International Journal of Health Sciences (IJHS)

Special Issue IX

The International Journal of Health Sciences (IJHS), an academic, interdisciplinary, and double-blind peer-reviewed publication ISSN 2550-696X (Online) ISSN 2550-6978 (Print), publishes scholarly articles on international students in tertiary education, secondary education, and other educational settings that make significant contributions to research, policy, and practice in the internationalization of higher education. Articles in the journal are freely available to the public thanks to our institutional sponsors.

Cover

DOI: https://doi.org/10.53730/ijhs.v6nS9.2022

PUBLISHED: 31-12-2023

Peer Review Articles

Assessment of narrow alveolar ridge expansion by ossiodensification vs. ridge splitting technique for dental implant placement

Clinical and radiographic study

Omar El Farouk Mossad Sadek Ahmed, Ashraf Abdel Fattah Mahmoud, Hossam Eldin Mohammed Ali, Mohamed Mahgob AlAshmawy, Abdelaziz Baiomy Abdullah, Mohamed Ashraf Abdel Fattah, Ali Ali Tawfik Abdo

DOI : 10.53730/ijhs.v6nS9.12291

PDF

Yang's keyhole plate versus conventional plate for treatment of mandibular sub-condylar fractures

Clinical and radiographic evaluation

Ali Ali Tawfik Abdo, Ashraf Abdel Fattah Mahmoud, Abdel Aziz Baiomy Abdullah, Mohamed Mahgob AlAshmawy, Hossam Eldin Mohammed Ali, Omar El Farouk Mossad Sadek Ahmed, Mohamed Ashraf Abdel Fattah

DOI : 10.53730/ijhs.v6nS9.12292

PDF

An Indonesian adolescent with delayed management of airway foreign body (straight pins) aspiration

A case report

Lucia Miranti Hardianingwati, Rizka Fathoni Perdana

DOI : 10.53730/ijhs.v6nS9.12298

PDF

Reducing dependence on moneylenders with Mawar Emas Program

Supiandi, Risky Angga Pramuja, Muhammad Azizurrohman

DOI : 10.53730/ijhs.v6nS9.12337

PDF

Hypocalcemic seizure caused by vitamin D deficiency in infant

Fatimah Arief, Nur Rochmah, Muhammad Faizi, Prastiya Indra Gunawan, Riza Noviandi

DOI : 10.53730/ijhs.v6nS9.12342

PDF

Management of persistent hyperinsulinemia hypoglycemia of infancy

Adkhiatul Muslihatin, Nur Rochmah, Muhammad Faizi, Qurrota Ayuni Novia Putri

DOI : 10.53730/ijhs.v6nS9.12350

PDF

Sociological approach through holistic pattern in solving the problem of homosexuality from the Qur'an perspective

Ahmad Zain Sarnoto, Nurdin

DOI : 10.53730/ijhs.v6nS9.12353

PDF

Yuni Hisbiyah, Anang Endaryanto, Bagoes Setyoboedi, Nur Rochmah, Muhammad Faizi, Citrawati Dyah Kencono Wungu, Qurrota Ayuni Novia Putri
1395-1410

DOI : 10.53730/ijhs.v6nS9.12765

PDF

A proposed model for amending tax controls in Iraq to achieve a better tax outcome

Ali Abbas Kareem Al-Khafaji, Ali Mutashar Muhammad Al-Zuhairy
1411-1420

DOI : 10.53730/ijhs.v6nS9.12552

PDF

The role of forensic medicine in achieving criminal justice

Mohamed Bounaanaa, Mohamed Karym
1421-1436

DOI : 10.53730/ijhs.v6nS9.12553

PDF

Independent isolation of infectious waste management in the COVID-19 era

A case study in Java-Bali Indonesia

Endang Wahyuningsih, Sutaryono, Jaka Widada, Heru Subaris Kasjono
1437-1444

DOI : 10.53730/ijhs.v6nS9.12314

PDF

Changes in markers ferritin and c-reactive protein in patients with COVID-19 in Iraq

A case-control study

Haider Abd Jabbar, Aqeel Raheem Hasan, Mohammed Ali Mones, Abdalkhaliq A. Abdalameer, May Jaleel Abed
1445-1453

DOI : 10.53730/ijhs.v6nS9.12284

PDF

Clinical comparison of antioxidant for pregnant women with iron deficiency anemia

Zinah Naeem Mtele
1466-1473

DOI : 10.53730/ijhs.v6nS9.12286

PDF

To evaluate effect of three different reducing agents in recovery of bond strength to sodium hypochlorite treated dentin with composite resin

An in vitro study

Abhishek Shelke, Aniket Jadhav, Anupam Sharma, Abhijit Jadhav, Shivani Chavan, Damini Bhagwat
1474-1480

DOI : 10.53730/ijhs.v6nS9.12331

PDF

Comparative evaluation of shear bond strength of universal bonding agent and total-etch bonding agent on superficial and deep dentin

An in vitro study

Damini Bhagwat, Ashwini Gaikwad, Varsha Pandit, Mrunal Shinde, Ruchira Bhamare, Sailee Kalyankar
1481-1490

PDF

Role of RASSF1-A gene in early detection of colorectal carcinogenesis

Thaer Ali Hussein, Ahmad Shandookh Hameed, Mohamed Hussein Amer

DOI : 10.53730/ijhs.v6nS9.12831

PDF

Occupational contact dermatitis among healthcare workers in the COVID-19 Isolation ward

