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Serum Interleukin-17, Islet Autoantibodies and Human Leukocyte Antigen-DQA1*03 Carriage in Latent Autoimmune Diabetes in Adults: A Descriptive Case-Control Study

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ABSTRACT

Background: Latent autoimmune diabetes in adults (LADA) is an adult-onset form of autoimmune diabetes characterised by islet autoantibodies. Circulating interleukin-17 (IL-17) in LADA, and its relation to autoantibody levels and human leukocyte antigen (HLA)-DQA1*03 carriage, have rarely been reported.

Objective: To describe serum IL-17 in patients with LADA compared with healthy controls and, within the LADA group, its relation to autoantibodies against glutamic acid decarboxylase 65 (GAD65), islet antigen-2 (IA-2) and zinc transporter 8 (ZnT8) and to HLA-DQA1*03 carrier status.

Methods: In this single-centre descriptive case-control study, 35 patients with LADA and 35 age- and sex-matched normoglycaemic controls were enrolled. Serum IL-17 and autoantibodies were measured by enzyme-linked immunosorbent assay, and HLA-DQA1*03 carriage by sequence-specific primer polymerase chain reaction.

Results: Median serum IL-17 was higher in patients than in controls (36.7 versus 14.6 pg/mL; $p<0.001$); as expected from the inclusion criteria, autoantibody levels were also higher (all $p<0.001$). HLA-DQA1*03 was carried by 82.9% of patients and 25.7% of controls (odds ratio 13.96, 95% confidence interval 4.37-44.57). Within the LADA group, IL-17 did not correlate with any autoantibody (all $p>0.05$) and was higher in HLA-DQA1*03-negative (n=6) than in HLA-DQA1*03-positive patients (n=29; $p=0.034$), a difference that did not survive correction for multiple comparisons.

Conclusion: Serum IL-17 was higher in patients with LADA than in healthy controls and was unrelated to autoantibody levels. Without diabetic comparator groups and clinical data, this difference cannot be attributed to autoimmunity rather than to hyperglycaemia, adiposity, metabolic inflammation or treatment. The findings are descriptive and require confirmation.

Keywords: Autoantibodies; Diabetes Mellitus, Type 1; HLA-DQ alpha-Chains; Interleukin-17; Latent Autoimmune Diabetes in Adults

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INTRODUCTION

Latent autoimmune diabetes in adults (LADA) is a slowly progressive form of autoimmune diabetes that presents in adulthood. Because of its non-acute onset and the absence of an immediate requirement for insulin, it is often initially classified as type 2 diabetes mellitus (T2DM) (1). LADA shares the autoimmune basis of type 1 diabetes mellitus (T1DM) but follows a slower course of beta-cell loss (2). It is usually defined by onset in adulthood, the presence of at least one islet autoantibody and insulin independence for at least six months after diagnosis (3,4).

The identification of LADA relies mainly on the detection of islet autoantibodies, most often those against glutamic acid decarboxylase 65 (GAD65), islet antigen-2 (IA-2) and zinc transporter 8 (ZnT8) (5,6). These antibodies are markers of humoral islet autoimmunity rather than direct mediators of beta-cell damage, which in autoimmune diabetes is attributed mainly to cellular immune mechanisms (7,8). Autoantibody levels alone may therefore not reflect the full immunological picture.

Interleukin-17 (IL-17) is a pro-inflammatory cytokine that has been implicated in several autoimmune diseases, including autoimmune diabetes (9,10). In addition to T helper 17 (Th17) cells, IL-17 is produced by gamma-delta (γδ) T cells, innate lymphoid cells, neutrophils and mast cells (11), so its serum concentration cannot be taken as a measure of Th17 activity. Increased IL-17 production by circulating T cells has been described in T1DM (12-14), but increased IL-17 secretion by stimulated blood cells and higher plasma IL-17 have also been reported in T2DM and obesity (15-17), indicating that IL-17 is not specific to autoimmune diabetes. In LADA, previous studies have examined IL-17 secretion by stimulated peripheral blood mononuclear cells or the frequency of circulating Th17 cells (18-20); to our knowledge, circulating IL-17 concentrations in LADA, and their relation to islet autoantibody levels, have rarely been reported.

Human leukocyte antigen (HLA) class II genes are the strongest known genetic determinants of autoimmune diabetes (21,22). Alleles of the HLA-DQA1*03 group are carried on the high-risk DRB1*04-DQA1*03-DQB1*03:02 (DR4-DQ8) haplotype (23), and DQA1*03-containing haplotypes have been associated with susceptibility to LADA (21). Few studies have examined whether DQA1*03 carriage is related to circulating cytokine or autoantibody levels in adult-onset autoimmune diabetes (24).

