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Original article

Meta-analysis of Interleukin-6 association with glycated hemoglobin (HbA1c) in pediatric type 1 diabetes mellitus

Sally Rizkita Lestari[1,2], *Anang Endaryanto*[1,2], *Nur Rochmah*[1,2], *Citrawati Dyah Kencono Wungu*[3,4]

[1]Department of Child Health, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia; [2]Department of Child Health, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia; [3]Department of Physiology and Medical Biochemistry, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia; [4]Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia

Abstract. Background and aim: Type 1 diabetes mellitus (T1DM) is a chronic illness characterized by the destruction of insulin-secreting pancreatic β-cells. Poor glycemic control in T1DM patients, as reflected by glycated hemoglobin A1c (HbA1c) levels, increases pro-inflammatory cytokine levels, including interleukin-6 (IL-6). This could potentially lead to complications. Research on the correlation between IL-6 and HbA1c levels in children with T1DM has shown conflicting results. Methods: A literature search was conducted on four databases for observational studies investigating the correlation between IL-6 and HbA1c levels in children with T1DM up to June 2024. A random meta-analysis model was performed. Fisher's r-to-z transformation was applied to standardize effect sizes for each correlation coefficient. Statistical significance was set at $p < 0.05$ for all analyses. Results: This study included 12 observational studies, six of which were cross-sectional. Published between 2003 and 2024, these studies involved 967 children. A pooled correlation coefficient value of 0.29 (95% CI: -0.04 - 0.56) with a p-value of 0.08 was obtained. Conclusions: The correlation between IL-6 and HbA1c levels in children with T1DM showed a trend toward statistical significance. Although not statistically significant, this trend may still be important for understanding the inflammatory processes in T1DM. The weak correlation found between IL-6 and HbA1c levels in these children suggests that elevated pro-inflammatory cytokine concentrations were associated to poor glycemic control. (www.actabiomedica.it)

Key words: child, type 1 diabetes mellitus, interleukin-6, glycated hemoglobin a, meta-analysis

Introduction

Type 1 diabetes mellitus (T1DM) is a chronic illness characterized by the destruction of insulin-secreting pancreatic β-cells. Consequently, patients require long-term insulin treatment (1). Among children and adolescents, T1DM is the predominant form of diabetes, comprising over 90% of diabetes cases in numerous Western nations, surpassing other varieties, such as type 2 diabetes mellitus (T2DM) and monogenic diabetes (2). The incidence is increasing in most populations, with an annual average increase of 3-4% (3). Recent studies have emphasized the significant role of cellular autoimmunity in T1DM (4-6). Pro-inflammatory cytokines, such as interleukin-6 (IL-6), have been identified as contributors to the pathogenesis of T1DM (7,8) and play a role in T1DM complications, including the early stages of atherogenesis and microvascular complications (9). While its precise function remains unclear, IL-6 has been explored as a potential therapeutic target for T1DM (7). Research on adolescents with T1DM revealed that poor glycemic control,

as reflected by glycated hemoglobin A1c (HbA1c) levels, increases pro-inflammatory cytokine levels, potentially leading to a higher incidence of peripheral neuropathy and reduced bone mineral density (10). An additional study focusing on children revealed a substantial correlation between tumor necrosis factor-alpha (TNFα) and IL-6 with HbA1c; however, their levels were not notably increased in the diabetes group compared to those in the control group (11), whereas other studies revealed a negative correlation (12,13). Given these findings, a thorough review and meta-analysis are needed to examine the correlation between interleukin-6 levels, an inflammatory marker, and HbA1c levels, which reflect glycemic control, in children with type 1 diabetes mellitus.

Methods

This review adhered to the PRISMA 2020 protocol guidelines for systematic reviews and meta-analyses (14). The research was formally registered in the PROSPERO database with the identifier CRD42024518546.

Searching strategy

Electronic databases such as PubMed, Science Direct, and Scopus were extensively searched. Gray literature with a Google Scholar search was also examined for relevant articles to mitigate publication bias, as database searches alone are not sufficiently comprehensive. Search terms were constructed using a combination of Medical Subject Heading terms and free text, incorporating the following concepts: "type 1 diabetes" OR "insulin-dependent diabetes" OR "T1DM" OR "A1c" OR "HbA1c" AND "interleukin-6" OR "IL-6". The search encompassed studies published from each database's inception until June 25, 2024. Table 1 provides a detailed overview of the complete search strategy employed.

Eligibility criteria

The study selection was based on the following inclusion criteria: (1) research with the presence of correlation coefficient (r) regarding the correlation between IL-6 and HbA1c levels in children with T1DM, (2) publications in English, and (3) observational study methodology. Studies were excluded if they were: (1) non-research publications (such as conference papers, book chapters, or reports), review articles, or laboratory studies involving animals; (2) duplicate publications; (3) lacking complete or adequate data; or (4) limited to abstracts or conference presentations only.