Cita Rosita Sigit Prakoeswa, Damayanti, Sylvia Anggraeni, Menul Ayu Umborowati, Sawitri, Astindari, Andre Yuindartanto

DOI : 10.53730/ijhs.v6nS9.12856

PDF

Analysis of the ZNT8, GAD65, HLA-DQA1, HLA-DQB1, and C-peptides in Indonesian children with type 1 diabetes mellitus

Nur Rochmah, Muhammad Faizi, Yuni Hisbiyah, Rayi Kurnia Perwitasari, Tyas Maslakhatien Nuzula, Anang Endaryanto, Soetjipto Soetjipto

DOI : 10.53730/ijhs.v6nS9.12857

PDF

Chemical castration with silver nitrate and potassium permanganate of local male bucks

Dler Muwafaq Shukur, Qayes Taref Ali

DOI : 10.53730/ijhs.v6nS9.12836

PDF

Preparation and identification of green polymers towards the production of sustainable latex from β-myrcene and some methacrylate monomers

Fouad M. Hussein, Ali S. Ismail

DOI : 10.53730/ijhs.v6nS9.12837

PDF

Study of spectroscopic analysis performed of laser produced Sn and Sn:Cr plasma

Raghad T. Ahmed, Ala F. Ahmed, Kadhim A. Aadim

DOI : 10.53730/ijhs.v6nS9.12839

PDF

Traumatic memory of Martyrs' Sons

Zinah Ali Salih, Lena Adnan Khalaf Rashad

DOI : 10.53730/ijhs.v6nS9.12840

PDF

Unrealistic optimism

Zinah Ali Salih, Hanan Majiad Noor eabd

DOI : 10.53730/ijhs.v6nS9.12843

PDF

Improving the quality of counseling services for students based on digital applications in line with the implementation of the Merdeka Curriculum

B. M. A. S. Anaconda Bangkara, Irma Chmawati Maruf, Abdul Latif, Hasna Hashibah, Ikhsan

DOI : 10.53730/ijhs.v6nS9.12875

PDF

Knowledge, attitude and acceptance of amputation among amputee patients admitted in National Orthopaedic Hospital Enugu - Nigeria

Justin Agorye Ingwu, Happiness Ogadi Anikwe, Chinenye Anehkhati, Hope Opara, Patricia Okpala, Mathias Agba

DOI : 10.53730/ijhs.v6nS9.12881

PDF

Study of endothelial cell loss in small incision cataract surgery (SICS)

Sujata R. Charel, Hetaj K. Sheth, Astha Domadia, Jash Bavishi, Niyant N. Pandya

DOI : 10.53730/ijhs.v6nS9.12886

PDF

Screening of catharanthus roseus stem extract for anti-ulcer potential in wistar rat

Suraj Mandal, Sweta Goel, Monika Saxena, Polly Gupta, Jyoti Kumari, Prashant Kumar, Mukesh Kumar, Rahul Kumar, Km. Shiva

DOI : 10.53730/ijhs.v6nS9.12889

PDF

The glycemic control among type 1 diabetes children pre and during COVID-19 pandemic

A systematic review and meta-analysis

Wika Y. Deakandi, Farahdina Farahdina, Qurrota A. N. Putri, Tyas M. Nuzula, Katherine Fedora, Qorri Aina, Nur Rochmah, Muhammad Faizi

DOI : 10.53730/ijhs.v6nS9.12893

PDF

Isolation, Screening and molecular characterization of bio surfactant producing microbes from hydrocarbon polluted soil

Putha Deepika Sai Lakshmi, Beesa Hrushik Samyukth, Golamari Siva Reddy, Boddu Sumalatha

DOI : 10.53730/ijhs.v6nS9.12899

PDF

Postoperative bone defects' reconstruction in patients with focal form of chronic post-traumatic osteomyelitis

Aleksandr G. Sonis, Evgeniy A. Stolyarov, Jean Geringer, Denis G. Alekseev, Sergey V. Ladonin, Maria Yu. Sefedinova, Maria A. Bezrukova

DOI : 10.53730/ijhs.v6nS9.12901

PDF

Clinic, diagnosis and treatment of dunbar syndrome in children

Andrey V. Andreev, Mikhail V. Krasnov, Larisa P. Nikitina

International Journal of Health Sciences (IJHS)