This study was designed as a descriptive case-control study. Its primary aim was to describe serum IL-17 concentrations in patients with LADA in comparison with healthy, normoglycaemic controls. The secondary aims were (i) to examine whether serum IL-17 correlated with GAD65, IA-2 and ZnT8 autoantibody levels within the LADA group and (ii) to compare IL-17 and autoantibody levels between HLA-DQA1*03 carriers and non-carriers with LADA. Islet autoantibody levels and HLA-DQA1*03 frequency in patients and controls are reported to characterise the study cohort. Because the controls did not have diabetes, the study was not designed to evaluate any marker for distinguishing LADA from other forms of diabetes.

MATERIALS AND METHODS

Study Design and Population

This descriptive case-control study included 70 participants: 35 patients with LADA and 35 healthy controls. The sample size was calculated to detect a difference in the primary immunological variables between the groups with 80% power and a two-sided alpha of 0.05. Participants were recruited at Al-Shifa Clinic for Internal Medicine and Diabetes, affiliated with Dhi-Qar University. The study was conducted in accordance with the Declaration of Helsinki

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and was approved by the Institutional Review Board of the College of Science, Dhi-Qar University (ethical approval code: 5846; date of approval: September 2024). Written informed consent was obtained from all participants before enrolment and sample collection.

Inclusion and Exclusion Criteria

Patients were eligible if they met the following criteria for LADA (3): age at diagnosis of diabetes of 30 years or older, no requirement for insulin during the first six months after diagnosis, and positivity for at least one islet autoantibody at diagnosis. Eligibility was established from the patients' medical history and the diagnosis of LADA made by the treating specialist physician, including documented positivity for at least one islet autoantibody at diagnosis. This diagnostic testing was performed as part of routine clinical care before enrolment and was therefore separate from the ELISAs used for the measurements reported in the present study; however, the assay and positivity cut-off used at diagnosis were not documented in the available records.

Controls were age- and sex-matched individuals with normoglycaemia and no personal or family history of autoimmune or metabolic disease. Participants in either group were excluded if they had another autoimmune disorder, an acute or chronic infection, advanced macrovascular or microvascular complications, or hepatic or renal impairment, or if they were receiving immunomodulatory, anti-inflammatory or immunosuppressive treatment at the time of recruitment.

Clinical and Metabolic Data

Individual clinical and metabolic data, including age at diagnosis, disease duration, body mass index (BMI), glycated haemoglobin (HbA1c), fasting glucose, fasting C-peptide and current medications, were not available for this cohort and therefore could not be reported or included in the analyses.

Biochemical and Immunological Assays

Fasting peripheral venous blood samples were collected from all participants. The samples were centrifuged, and the separated serum was aliquoted and stored at -80°C until analysis.

Serum GAD65, IA-2 and ZnT8 autoantibodies were measured by enzyme-linked immunosorbent assay (ELISA) with commercial kits used according to the manufacturers' instructions: a human GAD65 antibody (IgG) ELISA kit (Cat. No. MBS705648; MyBioSource, San Diego, CA, USA), a human IA-2 antibody ELISA kit (Cat. No. E0605Hu; Bioassay Technology Laboratory, Jiaxing, China) and a human anti-ZnT8 antibody ELISA kit (Cat. No. MBS7275610; MyBioSource). Serum IL-17 was measured with an ELISA kit from Bioassay Technology Laboratory (Cat. No. E0142Hu). Optical density was read on an automated microplate reader at the wavelength specified for each kit, and concentrations were derived from the standard curve generated in each run.

According to the manufacturer's insert, the IL-17 kit is a sandwich ELISA for human IL-17A, with a standard curve range of 2-600 ng/L (equivalent to pg/mL), a sensitivity of 1.06 ng/L, intra-assay coefficients of variation (CV) of 3.2-5.4% and an inter-assay CV below 10%.

These kits were used because they allow quantitative measurement of each analyte in small volumes of serum on the standard microplate-reader platform available in the laboratory. All are research-use-only assays that are not intended for diagnostic use. To our knowledge, the performance of the autoantibody kits has not been evaluated against the reference methods of the Islet Autoantibody Standardization Program (IASP) (25), and they are not equivalent to the assays used for clinical autoantibody testing. In the present study, autoantibody levels were therefore analysed as continuous variables and were not used to classify participants as autoantibody-positive or

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autoantibody-negative.