Selection of studies and extraction of data

For duplicate removal and study screening, Mendeley Desktop version 1.19.8 (Elsevier, Mendeley Ltd.) was employed. Data extraction included: lead author, publication year, country, sample size, age,

Table 1. The detailed overview of the complete search strategy.

Database	Search terms
PubMed	((((((((((((((type 1 diabetes mellitus[MeSH Terms]) OR (autoimmune diabetes[MeSH Terms])) OR (insulin dependent diabetes mellitus[MeSH Terms])) OR (type 1 diabet*[Title/Abstract])) OR (autoimmune diabet*[Title/Abstract])) OR (insulin dependent diabet*[Title/Abstract])) OR ("t1d"[Title/Abstract])) OR ("t1dm"[Title/Abstract])) OR ("idd"[Title/Abstract])) OR ("iddm"[Title/Abstract])) OR ("tid"[Title/Abstract])) OR ("tidm"[Title/Abstract])) OR (hb a1[MeSH Terms])) OR (glycated hemoglobins[MeSH Terms])) OR ("a1c"[Title/Abstract])) OR (hba1*[Title/Abstract])) OR ("glycated hemoglobin"[Title/Abstract]) AND ((interleukin 6[MeSH Terms]) OR ("interleukin 6"[Title/Abstract])) OR ("il 6"[Title/Abstract])
Science Direct	((type 1 diabetes) OR (insulin dependent diabetes) OR (autoimmune diabetes) OR (T1D) OR (A1c) OR (glycated hemoglobin) OR (HbA1c)) AND ((interleukin-6) OR (IL-6))
Scopus	(("type 1 diabetes") OR (T1DM) OR (T1D) OR (IDDM) OR (IDD) OR ("hemoglobin A1c") OR (HbA1c) OR ("glycated hemoglobin*")) AND (("Interleukin 6") OR (IL6) OR ("IL 6"))

study design, IL-6 and HbA1c results, diagnostic method, and correlation coefficient (r). Two separate researchers entered eligible studies into a predetermined spreadsheet. A third researcher resolved any disputes regarding study inclusion or exclusion. The Newcastle-Ottawa scale (NOS) was used by two independent researchers to evaluate the quality of observational studies, including cohort, case-control, and cross-sectional designs. This assessment examined information bias, selection bias, and confounding factors. Based on NOS scores, studies were classified as high quality (7-9 points), moderate quality (4-6 points), or low quality (0-3 points) (15).

Analysis of statistical data

To standardize effect sizes for each correlation coefficient, Fisher's r-to-z transformation was employed. This process involved converting Spearman's or Pearson's correlation coefficient (r) into approximately normally distributed Z-values. The Z-value's standard error was then calculated, and inverse Fisher's transformation was utilized to produce r and 95% CI. Chi-squared and I-squared (I2) statistics were used to assess heterogeneity, with I-squared values of 25%, 50%, and 75% interpreted as low, moderate, and high heterogeneity, respectively (16). All pooled analyses utilized a random-effects model. To ensure result consistency, a sensitivity analysis was performed by excluding factors that might influence outcomes. Furthermore, a one-leave-out sensitivity analysis was conducted by removing individual studies. Publication bias was visually examined through funnel plot asymmetry and evaluated using Egger's and Begg's tests. For all analyses, statistical significance was set at $p < 0.05$. The meta-analysis was performed using Review Manager 5.4 (Cochrane Collaboration, London, UK).

Results

Study identification

The initial literature search yielded 7,908 potential studies. Automated screening tools eliminated 5,803 articles, and 117 duplicates were removed, leaving 1,988 articles for further review. Screening of titles and abstracts excluded 1,752 articles, with 236 remaining for full-text evaluation. An additional 45 articles were excluded due to conference abstracts, posters, or unavailability of full-text articles, resulting in 191 articles for comprehensive analysis. Following a comprehensive evaluation, 181 studies were eliminated due to no correlation analysis between interleukin-6 and HbA1c levels, lack of sufficient data, non-English language, or unsuitable study design. Thirteen additional records were identified through website searches and reference list examinations. Of these, eleven were subsequently excluded because of unavailable full texts or duplication. The final selection process yielded 12 studies that satisfied the inclusion criteria. A PRISMA flow diagram illustrating the study selection process is presented in Figure 1.

Characteristics of the study

This meta-analysis incorporated twelve observational studies, comprising six cross-sectional, two cohort, and four case-control designs. The research spanned multiple continents, with three studies from Asia, four from Africa, three from Europe, and two from America. Published between 2003 and 2024, these investigations included 967 children, with individual study sample sizes varying from 10 to 314 participants. The subjects differed in age, duration of diabetes, presence of acute illness or complications, and glycemic control at the time of assessment. ELISA was the predominant method (83% of studies) for examining IL-6. A detailed summary of the included studies' characteristics is presented in Table 2. Four studies demonstrated a positive correlation between IL-6 and HbA1c levels in children with type 1 diabetes mellitus (9-11,17). Conversely, two studies reported a negative correlation (12,13). The remaining six studies showed no significant relationship (12,18-22).