Editorial Team

Editor-in-Chief

ijhs@utm.edu.ec | ijhs@sciencescholar.us | editorsciencescholar@gmail.com

M. R. Herrera, Scopus ID: 7202050008, Nursing, Universidad Estatal del Sur de Manabí, Ecuador

Chief Executive Editor

executive_editor@utm.edu.ec | executive_editor@sciencescholar.us

M. R. Gámez, Scopus ID: 57204684841, Universidad Técnica de Manabí, South America

Founder & Managing Editor

iwayansuryasa@utm.edu.ec | suryasa@stikom-bali.ac.id

W. Suryasa, Scopus ID: 57200211897, ITB STIKOM Bali, Indonesia

International Advisory Board

Editorial Board

Production Editor

Editorial Office

Retired Editor

CITESCORE 2021

2.0 2021 CiteScore

63rd percentile

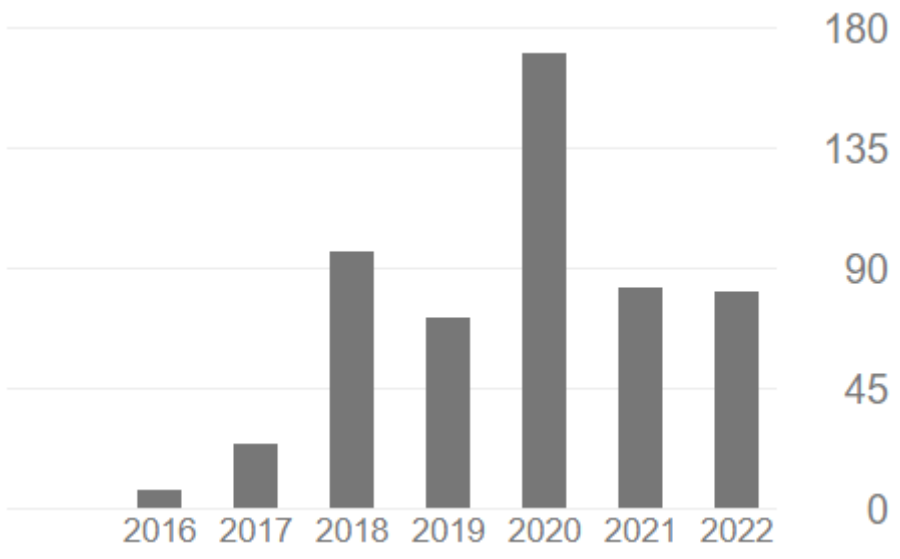
Powered by Scopus

GOOGLE SCHOLAR

Google Scholar

Cited by

	All	Since 2018
Citations	550	540
h-index	14	14
i10-index	23	23



Last updated: 1 January 2023

MAIN MENU

Current Issues

Previous Issues

FOR AUTHORS

Aims & Scope

How to Cite:
Rochmah, N., Faizi, M., Hisbiyah, Y., Perwitasari, R. K., Nuzula, T. M., Endaryanto, A., & Soetjipto, S. (2022). Analysis of the ZNT8, GAD65, HLA-DQA1, HLA-DQB1, and C-peptides in Indonesian children with type 1 diabetes mellitus. *International Journal of Health Sciences*, *6*(S9), 1927–1936. https://doi.org/10.53730/ijhs.v6nS9.12857

Analysis of the ZNT8, GAD65, HLA-DQA1, HLA-DQB1, and C-peptides in Indonesian children with type 1 diabetes mellitus

Nur Rochmah
Faculty of Medicine, Department of child health, Dr. Soetomo General Hospital, Universitas Airlangga, Surabaya, East Java, Indonesia

Muhammad Faizi
Faculty of Medicine, Department of child health, Dr. Soetomo General Hospital, Universitas Airlangga, Surabaya, East Java, Indonesia

Yuni Hisbiyah
Faculty of Medicine, Department of child health, Dr. Soetomo General Hospital, Universitas Airlangga, Surabaya, East Java, Indonesia

Rayi Kurnia Perwitasari
Faculty of Medicine, Department of child health, Dr. Soetomo General Hospital, Universitas Airlangga, Surabaya, East Java, Indonesia

Tyas Maslakhatien Nuzula
Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia

Anang Endaryanto
Faculty of Medicine, Department of child health, Dr. Soetomo General Hospital, Universitas Airlangga, Surabaya, East Java, Indonesia

Soetjipto Soetjipto
Faculty of Medicine, Department of Biochemistry, Universitas Airlangga, Surabaya, East Java, Indonesia
Corresponding author email: soetjipto@fk.unair.ac.id

***Abstract*--**Autoimmune reaction in Type 1 Diabetes Mellitus (T1DM) is caused by genetic and environmental factors. The genes HLA-DQA1 and HLA-DQB1 are strongly associated with T1DM. Other established markers of T1DM were Zinc Transporter 8 Antibody (ZnT8), Glutamic Acid Decarboxylase Antibody-65 (GAD65), and C-peptide. This study aims to analyze ZnT8, GAD65, HLA-DQA1, HLA-DQB1, and C-peptide in Indonesian children with T1DM. A cross-sectional study of T1DM children was conducted in Dr. Soetomo Hospital, Indonesia. ZnT8,

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
Manuscript submitted: 9 May 2022, Manuscript revised: 18 July 2022, Accepted for publication: 27 August 2022

GAD65, HLA-DQA1, HLA-DQB1, and C-peptide were examined with an ELISA kit. Mann-Whitney test was performed with a significant value of $p<0.05$. A total of 62 participants consisting of 31 children for each group were enrolled. The prevalence of ZnT8, GAD65, and C-peptide in T1DM patients was 77.4%, 90.3%, and 87.1%. There are 74% of T1DM children had two positive antibodies and 55% had two positive HLA peptides. There was no difference in HLA-DQA1 and HLA-DQB1 peptides between T1DM and control groups ($p=0.12$; $p=0.19$). Meanwhile, the comparison between ZnT8, GAD65, and C-Peptide values between T1DM and control groups shows a significant difference ($p<0.05$). HLA-DQA1 peptide value was higher in T1DM children and HLA-DQB1 peptide value was higher in non-T1DM children.

***Keywords*---**T1DM, peptide, children, antibody, diabetes

Introduction

The incidence of Type 1 Diabetes Mellitus (T1DM) is increasing worldwide. Every year, it is estimated that 96,000 children under the age of 15 years are diagnosed with T1DM (IDF, 2017). Furthermore, approximately 600,000 children below 15 are currently living with T1DM. This number almost doubles to 1.1 million for persons under 20 years (Patterson et al., 2019). According to the Indonesian Paediatrician Association, there were 1,220 Indonesian children diagnosed with T1DM in 2018 (Pulungan et al., 2019). Insulin deficiency due to the damage of beta cells pancreas underlies the development of T1DM. The causes of T1DM are complex and multifactorial, with a combination of genetic and environmental factors resulting in an autoimmune reaction (Robertson and Rich, 2018; Lete et al., 2016; Noble, 2015).