Molecular Genotyping

Genomic DNA was extracted from whole blood with the gSYAN DNA extraction kit (Geneaid, USA) according to the manufacturer's instructions. HLA-DQA1*03 carrier status was determined by sequence-specific primer polymerase chain reaction (SSP-PCR), following the principle originally described for HLA-DQA1 by Olerup et al. (26).

A single allele-specific primer pair, synthesised by Scientific Researcher Co. Ltd. (Iraq), was used: forward 5′-TTCACTCGTCAGCTGACCAT-3′ and reverse 5′-CAAATTGCGGGTCA AATCTTCT-3′, giving a product of 183 base pairs (bp). Amplification was performed with GoTaq® G2 Green Master Mix (Promega, USA) according to the manufacturer's instructions. PCR products were separated by agarose gel electrophoresis; samples showing the 183-bp product were scored as DQA1*03-positive, and samples without it as DQA1*03-negative.

This assay identifies carriage of the DQA1*03 allele group; it does not resolve individual DQA1*03 alleles or zygosity, and the DRB1 and DQB1 loci were not typed. The results therefore represent DQA1*03 carrier status only, and the haplotype on which DQA1*03 was carried could not be determined (23).

Statistical Analysis

Data were analysed with IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Normality was assessed with the Shapiro-Wilk test. Because several variables were not normally distributed, continuous variables were compared between the two groups with the Mann-Whitney U test and are reported as median and interquartile range (IQR); age is reported as mean ± standard deviation (SD). Categorical variables were compared with Pearson's chi-square test and are reported as counts and percentages, and the odds ratio (OR) for HLA-DQA1*03 carriage was calculated with its 95% confidence interval (CI). Correlations between IL-17 and autoantibody levels in the LADA group were assessed with Spearman's rank correlation coefficient (r). A two-sided p value below 0.05 was considered statistically significant. The secondary analyses (three correlations and four genotype-stratified comparisons) were exploratory; to indicate their robustness, the Bonferroni-adjusted significance threshold for these seven tests (0.05/7 = 0.007) is also reported. Because the controls did not have diabetes, no analysis of diagnostic performance was undertaken.

RESULTS

Baseline Characteristics

The two groups were comparable in age (42.7 ± 7.2 versus 43.0 ± 7.2 years; p=0.842) and in sex distribution (males 45.7% versus 48.6%; p=0.812) (Table 1).

Islet Autoantibody and IL-17 Levels

As expected from the inclusion criteria, median levels of all three islet autoantibodies were higher in patients with LADA than in controls: GAD65 55.7 versus 19.6 U/mL, IA-2 25.8 versus 11.5 U/mL and ZnT8 45.8 versus 19.9 U/mL (all p<0.001) (Table 2).

Median serum IL-17 was also higher in patients than in controls (36.7 [IQR 9.4] versus 14.6 [IQR 7.7] pg/mL; p<0.001) (Table 3).

*Frequency of HLA-DQA1*03*

HLA-DQA1*03 was carried by 29 of 35 patients (82.9%) and by 9 of 35 controls (25.7%; p<0.001), corresponding to an OR of 13.96 (95% CI 4.37-44.57) (Table 4).

Distribution of Continuous Variables

GAD65 levels were normally distributed in both groups, whereas IA-2, ZnT8 and IL-17 levels deviated from normality in at least one group; non-parametric tests were therefore applied (Table 5).

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Table 1. Demographic characteristics of the study participants.

Characteristic	LADA group (n=35)	Control group (n=35)	p-value
Age (years), mean ± SD	42.7 ± 7.2	43.0 ± 7.2	0.842
Male, n (%)	16 (45.7%)	17 (48.6%)	0.812
Female, n (%)	19 (54.3%)	18 (51.4%)	—

Data are presented as mean ± SD or n (%). Age was compared with the Mann-Whitney U test and sex distribution with the chi-square test. Clinical and metabolic data (age at diagnosis, disease duration, body mass index, glycated haemoglobin, fasting glucose, C-peptide and current medications) were not available for this cohort. LADA, latent autoimmune diabetes in adults; SD, standard deviation.

Table 2. Islet autoantibody levels in patients with LADA and healthy controls.