Evaluation of study quality

To assess the quality of the twelve included studies, researchers utilized the Newcastle-Ottawa Scale (NOS), which was deemed suitable for the design of each study. The evaluation determined that nine studies

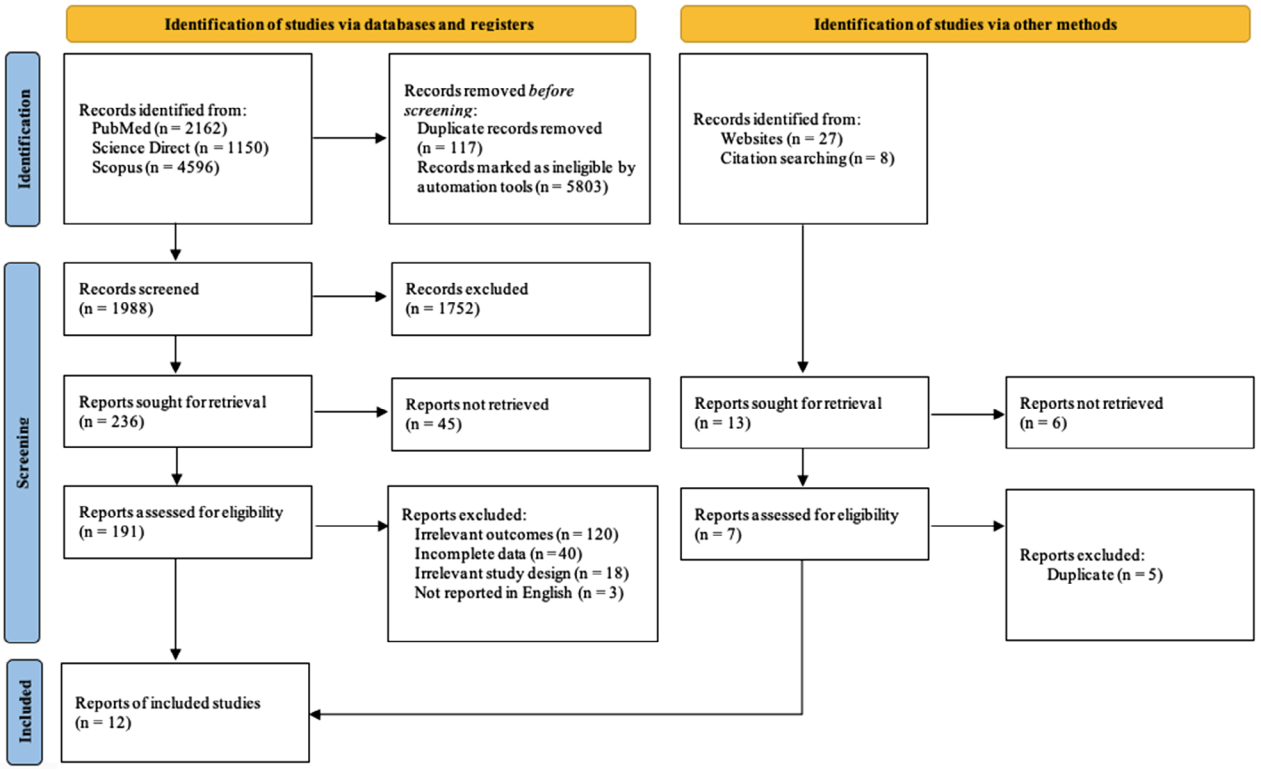

Figure 1. The study selection process using the PRISMA flow diagram.

were of high quality, while three were considered moderate quality. A comprehensive quality assessment for each study, using the NOS critical appraisal checklist, is provided in Table 3.

Correlation between IL-6 and HbA1c levels in children with type 1 diabetes mellitus

Examination of 12 studies showed Fisher's r-to-z transformed correlation coefficients spanning from -0.34 to 1.65, with a positive correlation observed in the majority (66.67%) of cases. High heterogeneity was detected, with an I2 value of 96% and a p-value of ≤0.001, necessitating a random-effects meta-analysis. A random-effects model yielded an estimated Fisher r-to-z transformed correlation coefficient of 0.30 (95% CI: -0.04 - 0.64), as shown in Figure 2. This value was subsequently converted to a pooled correlation coefficient of 0.29 (95% CI: -0.04 - 0.56), p = 0.08.

Sensitivity and subgroup analysis

Table 4 displays the outcomes of the sensitivity and subgroup analyses for the pooled correlation between IL-6 and HbA1c levels. Sensitivity analysis revealed that the correlation remained statistically non-significant, despite most pooled correlation coefficients being higher than those in the primary analysis. The considerable statistical heterogeneity in the primary analysis can be explained by subgroup effects related to continents and measurement methods. Among the non-Asian populations, the pooled correlation coefficient between IL-6 and HbA1c levels was notably lower (0.18 [0.07, 0.27], p ≤ 0.001). Moreover, in measurements using methods other than ELISA, the pooled correlation coefficient was 0.19 (0.08, 0.30), with a p-value ≤0.001.