The major genetic determinants of T1DM are polymorphisms of Human Leukocyte Antigen (HLA) Class II, consisting of alpha and beta chains. The encoding process from different alleles generates high polymorphism characteristics in this locus. Furthermore, the genes encoding the HLA-DQ and HLA-DR proteins are the main risk factors associated with several autoimmune diseases (Carlsson et al., 2012; Stayoussef et al., 2009; Farina et al., 2019). Several studies demonstrated that specific alleles at the DRB1, DQA1, and DQB1 loci are strongly associated with T1DM (Noble, 2015 and Farina et al., 2019). According to the central dogma theory, the passage of genetic information from genes into RNA, which then then pass to amino acid (Costa et al., 2021). The HLA-DQA1 and HLA-DQB1 genes synthesize HLA-DQA1 and HLA-DQB1 peptides, respectively. The HLA genes encoding HLA class I and II proteins represent peptides that form protein degradation (Sperling, 2020; Dudek and Purcell, 2016; Van et al., 2016). Other established markers of the T1DM-associated autoimmune process are Islet Cell Autoantibody (ICA), Glutamic Acid Decarboxylase Antibody (GAD65), Zinc-Transporter 8 antibody (ZnT8), and Insulin Autoantibody (IAA) (Robertson and Rich, 2018; Koo et al., 2014; Miersch et al., 2013). Genetic polymorphism and antibody levels in individuals with T1DM varied by ethnicity (Robertson and Rich, 2018 and Noble, 2015). The autoimmune process was characterized by a positive

autoimmune marker followed by beta cell pancreas destruction. Examination of C-peptide defines residual pancreatic cells (Sperling, 2020).

Genetic and autoantibody variation at these loci may interfere with the peptide pool to initiate an immune response that plays a vital role in the pathogenesis of T1DM. However, studies about this concern of T1DM children in Indonesia remain limited. Therefore, this study aimed to analyze ZnT8, GAD65 antibody, HLA-DQA1, HLA-DQB1, and C-peptide of children with T1DM in Indonesia. Recognizing this relationship should be essential in determining pediatric susceptibility to T1DM.

Method

This cross-sectional study was conducted in the pediatric outpatient clinic of Dr. Soetomo General Hospital Surabaya, Indonesia, and has been approved by the Ethical Board Committee (approval no. 1889/KEPK/III/2020). Informed consent was obtained from the participants and their guardians. This study was performed following The Declaration of Helsinki. A total of 31 patients, aged 4-18 years old, diagnosed with T1DM according to American Diabetes (ADA, 2011), and routinely controlled were included. Comparatively, as controls, this study included 31 healthy children that also visited the outpatient clinic and had no history of T1DM, autoimmune disease, allergy, malignancy, or ongoing infection. The sample size was based on the calculation formula in a cross-sectional study. Participants' clinical characteristics such as sex, age, ethnicity, age of onset, duration of T1DM, weight, and height were obtained.

Sample Collection and Laboratory Assay

Peripheral blood mononuclear cells (PBMC) samples were drawn from each participant for plasma protein examination, including ZnT8, GAD65, HLA-DQA1, HLA-DQB1, and C-peptide. This examination was performed with an Enzyme-linked Immunosorbent Assay (ELISA) kit. The GAD65 antibody was assessed with Human GAD 1 ELISA kit from Merck, while the ZnT8 antibody was examined with Human ZnT8 ELISA Kit from Bioassay Technology Laboratory. The C-peptide was analyzed using Maglumi C-peptide (CLIA) from Bioassay Technology Laboratory. Analysis of the HLA-DQA1 peptide was conducted utilizing the HLA Class 2 Histocompatibility Antigen-DQ Alpha 1 Chain ELISA Kit from My BioSource (Cat.NO MBS1603573). Meanwhile, the HLA-DQB1 peptide was examined with HLA Class 2 Histocompatibility Antigen-DQ Beta 1 Chain ELISA Kit from My BioSource (Cat.NO MBS1603563). The interpretation of these examinations was a numeric number with units of ng/ml.

Statistical Analysis

The data were analyzed with Statistical Package for Social Sciences ver. 17.0 (SPSS Inc., Chicago, USA). Description analysis was performed to evaluate the distribution of the participants' characteristics. Furthermore, nominal variables are expressed by numbers (percentages), while values were described using mean ± standard deviation or median (minimum-maximum) based on their Kolmogorov-

Smirnov normality test. The differences in nonparametric data were determined using Mann-Whitney Test, with $p<0.05$ considered statistically significant.

Results

There were 31 subjects in the T1DM group, which included 19 males and 12 females, aged 15.04 ± 3.88 years. Furthermore, the control group consists of 31 healthy children, including 16 males and 15 females, aged 10.57 ± 2.39 years. The mean duration of illness in the T1DM group was 7.06 ± 4.18 years. Table 1 summarizes the baseline characteristics of the subjects. There was no significant difference in HLA-DQA1 and HLA-DQB1 peptide levels between T1DM and control groups ($p = 0.12$; $p = 0.19$). Meanwhile, the values of ZnT8, GAD65, and C-Peptide between T1DM and control groups showed a significant difference ($p<0.05$). The results of the peptide examination are shown in Table 2. Furthermore, 74% of T1DM children had two autoantibodies, and 55% had two HLA peptides. Table 3 shows no correlation between the number of antibodies and clinical characteristics in patients with T1DM.