Autoantibody	LADA median (IQR)	Control median (IQR)	p-value
GAD65 (U/mL)	55.7 (27.5)	19.6 (12.0)	<0.001***
IA-2 (U/mL)	25.8 (15.4)	11.5 (7.9)	<0.001***
ZnT8 (U/mL)	45.8 (20.0)	19.9 (13.3)	<0.001***

Data are presented as median (IQR). Groups were compared with the Mann-Whitney U test. ***p<0.001. Patients were selected for islet autoantibody positivity at diagnosis, so this comparison characterises the cohort and is not an independent finding. LADA, latent autoimmune diabetes in adults; IQR, interquartile range; GAD65, glutamic acid decarboxylase 65; IA-2, islet antigen-2; ZnT8, zinc transporter 8.

Table 3. Serum interleukin-17 (IL-17) concentrations in patients with LADA and healthy controls.

Parameter	LADA median (IQR)	Control median (IQR)	p-value
IL-17 (pg/mL)	36.7 (9.4)	14.6 (7.7)	<0.001***

Data are presented as median (IQR). Groups were compared with the Mann-Whitney U test. ***p<0.001. LADA, latent autoimmune diabetes in adults; IQR, interquartile range.

Table 4. Frequency of HLA-DQA1*03 carriage in patients with LADA and healthy controls.

HLA-DQA1*03	LADA (n=35)	Control (n=35)	p-value	OR	95% CI
Positive, n (%)	29 (82.9%)	9 (25.7%)	<0.001***	13.96	4.37-44.57
Negative, n (%)	6 (17.1%)	26 (74.3%)	—	—	—

Chi-square test. ***p<0.001. Positive indicates carriage of at least one DQA1*03 allele; zygosity and allele-level subtypes were not determined. HLA, human leukocyte antigen; LADA, latent autoimmune diabetes in adults; OR, odds ratio; CI, confidence interval.

Table 5. Shapiro-Wilk normality tests for the continuous immunological variables.

Variable	LADA W	LADA p	Control W	Control p	Distribution
GAD65	0.958	0.194	0.945	0.082	Normal
IA-2	0.903	0.005	0.953	0.141	Non-normal
ZnT8	0.912	0.009	0.917	0.012	Non-normal
IL-17	0.949	0.106	0.884	0.002	Non-normal

The Shapiro-Wilk W statistic and p value are reported for each group. p<0.05 indicates departure from normality; non-parametric tests were used for these variables. LADA, latent autoimmune diabetes in adults; GAD65, glutamic acid decarboxylase 65; IA-2, islet antigen-2; ZnT8, zinc transporter 8; IL-17, interleukin-17.

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Table 6. Spearman correlations between serum interleukin-17 (IL-17) and islet autoantibody levels in patients with LADA.

Correlation pair	Spearman r	p-value
IL-17 vs GAD65	-0.293	0.088
IL-17 vs IA-2	-0.265	0.124
IL-17 vs ZnT8	0.188	0.281

Spearman's rank correlation coefficient (r). The analysis was restricted to patients with LADA (n=35). None of the correlations reached statistical significance; the sample size limits the power to detect weak associations. LADA, latent autoimmune diabetes in adults; GAD65, glutamic acid decarboxylase 65; IA-2, islet antigen-2; ZnT8, zinc transporter 8.

Table 7. Serum interleukin-17 (IL-17) concentrations in patients with LADA according to HLA-DQA1*03 carrier status.

Parameter	HLA-DQA1*03 positive (n=29) median (IQR)	HLA-DQA1*03 negative (n=6) median (IQR)	p-value
IL-17 (pg/mL)	33.7 (9.9)	40.0 (3.3)	0.034*

Data are presented as median (IQR). Comparison by Mann-Whitney U test. *p<0.05; not significant at the Bonferroni-adjusted threshold for the seven secondary comparisons (p<0.007). The HLA-DQA1*03-negative subgroup comprised only six patients. LADA, latent autoimmune diabetes in adults; HLA, human leukocyte antigen; IQR, interquartile range.

Table 8. Islet autoantibody levels in patients with LADA according to HLA-DQA1*03 carrier status.

Autoantibody	HLA-DQA1*03 positive (n=29) median (IQR)	HLA-DQA1*03 negative (n=6) median (IQR)	p-value
GAD65 (U/mL)	62.5 (24.2)	43.7 (16.3)	0.110
IA-2 (U/mL)	25.8 (15.3)	26.6 (12.7)	0.776
ZnT8 (U/mL)	44.3 (21.0)	48.2 (6.4)	0.555

Data are presented as median (IQR). Comparison by Mann-Whitney U test. No significant differences were observed between the genotype subgroups (all p>0.05). LADA, latent autoimmune diabetes in adults; HLA, human leukocyte antigen; IQR, interquartile range; GAD65, glutamic acid decarboxylase 65; IA-2, islet antigen-2; ZnT8, zinc transporter 8.