A sensitivity analysis was not conducted for age categories or groups with controlled diabetes, as all studies involved adolescent age groups and participants

Table 2. Characteristics of the included studies

First author (year)	Country	Study design	Sample size	Characteristics of population	Age (year)	IL-6 (pg/ml)	HbA1c (%)	Laboratory measurement method for IL-6	Sample	Laboratory measurement method for HbA1c	Correlation coefficient (r), p value	NOS
Jain et al., 2003 (20)	US	cross sectional	34	T1DM children were divided into ketosis and non-ketosis groups	13 ± 1	-	10.8 ± 1	ELISA	Plasma	-	r = 0.13, p = 0.45	6
Wedrych wicz et al., 2004 (22)	Poland	cross sectional	10	T1DM children at onset	14.1 ± 1.7	3.79 ± 3.5	11.94 ± 3.3	ELISA	Serum	-	r = -0.02, p = 0.87	6
Fawaz et al., 2009 (17)	Egypt	cross sectional	70	T1DM children with duration more than 2 years, no symptoms of infection, malignancy, other systemic diseases were divided into controlled and uncontrolled	8.4 ± 3.84 10.17 ± 2.73	1.7 ± 0.3 3.5 ± 0.5	6.6 ± 0.21 10.3 ± 0.96	ELISA	Serum	-	r = 0.929, p < 0.0001	7
AboElAsrar et al., 2012 (10)	Egypt	cohort	60	T1DM adolescents	14.67 ± 1.54	290.53 ± 68.6	9.14 ± 2.88	ELISA	Serum	high performance liquid chromatography	r = 0.42, p = 0.022	7
Hammed et al., 2012 (9)	Iraq	case control	45	T1DM children with duration less than 5 years without complications and other acute or chronic diseases	10.98 ± 3.45	30.9 ± 10.85	8.35 ± 2.45	ELISA	Serum	high performance liquid chromatography	r = 0.882, p ≤ 0.001	8
Fahad et al., 2014 (19)	Bahrain	cross sectional	66	T1DM children were divided into newly diagnosed (≤3 months) and chronic (>3 months) groups	7.7 ± 4.2 11.75 ± 4.19	6.03 ± 2.29 2.58 ± 1.3	10.3 ± 0.36 7.43 ± 0.29	ELISA	Serum	quantitative coloreimetric determination of HbA1c analysis	r = 0.119, p > 0.05	7
Heier et al., 2015 (11)	Norway	cohort	314	T1DM children	13.7 ± 2.8	0.95 (0.68-1.4)	8.4 ± 1.2	enzyme immunoassays	-	high performance liquid chromatography	r = 0.207, p < 0.001	8

Table 2 (*Continued*)

First author (year)	Country	Study design	Sample size	Characteristics of population	Age (year)	IL-6 (pg/ml)	HbA1c (%)	Laboratory measurement method for IL-6	Sample	Laboratory measurement method for HbA1c	Correlation coefficient (r), p value	NOS
Abdel-Latif et al. (1), 2017 (12)	Egypt	cross sectional	100	T1DM children with negative antibody results against enterovirus	-	-	-	ELISA	Serum	HbA1c assays with commercial kits	r = 0.02, p = 0.808	7
Abdel-Latif et al. (2), 2017 (12)	Egypt	cross sectional	100	T1DM children with positive antibody results against enterovirus	-	-	-	ELISA	Serum	HbA1c assays with commercial kits	r = -0.33, p = 0.0009	7
Duque et al., 2017 (18)	Brazil	case control	24	T1DM children with dental conditions without extensive caries, who had not used antibiotics previously, without systemic diseases, without other immune diseases, were not undergoing dental treatment, and did not smoke	9.45 ± 1.69	1.26 ± 0.3	6.94 ± 1.58	ELISA	Serum	-	r = 0.0771, p = 0.844	6
Al-Dubayee et al., 2023 (13)	Saudi Arabia	case control	121	T1DM children without infectious diseases, other autoimmune diseases, asthma, allergies	10 (8-12)	-	9.6 (8.3-10.5)	ELISA	Plasma	the ARCHITECT / AEROSET system	r = -0.18, p < 0.05	9
Reis et al., 2024 (21)	Portugal	case control	23	T1DM children with duration of 2 years after diagnosis	15 (14-16)	7.1 (0.1-16)	7.5 (7.0-8.5)	multiplex immunoassays	-	-	r = -0.011, p > 0.05	7

ELISA, enzyme-linked immunosorbent assay; HbA1c, glycated hemoglobin A1c; IL-6, interleukin-6; NOS, Newcastle-Ottawa Scale; T1DM, type 1 diabetes mellitus.

