	0.597(0.354-1.007)	
	3 generations	77 (86.5%)	12 (13.5%)	0.488(0.218-1.026)	
Type of diabetes	T2DM	234 (92.5%)	19 (7.5%)	Ref	<0.001
	T1DM	180 (71.1%)	73 (28.9%)	4.995(2.908-8.579)	
	Insulin	244(58.9%)	81(88.0%)		
Treatment	Tableted	101(24.4%)	8(8.7%)	0.341 (0.198-0.589)	<0.001
	Both (Tab& Insulin)	23(5.6%)	1(1.1%)		
	No Treatment	46(11.1%)	2(2.2%)		
Duration of Diabetes	≤5 Years	242(58.5%)	42(45.7%)	1.267 (0.938-1.712)	0.123
	6-10 Years	114(27.5%)	37(40.2%)		
	>10 Years	58(14.0%)	13(14.1%)		

\*Fisher exact test

The onset age of diabetes demonstrated an area under the curve (AUC) of 0.714, indicating good discriminatory ability. An optimal cut-off value of 20 years for onset age yielded a sensitivity of 69.6% and specificity of 69.3%. Similarly, BMI showed an AUC of 0.702, with an optimal cut-off at 23 kg/m<sup>2</sup>, yielding a sensitivity of 62.0% and specificity of 68.4%. These findings highlight that both younger onset age and lower BMI serve as clinically relevant predictors of anti-GAD antibody positivity in young diabetic patients (fig. 2).

In the unadjusted cross-tabulation analysis (Table 2), younger age at diabetes onset (<20 years), BMI <23 kg/m<sup>2</sup>, and a diagnosis of T1DM were all significantly associated with anti-GAD antibody positivity. These variables were associated with a 3–5-fold higher odds of antibody positivity compared with their respective reference categories. Conversely, female sex and a family history of diabetes involving two or three generations did not show any statistically significant association with GAD antibody positivity.

In regression analyses, the classification tables for model 1 and 2 showed an accuracy of 81.8%. In model 1, onset age of diabetes (<20 years) and BMI <23 Kg/m<sup>2</sup> demonstrated 2-4 times greater odds of anti-GAD antibodies positivity. Model 2 included additional covariates, including sex, type of diabetes, treatment modality, and duration of diabetes, to assess the independent contributions of each factor.

After adjustment, age at onset <20 years, BMI <23 kg/m<sup>2</sup>, and T1DM remained significantly associated with increased odds of GAD antibody positivity, each conferring approximately a 2-fold higher risk. However, variables such as sex, family history of diabetes, treatment modality, and duration of disease did not reach statistical significance in this model. Complete details of the adjusted odds ratios (aORs), confidence intervals, and significance levels are presented in table 3.

## DISCUSSION

The classification of diabetes mellitus is increasingly recognized as complex and heterogeneous, extending beyond the traditional T1DM and T2DM categories. Overlap in clinical features is common, with 12-14% of T1DM patients showing characteristics of T2DM (Mahayidin *et al.*, 2020). Increasing rate of obesity in youth further complicate the accurate classification of diabetes. Testing for diabetes-associated antibodies (DAAs) aids not only in confirming T1DM but also in identifying autoimmune components in atypical or mixed phenotypes. DAA positivity reflects ongoing  $\beta$ -cell autoimmunity and can predict progression to insulin dependence (Cui *et al.*, 2024).

This study found a GAD antibody prevalence of 18.2% among young diabetic patients in Faisalabad, with higher

**Table 3:** Adjusted odds of Anti-GAD antibodies positivity

		aOR	95% CI		Sig.
			Lower	Upper	
Model 1	Onset age of diabetes ( $\geq 20$ / $< 20$ years)	3.808	2.202	6.585	<0.001
	BMI ( $\geq 23$ / $< 23$ Kg/m <sup>2</sup> )	2.014	1.176	3.450	0.011
	Family history: 2-generation vs 1-generation	1.030	0.598	1.776	0.914
	Family history: 3-generation vs 1-generation	0.763	0.359	1.621	0.482
Variable(s) entered in Model 1: Onset age of DM (years), BMI (Kg/m <sup>2</sup> ), and family history of diabetes.					
Model 2	Onset age of diabetes ( $\geq 20$ / $< 20$ years)	2.412	1.177	4.940	0.016
	BMI ( $\geq 23$ / $< 23$ Kg/m <sup>2</sup> )	2.080	1.200	3.604	0.009
	Family history: 2-generation vs 1-generation	1.071	0.617	1.856	0.808
	Family history: 3-generation vs 1-generation	0.771	0.360	1.651	0.504
	Sex (Female/Male)	1.540	0.925	2.565	0.097
	Type of diabetes (T2DM/T1DM)	2.170	1.019	4.621	0.045
	Duration of diabetes	1.024	0.735	1.426	0.890
	Treatment	0.631	0.390	0.956	0.086