Table 1. Participants' clinical characteristic

Characteristic	T1DM group (n = 31)	Control group (n = 31)
Sex		
Male	19 (61.3)	16 (51.6)
Female	12 (38.7)	15 (48.4)
Ethnicity		
Javanese	27 (87.1)	31 (100)
Maduranese	1 (3.2)	0 (0)
Chinnese	1 (3.2)	0 (0)
Malay	2 (6.4)	0 (0)
Age (years)	15.04 ± 3.88	10.57 ± 2.39
Age of onset (years)	9 (1-16)	-
Duration of T1DM (years)	7.06 ± 4.18	-
Height (m)	1.45 ± 0.18	1.29 ± 0.15
Weight (kg)	45 (9-61)	23 (13-53)
BMI (kg/m^2)	20 (10.94-30.18)	17.7 (13.42-22.91)

T1DM, Type 1 Diabetes Mellitus; BMI, Body Mass Index

Table 2. Tested autoantibodies and HLA protein in T1DM and control groups

	T1DM group	Control group	p-value
ZnT8-ab (%)	24 (77.4)	2 (6.5)	0.00*
ZnT8-ab titre (ng/ml)	0.35 (0.18-5.48)	0.27 (0.12-3.68)	0.00*
GAD65-ab (%)	28 (90.3)	2 (6.5)	0.00*
GAD65-ab titre (ng/ml)	10.18 (3.83-24.88)	4.11 (3.95-5.00)	0.00*
C-peptide (%)	27 (87.1)	11 (35.5)	0.00*
C-peptide titre (ng/ml)	0.68 (0.61-2.42)	1.00 (0.70-4.92)	0.00*

HLA-DQA1 peptide (%)	30 (96.8)	29 (93.5)	0.50
HLA-DQA1 peptide titre (ng/ml)	2.12 (0.84-6.60)	1.89 (0.75-3.65)	0.12
HLA-DQB1 peptide (%)	17 (54.8)	19 (61.3)	0.80
HLA-DQB1 peptide titre (ng/ml)	1.72 (1.05-9.27)	2.12 (1.02-8.89)	0.19

*Statistically significant; T1DM, Type 1 Diabetes Mellitus; ZnT8, Zinc Transporter 8; GAD65, Glutamic Acid Decarboxylase-65; HLA-DQA1, Human Leukocyte Antigen-DQ Alpha chain 1; HLA-DQB1, Human Leukocyte Antigen-DQ Beta chain 1

Table 3. Associations of the number of autoantibodies with clinical characteristic T1DM patients

	Autoantibody			
	0 AAb	1 AAb	2 AAb	P-Value
Age (years)	13.79 ± 0.33	15.07 ± 4.93	15.15 ± 3.85	0.89[a]
Age of onset (years)	3.00 ± 1.42	7.50 ± 3.51	8.74 ± 3.62	0.11
Duration of T1DM (years)	11.00 ± 1.41	7.50 ± 6.35	6.61 ± 3.60	0.36[a]
Height (meter)	1.45 ± 0.12	1.48 ± 0.22	1.45 ± 0.19	0.94[a]
Weight (kg)	48.50 ± 16.26	42.47 ± 15.34	42.15 ± 14.56	0.88
BMI (kg/m^2)	22.82 ± 3.98	19.05 ± 5.96	19.15 ± 4.14	0.39

a, One-way Anova; k, Kruskal-Wallis; AAb, auto-antibody; T1DM, Type 1 Diabetes Mellitus; BMI, Body Mass Index

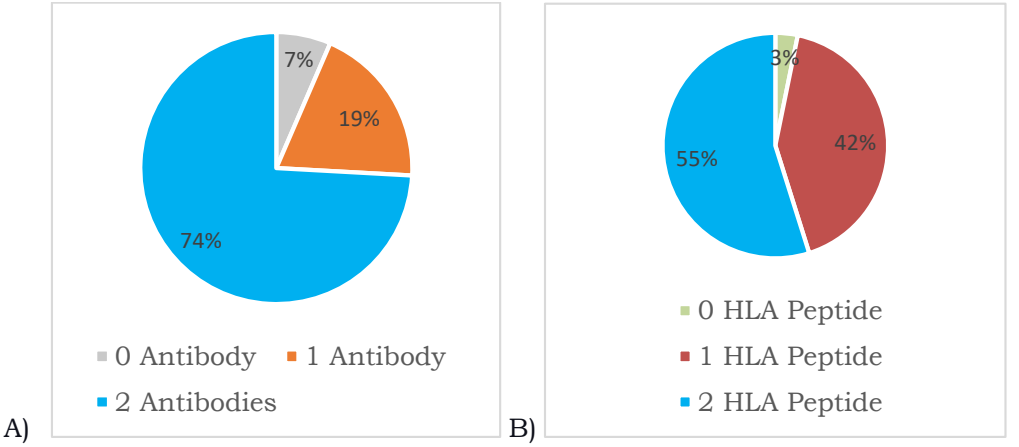


Figure 1. Summary of peptide examination on T1DM subjects. (A) Number of T1DM subjects with 0,1, and 2 autoantibodies (ZnT8 and GAD65). (B) Number of T1DM subjects with 0,1, and 2 HLA peptide (HLA-DQA1 and HLA-DQB1).