Table 3. Results of quality assessment based on the Newcastle-Ottawa Scale.

First author (year)	Selection	Comparability	Outcome	Total score	Judgment
Jain et al., 2003 (20)	2	2	2	6	Moderate
Wedrychowicz et al., 2004 (22)	2	2	2	6	Moderate
Fawaz et al., 2009 (17)	4	2	3	9	High
AboElAsrar et al., 2012 (10)	3	2	2	7	High
Hammed et al., 2012 (9)	4	2	2	8	High
Fahad et al., 2014 (19)	3	2	2	7	High
Heier et al., 2015 (11)	3	2	3	8	High
Abdel-Latif et al. (1), 2017 (12)	3	2	2	7	High
Abdel-Latif et al. (2), 2017 (12)	3	2	2	7	High
Duque et al., 2017 (18)	2	2	2	6	Moderate
Al-Dubayee et al., 2023 (13)	4	2	3	9	High
Reis et al., 2024 (21)	3	2	2	7	High

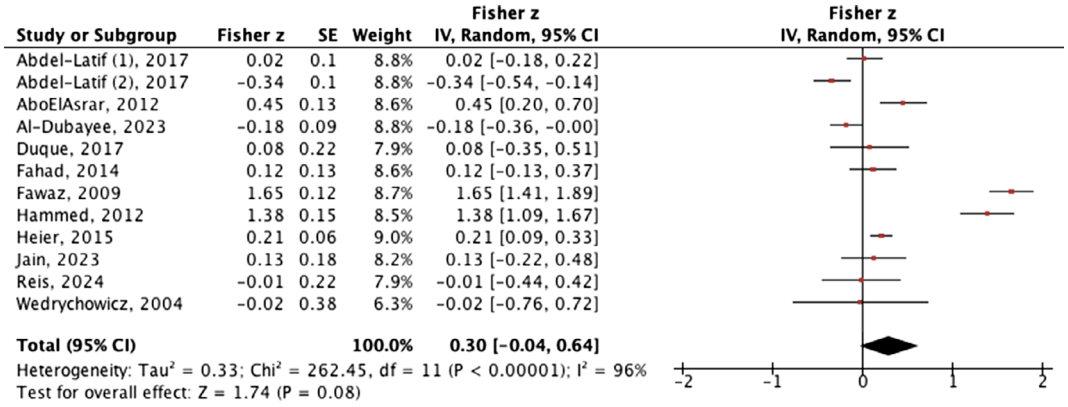

Figure 2. A forest plot illustrating the combined r value for the correlation between levels of interleukin-6 and HbA1c in pediatric patients diagnosed with type 1 diabetes mellitus.

with uncontrolled diabetes. An additional sensitivity analysis was conducted using a leave-one-out approach, in which each study was sequentially removed, and the meta-analysis was recalculated. This analysis identified that the study by Abdel-Latif et al. (2) showed a significant risk of bias, with a markedly lower correlation coefficient between IL-6 and HbA1c levels (-0.34[-0.54,-0.14], p = 0.0009). After excluding this study, the pooled correlation coefficient was 0.35 (95% CI: 0.01-0.61) with a p-value of 0.04.

Publication bias

The studies included in this research were deemed to have no publication bias, as evidenced by three factors: the nearly symmetrical appearance of the funnel plot (Figure 3), the Egger test results yielding a p-value of 0.79, and the Begg's test outcome producing a p-value of 0.68.

Discussion

Research on the correlation between IL-6 and HbA1c levels in children with T1DM has shown conflicting results. Through a comprehensive literature search, we selected an adequate number of studies to conduct a meta-analysis, including twelve literatures published between 2003 and 2024. Although the correlation did not reach statistical significance, there was

Table 4. Sensitivity and subgroup analyses.

	Pooled correlation coefficient	**p-value**
Primary analysis	0.29 (-0.04, 0.56), I2 = 96%, 12 studies (n = 967)	0.08
Including studies with serum-only sample	0.41 (-0.11, 0.75), I2 = 97%, 8 studies (n = 475)	0.12
Including high quality studies only	0.35 (-0.04, 0.64), I2 = 97%, 9 studies (n = 899)	0.07
Excluding studies at high risk of bias	0.05 (-0.12, 0.21), I2 = 77%, 10 studies (n = 852)	0.59
Excluding studies with small sample size (≤25)	0.36 (-0.02, 0.65), I2 = 97%, 9 studies (n = 910)	0.06
Excluding studies with diabetes duration ≤5 years	0.53 (-0.49, 0.94), I2 = 98%, 3 studies (n = 159)	0.31
Excluding studies with complication/comorbid	0.73 (-0.28, 0.94), I2 = 98%, 4 studies (n = 260)	0.16
Subgroup analysis		
Continents		
Asia	0.41 (-0.11, 0.76), I2 = 98%, 7 studies (n = 562)	0.12
Not Asia	0.18 (0.07, 0.27), I2 = 0%, 5 studies (n = 405)	≤0.001
Measurement methods		
ELISA	0.33 (-0.10, 0.65), I2 = 97%, 10 studies (n = 630)	0.13
Not ELISA	0.19 (0.08, 0.30), I2 = 0%, 2 studies (n = 337)	≤0.001