Relationship between IL-17 and Islet Autoantibodies

Within the LADA group, serum IL-17 did not correlate significantly with GAD65 (r=-0.293, p=0.088), IA-2 (r=-0.265, p=0.124) or ZnT8 (r=0.188, p=0.281) (Table 6).

*Marker Levels According to HLA-DQA1*03 Status*

Median IL-17 was higher in HLA-DQA1*03-negative patients (40.0 [IQR 3.3] pg/mL; n=6) than in HLA-DQA1*03-positive patients (33.7 [IQR 9.9] pg/mL; n=29; p=0.034) (Table 7). This difference was not significant at the Bonferroni-adjusted threshold of 0.007.

Islet autoantibody levels did not differ significantly between the two genotype subgroups: GAD65 (p=0.110), IA-2 (p=0.776) and ZnT8 (p=0.555) (Table 8).

DISCUSSION

In this descriptive case-control study, serum IL-17 concentrations were higher in patients with LADA than in age- and sex-matched healthy controls but were not correlated with islet autoantibody levels. HLA-DQA1*03 carriage was more frequent among patients, and IL-17 was higher in the small subgroup

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of patients who did not carry this allele group.

The higher GAD65, IA-2 and ZnT8 levels in patients follow from the inclusion criteria, since all patients were required to have at least one islet autoantibody at diagnosis, and they should not be regarded as an independent finding. Moreover, because the assay and cut-off used for diagnostic testing were not documented, the agreement between autoantibody status at diagnosis and the levels measured in this study could not be assessed. They are nevertheless consistent with previous reports of islet autoimmunity in autoimmune diabetes (27,28). Because the autoantibodies were measured with research ELISA kits that have not been evaluated against IASP reference methods (25), the absolute values cannot be compared with those obtained with clinical assays in other studies.

Published human data on IL-17 in diabetes are inconsistent, and most studies have assessed IL-17 production by cells rather than circulating concentrations. In T1DM, activated circulating T cells secreted more IL-17 (12,13), and IL-17 responses to islet autoantigen peptides were detected in 54% of patients with new-onset disease compared with 10% of healthy controls (14); however, studies that measured serum IL-17 in T1DM, including recent-onset disease, did not find a significant difference from controls (29,30). In LADA, peripheral blood mononuclear cells stimulated with insulin secreted more IL-17 than those of patients with T1DM (18), whereas in a large study comparing the diabetes spectrum, the frequency of circulating Th17 cells was not increased in LADA and was raised only in T2DM, correlating with blood glucose (19); Th17-related findings in LADA also varied with GAD antibody titre (20). In T2DM, circulating IL-17 has been reported to be higher (16), unchanged (30,31) or lower (32) than in non-diabetic controls, and higher plasma IL-17 has also been found in obesity (17). Absolute IL-17 concentrations differ considerably between these studies, probably reflecting different assays, so values cannot be compared directly.

These observations indicate that circulating IL-17 is not specific to autoimmune diabetes and may be influenced by hyperglycaemia, adiposity and metabolic inflammation. IL-17 is also produced by γδ T cells, innate lymphoid cells, neutrophils and mast cells (11), and no T-cell data were collected in the present study. In addition, metformin has been reported to shift the balance between Th17 and regulatory T cells, although human data are scarce (33), and other glucose-lowering and lipid-lowering drugs may also have immunomodulatory effects. Because the controls were normoglycaemic and these factors were not taken into account, the higher IL-17 in our patients cannot be attributed to LADA autoimmunity or to Th17 activity, and it cannot be inferred that IL-17 contributed to beta-cell damage in this cohort.

IL-17 was not correlated with any of the three autoantibodies. This is compatible with cytokine levels and autoantibody levels reflecting different arms of the immune response, different cellular sources or different time courses (10). However, with 35 patients the study had limited power to detect weak correlations, so the absence of a significant association should not be taken as evidence that none exists.