Discussion

This study showed that ZnT8 and GAD65 antibodies were more frequent in the T1DM group. Several studies also reported that ZnT8 and GAD65 were the most prevalent autoantibody in T1DM children (Robertson and Rich, 2018; Koo et al., 2014; Miersch et al., 2013). Another study also showed that GAD65, ZnT8, IA-2A, and IAA antibodies are reliable biomarkers for diagnosing T1DM in children and adults (Jahromi and Al Ozairi, 2019).

The Glutamic Acid Decarboxylase antibodies were sdetected in 90.3% of children with T1DM. This GAD65 prevalence was higher than the other studies in Saudi Arabia (84,4%) (Al-Alwan et al., 2012), Sudan (77.5%) (Mahdi et al., 2019), Qatar (59,7%) (Haris et al, 2021), and India (53%) (Vipin et al., 2021). Zinc Transporter-8 antibody prevalence in T1DM children in this study was 77,4%. This result was similar to another study in Indonesia, where 73.3% of T1DM patients were positive for ZnT8 antibody compared to the control group, which was 27.8% (Rochmah et al., 2020). The result of ZnT8 positivity in another country was reported to be 72% in Czechs (Petruzelkova et al., 2014), 65% in Argentinians (Faccinetti et al., 2016), 58.6% in Turkish (Elmaoğulları et al., 2018), 29% in India (Vipin et al., 2021), 24.1% in Chinese (Yang et al., 2010), and 16.3% in Sudan (Mahdi et al., 2019).

The other results in this study showed no difference in HLA-DQA1 and HLA-DQB1 peptide values between the T1DM and control group. HLA-DQA1 peptide median was higher in T1DM children, while the HLA-DQB1 peptide median was higher in non-T1DM children. Currently, few studies describe HLA-DQA1 peptide levels on T1DM children. Most studies focused on the expression of HLA genes rather than their peptides. However, the central dogma theory could illustrate why children with T1DM have higher HLA-DQA1 peptide levels. Central dogma theory is the basis of cellular life, which fundamentally discusses the process of cell division through the information coded by DNA, transcribed into RNA, and then translated into proteins (Costa et al., 2021). Furthermore, the central dogma theory discusses the transfer of sequences during DNA replication, transcription, and translation into chains of amino acids to form proteins. According to this theory, higher levels of HLA-DQA1 peptide may be associated with increased levels of the HLA-DQA1 gene in children with T1DM.

HLA encoded by the significant MHC genes plays a crucial role in the antigen presentation to T lymphocytes. In conjunction with the inadequate function of regulatory T lymphocytes (TREG), some HLA genes cause an autoimmune disorder. In Caucasian populations, HLA-DR3-DQ2 and HLA-DR4-DQ8 haplotypes were related to T1DM (Chiarelli et al., 2019). Furthermore, polymorphisms of DQA1, DQB1, and DRB1 alleles were used to determine genetic susceptibility (Onengut-Gumuscu et al., 2015). Some studies showed that HLA class II dimer αβ encoded by HLA-DQA1*0102/DQB1*0602(DQ0602) was a protective allele in T1DM (Ettinger et al., 2000). The HLA-DQB1 and HLA-DQA1 peptides were bonded to form a functional protein complex called antigen-binding DQ-α-β heterodimer, presenting peptide non-self into the immune system (Yahya and Salisu, 2020). The most frequent HLA in Indonesian children with T1DM were HLA-DQA1 0101/0102 and HLA-DQB1 0301 (Soetjipto et al., 2022). Additionally,

HLA polymorphism was an adaptive mechanism with peptide antigens. Most nucleotide polymorphisms occur in exon 2 of the HLA class II (Mosaad, 2015). Post-translational modification of antigens affects the activation of immunogenic epitopes during antigen processing (Scally et al., 2013), thereby modifying the spectrum of presented peptides. Alterations of peptide antigens can influence their binding to specific HLA alleles (Purcell et al., 2019). Allele-encoding aspartic acid (Asp) at β57 of HLA-DQB1 is associated with the resistance of T1DM. Whereas alleles encoding a neutral residue, such as Alanine (Ala) or Serine (Ser) at β57 showed susceptibility of T1DM. The molecules Alanine and Serine are the risk factors for T1DM, specifically at the peptide-binding pocket nine (P9) of the DQB1-binding pocket that is involved in antigen presentation and T cell receptor interaction. The carboxylate group forms a salt bridge with Arginine (Arg) at α57 of HLA-DQA1, stabilizing the heterodimer between the DQA1 and DQB1 chains. Aspartate in this position affects the molecule's stability and antigen presentation, making the molecules easier to bind with autoreactive antigen. Individuals with T-cells recognize peptides that present HLA. This phenomenon is called HLA restriction (Mosaad, 2015). The understanding of T-cell reactivity and the role of post-translational modifications lead to a new diagnostic and treatment of T1DM (Purcell et al., 2019).

In this study, 93% of T1DM children have one or more antibodies. This result is in accordance with a study in Sudan, which showed that 91,2% of children with T1DM have at least one autoantibody (Mahdi et al., 2019). A similar result was reported in a different countries, including Lithuania (92.5%) (Verkauskiene et al,m 2016), India (72%) (Vipin et al., 2021), and United Arab Emirates (88%) (Al-Hassanni et al., 2014). Furthermore, this emphasizes the need for multiple antibody examinations before ruling out immune-mediated T1DM (Mahdi et al., 2019).