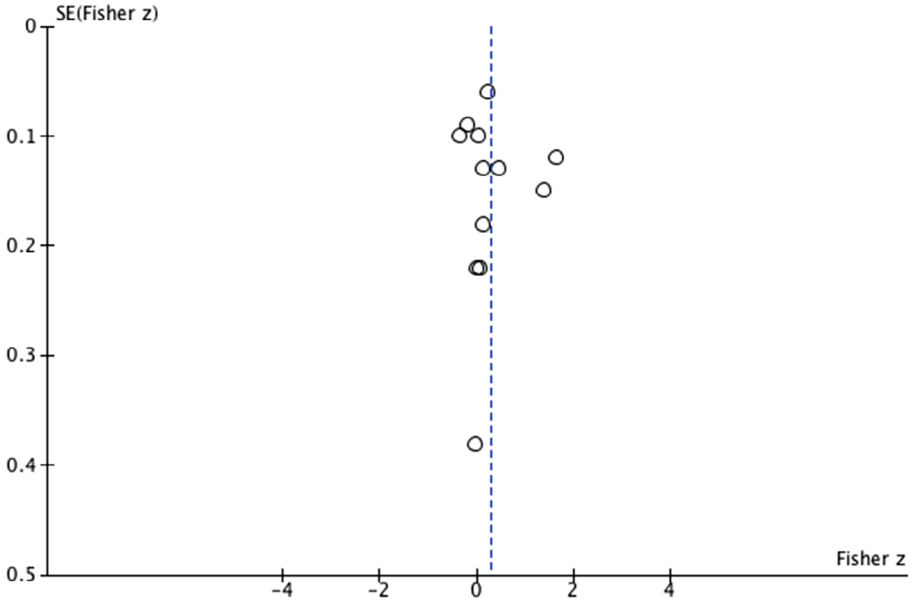

Figure 3. Funnel plot of the included studies.

a weak correlation between IL-6 and HbA1c levels in children with type 1 diabetes mellitus. Our finding aligns with the published studies (12,18-22). Several factors may have contributed to the lack of correlation between the two. These include age, diabetes duration, body mass index, history of complications and other illnesses, treatment history and adherence, and previous glucose control in each study. There was a balancing role of anti-inflammatory cytokines against pro-inflammation in diabetes. A study revealed no notable correlation between glycemic control and IL-6 levels. Nevertheless, they identified a statistically significant negative correlation between the levels of HbA1c and IL-10 (21). Diabetic patients might experience

elevated concentrations of interleukin-10 as a compensatory mechanism (23). These anti-inflammatory cytokines are thought to offer protective benefits, contributing to the mitigation of various inflammatory and autoimmune conditions (8). Another study conducted on children demonstrated a significant correlation between TNFα and HbA1c levels; however, the levels were not significantly elevated in the diabetes group when compared to the control group (11). Research indicates that inflammation is linked to biological variation in HbA1c among both diabetic and non-diabetic adults, independent of blood glucose levels and obesity (28). A study on adults with T1DM identified crucial clinical factors affecting immune dysregulation in long-term patients, revealing a strong link between diabetes duration and inflammation (24). For adolescents with T1DM, increased glucose fluctuations are associated with higher inflammation, though the long-term consequences of these factors remain unclear (26). The correlation between glycemic levels and immune cell quantity and function in circulation is not linear, suggesting that any level of glycemia may trigger changes in immune cell proliferation or demargination. As a result, the immune response alterations in T1DM patients may be more significantly influenced by the duration of chronic hyperglycemia exposure rather than the severity of glycemia itself (24). Furthermore, a previous study found a weak correlation between insulin requirements and inflammation. The correlation between immune cell function and insulin might be enduring, as evidenced by a small but consistent positive correlation between insulin needs and the adaptive immune response (24). The analysis revealed that the study conducted by Abdel-Latif et al. (2) had a high risk of bias. Upon exclusion, the pooled correlation coefficient indicated a weak, but statistically significant, correlation. There was an inverse correlation between IL-6 serum levels and HbA1c in 100 children with T1DM who tested positive for enterovirus antibodies. Conversely, no significant correlation was found in 100 T1DM children who tested negative for these antibodies (12). The etiology of T1DM is multifactorial; however, environmental factors, including viral infection, believed to be linked to T1D and the destruction of pancreatic β-cells are poorly understood (3). Research suggests that enteroviruses infection is associated with T1D (27). Enterovirus infection at several life stages-pregnancy, infancy, childhood, and adulthood-has been linked to the onset of islet autoimmunity, especially when the infection occurs in early childhood (3). Furthermore, research has demonstrated that interleukins 10, 6, and 13 play a role in the development of enterovirus infections (25). As far as we are aware, this research represents the first meta-analytic examination of the correlation between interleukin-6 and glycated hemoglobin levels in pediatric patients diagnosed with type 1 diabetes mellitus. However, this study had several limitations. Significant variations were observed among the reviewed studies in aspects such as diabetes duration, patient age, presence of acute illnesses or complication history, treatment history and adherence, and IL-6 assessment methods, including sampling hours. These factors could potentially confound the results and contribute to data heterogeneity. We conducted subgroup analyses to reduce the potential bias due to this limitation. The pooled correlation coefficients between IL-6 and HbA1c levels were notably lower in non-Asian populations and when measurement methods other than ELISA were used. We investigated the sources of heterogeneity, including age groups and populations with controlled diabetes. However, all studies included adolescents and participants with uncontrolled diabetes, suggesting that these factors may not be the primary cause of heterogeneity. The analysis also included studies with small sample sizes, which could have introduced additional confounding factors. Furthermore, detailed information on body mass index and treatment history was lacking for each study. Despite these limitations, this meta-analysis provides valuable insights into inflammatory processes in T1DM. Further research is necessary to establish the correlation between IL-6 and HbA1c levels in pediatric patients with type 1 diabetes mellitus. We suggest that future studies address these shortcomings by conducting research with larger, more homogeneous sample sizes, or standardized IL-6 measurement techniques.