The higher frequency of HLA-DQA1*03 carriage among patients agrees with the known association between HLA class II haplotypes and LADA (21,22). However, DQA1*03 alleles occur not only on the high-risk DRB1*04-DQA1*03-DQB1*03:02 haplotype but also on haplotypes that confer neutral or protective effects, such as DRB1*04:01-DQA1*03-DQB1*03:01 (23). Because DQA1*03 alleles, DRB1 and DQB1 were not typed, carrier status in this study is only a crude proxy for HLA-conferred risk. The higher IL-17 in non-carriers rests on six patients, was one of seven exploratory secondary comparisons and did not reach the Bonferroni-adjusted threshold; it may be a chance finding and requires confirmation in larger, adequately typed cohorts.

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Taken together, these data describe serum IL-17, islet autoantibody levels and HLA-DQA1*03 carriage in a small cohort of Iraqi patients with LADA, but they do not establish any of these markers as diagnostic or pathogenic. Because LADA is frequently misclassified as T2DM and misclassification may delay appropriate treatment (34,35), future studies should compare patients with LADA with patients with T2DM and T1DM, take clinical and metabolic covariates and treatment into account, use standardised autoantibody assays and high-resolution HLA typing, and assess IL-17-producing cell populations directly.

Limitations of the Study

This study has several limitations. First, the sample was small and drawn from a single centre, and the cross-sectional design does not allow changes over time or causal relationships to be assessed. Second, the controls were healthy, normoglycaemic individuals and no T2DM or T1DM comparator groups were included; differences between patients and controls may therefore reflect hyperglycaemia, adiposity or metabolic inflammation rather than autoimmunity, and the study does not address the differential diagnosis encountered in clinical practice. Third, clinical and metabolic data, including age at diagnosis, disease duration, BMI, glycaemic control and C-peptide, were not available, so IL-17 and autoantibody levels could not be related to or adjusted for these covariates. Fourth, information on current medications was not available; several drugs used in diabetes, including metformin (33), statins, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists and insulin, have been reported to have immunomodulatory effects and may have influenced IL-17 levels. Fifth, the ELISAs were research-use-only kits that were not independently validated in our laboratory and have not been standardised against IASP reference methods, and the assay used to establish autoantibody positivity at diagnosis was not documented. Sixth, no T-cell or Th17 data were collected, so the cellular source of serum IL-17 is unknown. Seventh, HLA typing was limited to DQA1*03 carrier status determined with a single SSP primer pair, without allele-level resolution, zygosity or DRB1 and DQB1 typing, and only six patients were DQA1*03-negative. Finally, several secondary comparisons were performed, and the only significant genotype-stratified difference did not remain significant after Bonferroni correction. The findings should therefore be regarded as descriptive and preliminary.

CONCLUSIONS

In this descriptive study, serum IL-17 concentrations were higher in patients with LADA than in healthy controls and were not related to islet autoantibody levels. IL-17 was higher in the small subgroup of patients who did not carry HLA-DQA1*03, but this difference did not withstand correction for multiple comparisons. Because T2DM and T1DM comparator groups, clinical and metabolic data, standardised assays and T-cell data were lacking, these observations cannot be attributed to LADA autoimmunity. They require confirmation in larger, adequately controlled studies before any clinical application can be considered.

ABBREVIATIONS

BMI, body mass index; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; ELISA, enzyme-linked immunosorbent assay; GAD65, glutamic acid decarboxylase 65; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; HLA, human leukocyte antigen; IA-2, islet antigen-2; IASP, Islet Autoantibody Standardization Program; IL-17, interleukin-17; IQR, interquartile range; LADA, latent autoimmune diabetes in adults; OR, odds ratio; PCR, polymerase chain reaction; SD, standard deviation; SSP-

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PCR, sequence-specific primer polymerase chain reaction; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; Th17, T helper 17; ZnT8, zinc transporter 8.

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AUTHORS' CONTRIBUTIONS

A.A.H. conceptualised and designed the study, supervised the immunological analyses and drafted the initial manuscript. A.N.A. performed the biochemical and immunological assays and contributed to data curation and statistical analysis. H.A. supervised clinical recruitment and sample collection and provided critical clinical input. R.H.T. contributed to the molecular genotyping, data interpretation and critical revision of the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the College of Science, Dhi-Qar University (ethical approval code: 5846; date of approval: September 2024). Written informed consent was obtained from all patients and healthy volunteers before enrolment and sample collection.

AVAILABILITY OF DATA AND MATERIALS

The de-identified individual-level data supporting the findings of this study, including the raw ELISA optical densities, standard curves and calculated concentrations and the HLA-DQA1*03 results, are not publicly available because institutional regulations on patient privacy and clinical data protection do not permit public release. They are available from the corresponding author on reasonable request and can be provided to the editor and reviewers for the purposes of peer review.

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