The mean age of onset in the autoantibody-positive group was higher than in the autoantibody-negative group. However, this result was not statistically significant ($p = 0.89$). Another study showed no difference in the mean age of T1DM diagnosis between the seropositive and seronegative groups (Mahdi et al., 2019). This is contrary to a study which stated that T1DM children with multiple antibodies had an earlier age of diagnosis compared to the single antibody group. Genetic susceptibility to HLA polymorphisms is associated with earlier age of diagnosis (Mrena et al., 2006).

There was no difference in the duration of T1DM between the negative and positive antibodies. This result was in accordance with the findings of a previous study (Mahdi et al., 2019 and Balasubramanian et al., 2003). The mean BMI was statistically insignificant between the three groups, with the negative autoantibody being higher (22.82 ± 3.98) than the one or two positive antibodies (19.05 ± 5.98; 19.15 ± 4.14). Furthermore, this was similar to a study in another country (Mahdi et al., 2019 and Balasubramanian et al., 2003). The limitation of this research is a single-centre study, which can lead to centre bias. Despite the limitation, the strength of this study was examined several peptides for T1DM where the study was still limited. The examination of peptides is less expensive and takes less time than genetic examination. Therefore, it is more applicable to use peptides examination for T1DM in children.

Conclusion

The most common antibody in the T1DM in this study was GAD65 antibody. HLA-DQA1 peptide value was higher in T1DM children and HLA-DQB1 peptide value was higher in non-T1DM children. Further research is required to identify another peptide of T1DM patients in Indonesia.

Acknowledgment

Authors would like to thank the patients, patient's family, and pediatric endocrine team of General Hospital Dr. Soetomo Surabaya.

Authors' contribution

NR and MF conceptualized, designed the study, analysed data, interpreted results, wrote the initial draft of the manuscript. YH and RKP analysed data, interpreted results, assisted in drafting the manuscript. SS and AE critically reviewed the manuscript, guided manuscript writing. TMN collected data, prepared the figure and tables, analysed data. All author agreed and give final approval to the submitted manuscript.

Funding
None

Competing interest
No conflicts of interest related to this work

References

Al-Alwan I., Bin Dajim N., Jawdat D., Tamim W., Al-Ahmdi R., Albuhairan F. (2012). Prevalence of autoantibodies in children newly diagnosed with type 1 diabetes mellitus. Br J Biomed Sci, 69(1):31-3.

Al-Hassani N., Chedid F., Hadi S., Kaplan W. (2014). Prevalence of autoantibodies in type 1 diabetes patients and its association with the clinical presentation – UAE Eastern Region experience. J Pediatr Endocrinol Metab,, 27(11-12):1157-9.

American Diabetes Association. (2011) Standards of medical care in diabetes 2012. Diabetes Care, 35(1):11-63.

Balasubramanian K., Dabadghao P., Bhatia V., *et al.* (2003). High Frequency of Type 1B (Idiopathic) Diabetes in North Indian Children with Recent-Onset Diabetes. Diabetes Care, 26(9):2697

Carlsson A., Kockum I., Lindblad B., Engleson L., Nilsson A., Forsander G., *et al.* (2012). Low risk HLA-DQ and increased body mass index in newly diagnosed type 1 diabetes children in the Better Diabetes Diagnosis study in Sweden. Int J Obes, 36(5):718–724.

Chiarelli F., Giannini C., Primavera M. (2019). Prediction and prevention of type 1 diabetes in children. Clin Pediatr Endocrinol, 28(3):43-57.

Costa Dos Santos G., Renovato-Martins M., de Brito N.M. (2021). The remodel of the "central dogma": a metabolomics interaction perspective. Metabolomics, 17:48.

Dudek N.L., Purcell A.W. (2014). The beta cell immunopeptidome. Vitam Horm, 95:115-44.

Elmaoğulları S., Uçaktürk S.A., Elbeg Ş., Döğer E., Tayfun M., Gürbüz F., *et al.* (2018). Prevalence of ZnT8 Antibody in Turkish Children and Adolescents with New Onset Type 1 Diabetes. J Clin Res Pediatr Endocrinol, 10(2): 108-12.

Ettinger R.A., Liu A.W., Nepom G.T., Kwok W.W. (2000). Beta 57-Asp Plays an Essential Role in the Unique SDS Stability of HLA-DQA1*0102/DQB1*0602 alpha beta Protein Dimer, the Class II MHC Allele Associated with Protection from Insulin-Dependent Diabetes Mellitus. J Immunol, 165(6):3232-8.

Faccinetti N.I., Guerra L.L, Penas Steinhardt A., Lacono R.F., Frechtel G.D., Trifone L., *et al.* (2016). Characterization of zinc transporter 8 (ZnT8) antibodies in autoimmune diabetic patients from Argentinian population using monomeric, homodimeric, and heterodimeric ZnT8 antigen variants. Eur J Endocrinol,174(2):157-65. s

Farina F., Picascia S., Pisapia L., Barba P., Vitale S., Franzese A., *et al.* (2019). HLA-DQA1 and HLA-DQB1 alleles, conferring susceptibility to Celiac Disease and Type 1 Diabetes, are more expressed than non-predisposing alleles and are coordinately regulated. Cells, 8(7):751.

Haris B., Ahmed I., Syed N., Almabrazi H., Saraswathi S., Al-Khawaga S., et al. (2021). Clinical features, epidemiology, autoantibody status, HLA haplotypes and genetic mechanisms of type 1 diabetes mellitus among children in Qatar. Sci Rep, 11:18887.