Conclusions

A trend toward statistical significance was observed in the correlation between IL-6 and HbA1c

levels in children with T1DM. Despite not reaching statistical significance, this trend might still offer insight into the inflammatory processes associated with T1DM. The subtle correlation observed between IL-6 and HbA1c levels in these children suggests that elevated pro-inflammatory cytokine concentrations are associated with poor glycemic control. It is also possible, however, that a non-linear correlation may exist at certain glycemic and inflammatory thresholds, which standard statistical analyses may fail to identify. Various factors in the study population, such as age differences, diabetes duration, presence of acute illnesses or complications, glycemic control status during the investigation, and the diversity in methods used for IL-6 and HbA1c measurements, could have acted as confounding variables.

Ethic Approval: Not applicable.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors' Contribution: SL, NR, and CW developed the concept framework; SL, AE, and CW designed the methodology; SL and CW prepared the initial draft; AE, NR, and CW reviewed and revised the manuscript; AE and NR supervised the work. All authors reviewed and approved the final published version.

References

1. Bogdani M. Thinking outside the cell: a key role for hyaluronan in the pathogenesis of human type 1 diabetes. Diabetes. 2016;65(8):2105–14. doi: 10.2337/db15-1750
2. Shah AS, Nadeau KJ. The changing face of paediatric diabetes. Diabetologia. 2020;63(4):683–91. doi: 10.1007/s00125-019-05075-6
3. Libman I, Haynes A, Lyons S, Dabelea D, ISPAD Clinical Practice Consensus Guidelines 2022: definition, epidemiology, and classification of diabetes in children and adolescents. Pediatr Diabetes. 2022;23(8):1160–74. doi: 10.1111/pedi.13454
4. Anand V, Li Y, Liu B, et al. Islet autoimmunity and HLA markers of presymptomatic and clinical type 1 diabetes: joint analyses of prospective cohort studies in Finland, Germany, Sweden, and the U.S. Diabetes Care. 2021;44(10):2269–76. doi: 10.2337/dc20-1836
5. Beyerlein A, Bonifacio E, Vehik K, et al. Progression from islet autoimmunity to clinical type 1 diabetes is influenced by genetic factors: results from the prospective TEDDY study. J Med Genet. 2018;56(9):602–5. doi: 10.1136/jmedgenet-2018-105532
6. Redondo MJ, Geyer S, Steck AK, et al. A type 1 diabetes genetic risk score predicts progression of islet autoimmunity and development of type 1 diabetes in individuals at risk. Diabetes Care. 2018;41(9):1887–94. doi: 10.2337/dc18-0087
7. Hundhausen C, Roth A, Whalen E, et al. Enhanced T cell responses to IL-6 in type 1 diabetes are associated with early clinical disease and increased IL-6 receptor expression. Sci Transl Med. 2016;8(356):356ra119. doi: 10.1126/scitranslmed.aad9943
8. Lu J, Liu J, Li L, Lan Y, Liang Y. Cytokines in type 1 diabetes: mechanisms of action and immunotherapeutic targets. Clin Transl Immunology. 2020;9(3):e1122. doi: 10.1002/cti2.1122
9. Hammed IK, Rashid NF, Abed BA. Serum interleukin-6 level in children with type 1 diabetes mellitus. J Fac Med Baghdad. 2012;54(3):228–30. doi: 10.32007/jfacmedbagdad.543723
10. AboElAsrar MA, Elbarbary NS, Elshennawy DE, Omar AM. Insulin-like growth factor-1 cytokines cross-talk in type 1 diabetes mellitus: relationship to microvascular complications and bone mineral density. Cytokine. 2012;59(1):86–93. doi: 10.1016/j.cyto.2012.03.019
11. Heier M, Margeirsdottir HD, Brunborg C, Hanssen KF, Dahl-Jørgensen K, Seljeflot I. Inflammation in childhood type 1 diabetes; influence of glycemic control. Atherosclerosis. 2015;238(1):33–7. doi: 10.1016/j.atherosclerosis.2014.11.018
12. Abdel-Latif M, Abdel-Moneim AA, El-Hefnawy MH, Khalil RG. Comparative and correlative assessments of cytokine, complement and antibody patterns in paediatric type 1 diabetes. Clin Exp Immunol. 2017;190(1):110–21. doi: 10.1111/cei.13001
13. Al-Dubayee M, Babiker A, Alkewaibeen A, et al. Correlation analysis between cytokines' profile, autoimmune antibodies and the duration of type 1 diabetes: a case control study in a specialized children's centre in Riyadh. Int J Immunopathol Pharmacol. 2023;37:03946320231209821. doi: 10.1177/03946320231209821
14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71
15. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603–5. doi: 10.1007/s10654-010-9491-z
16. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–58. doi: 10.1002/sim.1186