Variable(s) entered in Model 2: Onset age of diabetes (years), BMI (Kg/m<sup>2</sup>), family history of DM, Sex, and type of DM, treatment type, duration of DM,

rates in T1DM (28.9%) than T2DM (7.5%). These findings align with global trends while highlighting regional differences relevant to South Asian populations. Similar findings have been reported in Egypt (12.8%) (Ghanem *et al.*, 2019), Korea (15.3%) (Kim *et al.*, 2007) and Europe, where 4% to 14% of patients with T2DM show autoantibodies, with higher frequencies (7%–14%) in Northern Europe (Laugesen *et al.*, 2015). In contrast, Chinese populations exhibit substantially lower rates, with an overall GADA prevalence of 0.53% in the general population and 1.25% among individuals with diabetes (Li *et al.*, 2021). In Bangladesh, (Islam *et al.*, 2019) found GAD antibodies in 10% of adults newly diagnosed with diabetes, particularly in those over 35 years of age. These ethnic differences are not limited to variations in prevalence but may reflect differences in the biological mechanisms that drive autoimmune diabetes. Such observations raise important questions about the universality of current diagnostic criteria and suggest that ethnicity-specific thresholds or biomarkers may be more effective in guiding accurate diagnosis and clinical management.

In current study, the frequency of GAD antibody positivity in patients with T1DM was observed in 28.9%, which is consistent with findings from other studies. A retrospective study in Mumbai reported GAD-65 antibody positivity in 45.16% of diabetic patients, with higher prevalence in children  $\leq 12$  years (58.86%) and 43.50% in the 19-30 age group, highlighting its relevance in younger populations (Almeida *et al.*, 2023). (Dhanwal *et al.*, 2014) reported that 48% of individuals with youth-onset diabetes tested positive for anti-GAD antibodies, indicating a high

prevalence of autoimmunity in this population. Alterations in the gut microbiome have been implicated as a significant contributing factor to the rising incidence of T1DM, potentially promoting immune dysregulation and enhancing beta-cell autoimmunity. These microbial changes may also contribute to the increasing prevalence of T1DM across Asian populations (Sanyal *et al.*, 2019).

In T2DM, GAD antibody positivity was 7.5% which aligns with findings from other studies. Studies from Europe and North America reported LADA prevalence ranging from 4% to 14% among adults with T2DM with rates up to 25% in individuals under 35 years (Buzzetti *et al.*, 2020). An Egyptian study reported 12.8% GAD-positivity in T2DM (Bassyounia *et al.*, 2019). The difference in the frequency of autoantibody positivity in patients with T2DM could be primarily due to differences in the study design, selection criteria, ethnicity, and sensitivity and specificity of autoantibody assay. The clinical significance of antibody positivity in T2DM remains unclear at this time. However, studies have shown that GAD is a reliable biomarker for autoimmune diabetes (Akel and Lernmark, 2024). In T2DM, the presence of GAD signifies ongoing autoimmune damage, suggesting that the diabetes may progress toward LADA and thus lead to insulin dependency (Njabou Katte, 2023). Identifying these patients early enables timely initiation of insulin therapy and helps prevent prolonged use of oral hypoglycemic agents (OHA), which could result in metabolic decompensation.

The onset age of diabetes, body mass index (BMI), and T1DM showed a 3-5 times greater likelihood and a

significant association with the positivity of anti-GAD antibodies. Research has indicated that the age at which diabetes mellitus (DM) is diagnosed may also serve as a predictive factor for the presence of GAD antibodies (Nguyen, 2020). A significant association between early onset age and GADA positivity align with findings by (Fan *et al.*, 2023) who observed similar trends in European populations. Likewise, BMI was inversely related to GAD positivity, a pattern also noted by (Tuomi *et al.*, 1999) in studies on LADA. These associations reflect underlying immunopathogenic mechanisms, whereas younger age and lower BMI are indicative of an increased predisposition to beta-cell autoimmunity.

These findings have important clinical implications for diabetes management in South Asian populations. The substantial prevalence of GAD antibodies, particularly among younger patients and those with lower BMI, suggests that routine antibody testing could significantly improve diagnostic accuracy and treatment decisions. For healthcare systems in developing countries, these results provide valuable epidemiological data that can inform evidence-based screening protocols and resource allocation strategies.

## CONCLUSION

The study concludes that anti-GAD antibodies are prevalent among young diabetic patients in Faisalabad. Younger age at onset and lower BMI were significant predictors of GAD positivity; however, these factors should be considered in combination with other clinical, biochemical, and immunological factors. Therefore, routine anti-GAD antibody screening, particularly in younger individuals with lower BMI, may contribute to more accurate diagnosis and guide more appropriate treatment decisions.

### Limitations and recommendations

The cross-sectional design and the lack of other clinical parameters are the main limitations of this study. Future research that includes all autoantibodies along with other biochemical markers may significantly enhance our understanding of autoimmune diabetes. Despite these limitations, this study provides the first comprehensive data on GAD antibody prevalence in young Pakistani diabetic patients and identifies clinically relevant associations that warrant further investigation.

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### Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Author's contributions

Mazhar Iqbal conceived the study, collected data, performed data analysis, and drafted the manuscript. Dr. Shazia Anwer Bukhari contributed to study design, supervised data collection, and critically revised the manuscript. Dr. Muhammad Arif Nadeem Saqib provided guidance on methodology, interpretation of results, and critically reviewed the manuscript for intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

### Conflict of interest

All Authors declare no competing interests.

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