International Diabetes Federation. (2017). IDF Diabetes Atlas Eighth edition. IDF

Jahromi M., Al Ozairi E. (2019). Human Leukocyte Antigen (HLA) and Islet Autoantibodies Are Tools to Characterize Type 1 Diabetes in Arab Countries: Emphasis on Kuwait. Dis Markers, 9786078:1-10.

Koo B.K., Chae S., Kim K.M,, Kang M,J,, Kim E,G., Kwak S.H., *et al.* (2014). Identification of novel autoantibodies in type 1 diabetes patients using a high density protein microarray. Diabetes, 63:3022-32

Leete P., Willcox A., Krogvold L., Dahl-Jogersen K., Foulis A.K., Richardson S.J., *et al.* (2016). Differential insulitic profiles determine the extent of β- cell destruction and the age at onset of type 1 diabetes. Diabetes; 65 (5):1362- 9.

Mahdi Y.R., Hashim U., Abdullah M.A. (2019). Pancreatic Autoantibodies in Sudanese Children with Newly Diagnosed Type 1 Diabetes Mellitus. Int J Diabetes Clin Res, 6:107.

Miersch S., Bian X., Wallstrom G., Sibani S., Logvinenko T., Wasserfall C.H., *et al.* (2013). Serological autoantibody profiling of type 1 diabetes by protein array. J proteomics, 94:486-96.

Mosaad Y.M. (2015). Clinical Role of Human Leukocyte Antigen in Health and Disease. Scand J Immunol, 82(4):283–306.

Mrena S., Virtanen S.M., Laippala P., Kulmala P., Hannila M.L., Akerblom H.K., *et al.* (2006). Models for Predicting Type 1 Diabetes in Siblings of Affected Children. Diabetes Care, 29(3):662-7.

Noble J.A. (2015). Immunogenetics of type 1 diabetes: a comprehensive review. J Autoimmun, 64:101-12.

Onengut-Gumuscu S., Chen W.M., Burren O., Cooper N.J., Quinlan A.R., Mychaleckyj J.C., *et al.* (2015). Fine mapping of type 1 diabetes susceptibility loci and evidence for colocalization of causal variants with lymphoid gene enhancers. Nat Genet, 47:381-6.

Patterson C.C., Karuranga S., Salpea P., Saeedi P., Dahlquist G., Soltesz G., *et al.* (2019). Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract, 157:1

Petruzelkova L., Ananieva-Jordanova R., Vcelakova J., Vesely Z., Stechova K., Lebl J., *et al.* (2014). The dynamic changes of zinc transporter 8 autoantibodies in Czech children from the onset of Type 1 diabetes mellitus. Diabet Med, 31(2):165-71.

Pulungan A.B., Annisa D., Imada S. (2019) Diabetes Melitus Tipe-1 pada Anak: Situasi di Indonesia dan Tata Laksana. Sari Pediatri, 20(6):392-400.

Purcell A.W., Sechi S., DiLorenzo T.P. (2019). The Evolving Landscape of Autoantigen Discovery and Characterization in Type 1 Diabetes. Diabetes, 68(5):879–86.

Robertson C.C., Rich S.S. (2018) Genetics of type 1 diabetes. Current Opinion in Genetics & Development, 50:7–16.

Rochmah N., Faizi M., Windarti S.W. (2020). Zinc transporter 8 autoantibody in the diagnosis of type 1 diabetes in children. Clin Exp Pediatr, 63(10):402-5.

Scally S.W., Petersen J., Law S.C., Dudek N.L., Nel H.J., Loh K.L., *et al.* (2013). A molecular basis for the association of the HLA-DRB1 locus, citrullination, and rheumatoid arthritis. J Exp Med, 210(12):2569-82

Soetjipto, Rochmah N., Faizi M., Hisbiyah Y., Endaryanto A. (2022) HLA-DQA1 and HLA-DQB1 Gene Polymorphism in Indonesian Children with Type I Diabetes Mellitus. Appl Clin Genet, 15:11-17.

Sperling M. (2020). Sperling Pediatric Endocrinology fifth edition. Elsevier.

Stayoussef M., Benmansour J., Al-Jenaidi F.A. (2009). Influence of common and specific HLA-DRB1/DQB1 haplotypes on genetic susceptibilities of three distinct Arab populations to type 1 diabetes. Clin Vaccine Immunol, 16(1):136.

Van Lummel M., Van Veelen P.A., De Ru A.H., Pool J., Nikolic T., Laban S., *et al.* (2016). Discovery of selective islet peptidome presented by the highest risk HLA-DQ8trans molecule. Diabetes, 65(3):732-41.

Verkauskiene R., Danyte E., Dobrovolskiene R., Stankute I., Simoniene D., Razanskaite-Virbickiene D., *et al.* (2016). The course of diabetes in children, adolescents and young adults: does the autoimmunity status matter? BMC Endoc Disord, 16(1):61.

Vipin V.P., Zaidi G., Watson K., Colman P.G., Prakash S., Agrawal S., *et al.* (2021). High prevalence of idiopathic (islet antibody-negative) type 1 diabetes among Indian children and adolescents. Pediatr Diabetes, 22(1):47–51.

Yahaya T., Salisu T. (2020). Genes predisposing to type 1 diabetes mellitus and pathophysiology: a narrative review. Med J Indones, 29(1):100-9.

Yang L., Luo S., Huang G., Peng J., Li X., Yan X., *et al.* (2010) The diagnostic value of zinc transporter 8 autoantibody (ZnT8A) for type 1 diabetes in Chinese. Diabetes Metab Res and Rev, 26(7):579–584.