17. Fawaz L, Elwan AE, Kamel YH, Farid TM, Kamel A, Mohamed WA. Value of C-reactive protein and IL-6 measurements in type 1 diabetes mellitus. Arch Med Sci. 2009; 5(3):383–90
18. Duque C, Joao MFD, da Cruz GA, et al. Microbiological, lipid and immunological profiles in children with gingivitis and type 1 diabetes mellitus. J Appl Oral Sci. 2017;25(2):217–26. doi: 10.1590/1678-77572016-0196
19. Fahad HM, Jassim AN, Nada SM. Investigation of inflammatory markers (IL-6 and hs-CRP) in type 1 diabetes patients. Int J Adv Res. 2014;2(3):572–9
20. Jain SK, Kannan K, Lim G, Matthews-Greer J, McVie R, Bocchini JA Jr. Elevated blood interleukin-6 levels in hyperketonemic type 1 diabetic patients and secretion by acetoacetate-treated cultured U937 monocytes. Diabetes Care. 2003;26(7):2139–43. doi: 10.2337/diacare.26.7.2139
21. Reis M, Teixeira A, Cardoso J, Borges T, Caldas Afonso A, Correia-Costa L. Association between proinflammatory cytokines and arterial stiffness in type 1 diabetic adolescents. J Pediatr Endocrinol Metab. 2024;37(5):405–12. doi: 10.1515/jpem-2023-0530
22. Wedrychowicz A, Dziatkowiak H, Sztefko K, Wedrychowicz A. Interleukin-6 (IL-6) and IGF-IGFBP system in children and adolescents with type 1 diabetes mellitus. Exp Clin Endocrinol Diabetes. 2004;112(8):435–9. doi: 10.1055/s-2004-821189
23. Gouda W, Mageed L, El Dayem SMA, Ashour E, Afify M. Evaluation of pro-inflammatory and anti-inflammatory cytokines in type 1 diabetes mellitus. Bull Natl Res Cent. 2018;42:14. doi: 10.1186/s42269-018-0016-3
24. Ajie M, van Heck JIP, Janssen AWM, Meijer RI, Tack CJ, Stienstra R. Disease duration and chronic complications associate with immune activation in individuals with longstanding type 1 diabetes. J Clin Endocrinol Metab. 2023;108(8):1909–20. doi: 10.1210/clinem/dgad087
25. Chen Z, Li R, Xie Z, Huang G, Yuan Q, Zeng J. IL-6, IL-10 and IL-13 are associated with pathogenesis in children with Enterovirus 71 infection. Int J Clin Exp Med. 2014;7(9):2718–23
26. Hoffman RP, Dye AS, Huang H, Bauer JA. Glycemic variability predicts inflammation in adolescents with type 1 diabetes. J Pediatr Endocrinol Metab. 2016;29(10):1129–33. doi: 10.1515/jpem-2016-0139
27. Wang K, Ye F, Chen Y, et al. Association between Enterovirus infection and type 1 diabetes risk: a meta-analysis of 38 case-control studies. Front Endocrinol (Lausanne). 2021;12:706964. doi: 10.3389/fendo.2021.706964
28. Liu S, Hempe JM, McCarter RJ, Li S, Fonseca VA. Association between inflammation and biological variation in hemoglobin A1c in U.S. nondiabetic adults. J Clin Endocrinol Metab. 2015;100(6):2364–71. doi: 10.1210/jc.2014-4454

Correspondence:
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Anang Endaryanto
Department of Child Health, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
Department of Child Health, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
Prof. Dr. Moestopo 6 - 8, Surabaya, 60285, Indonesia
E-mail: anang.endaryanto@fk.unair.ac.id
ORCID: 0000-0002-7988-2274