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Correlation between Triglyceride Glucose Index and Diabetic Kidney in Type 2 Diabetic: Literature Review

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ABSTRACT

Introduction: One marker of insulin resistance in type 2 diabetes is the triglyceride index (TyG), which has been studied to predict the development of diabetic kidney disease (DKD). This study investigates the correlation between the triglyceride glucose index and diabetic kidney disease in type 2 diabetes mellitus.

Methods: A comprehensive search was conducted in PubMed, Proquest, ScienceDirect, Taylor and Francis, Cochrane Library and Google Scholar search using search terms including (''Triglyceride Glucose Index or TyG'') and (''Diabetic Kidney or Diabetic Nephropathy'') and ("Diabetes Mellitus" OR "Diabetes Mellitus Type II" OR "Type 2 Diabetes Mellitus").

Results: A total of 8 studies were screened based on titles and abstracts, of which 7 studies were included in the analysis of TyG and DKD. A prediction model including the TyG index demonstrated excellent calibration and discrimination for the probability of DKD in research involving patients recently diagnosed with type 2 diabetes mellitus (T2DM). This approach has potential applications in clinical practice. DKD and metabolic diseases are independently correlated with the TyG index. Recently, one sensitive method for identifying DKD with insulin resistance has been the TyG index. The TyG index is a readily available, affordable, and simple marker for identifying of microvascular problems in T2DM patients.

Conclusion: In our review, TyG and DKD were significantly positively correlated in patients with type 2 diabetic mellitus. TyG index has potential as a practical tool for determining insulin resistance and predicting the probabilities that individuals with type 2 diabetes are related to diabetic kidney disease.

Keywords: Triglyceride glucose (TyG) index; diabetic kidney disease (DKD); type 2 diabetes mellitus

Introduction

Diabetes mellitus (DM) is a chronic illness that affects people all over the world. There are 537 million adults with diabetes globally as of right now, based on data from the International Diabetes Federation Atlas Diabetes 2021.[1] One of the microvascular complications of diabetes mellitus is diabetic kidney disease (DKD) approximately 50 % of DM patients.[2] The risk of cardiovascular disease, end-stage renal disease (ESRD), and mortality has increased over the years in conjunction with the increased risk of chronic kidney disease (CKD). Kidney illness can be prevented or postponed with an early diagnosis and thorough treatment.[3,4]

In populations with diabetes mellitus, there is a strong correlation between kidney disease risk and insulin resistance (IR).[5] There is variation in the relationship between insulin resistance and the progression of CKD. For instance, in non-diabetic individuals with mild-to-moderate CKD, a study found no significant correlation between HOMA-IR, HbA1c, or C-peptide and CKD development.[6] Insulin resistance is commonly assessed in clinical practice utilizing fasting state measures and the homeostasis model assessment for insulin resistance (HOMA-IR).[7] Unfortunately, the plasma insulin assay has low repeatability, is costly, and is not readily available in many laboratories. New biomarkers that are less expensive and simpler to identify are therefore required. IR is frequently associated with abnormal fasting blood glucose (FBG) and triglyceride (TG) levels. The triglyceride–glucose index (TyG) has proved to be a useful marker for insulin resistance (IR) and its related problems, according to recent research. An indicator of insulin resistance and a predictor of DKD individuals with type 2 diabetes has been investigated is the Triglyceride Glucose (TyG) index.[8,9] The result of this review is to explore the correlation between the triglyceride glucose index and diabetic kidney disease in type 2 diabetic mellitus.

Methods

This review was carried out by the literature review reporting item (PRISMA ScR). Inclusion criteria included observational, cohort, and cross-sectional studies in adult subjects (18 years or older), type 2 diabetes mellitus with diabetic kidney disease and, measurement of TyG index. There is no exclusion criteria based on the language or country of publication. A comprehensive search was conducted in PubMed, Proquest, ScienceDirect, Taylor and Francis, Cochrane Library, and Google Scholar search using search terms including (''Triglyceride Glucose Index or TyG'') and (''Diabetic Kidney or Diabetic Nephropathy'') and ("Diabetes Mellitus" OR "Diabetes Mellitus Type II" OR "Type 2 Diabetes Mellitus"). Data extraction was carried out using a Google Sheet-based template to extract key data variables which included title, year, study design, study population, age of subjects, measured outcomes, and main findings. Then, we compiled the study according to the appropriate criteria, and the results are

included in this review.

Result

Based on the database, a total of 8 records were found. Seven papers were considered in this review after the titles and abstracts of the seven records were screened. Seven full-text articles were then evaluated for eligibility. The literature search and study selection process are summarized in Figure 1.
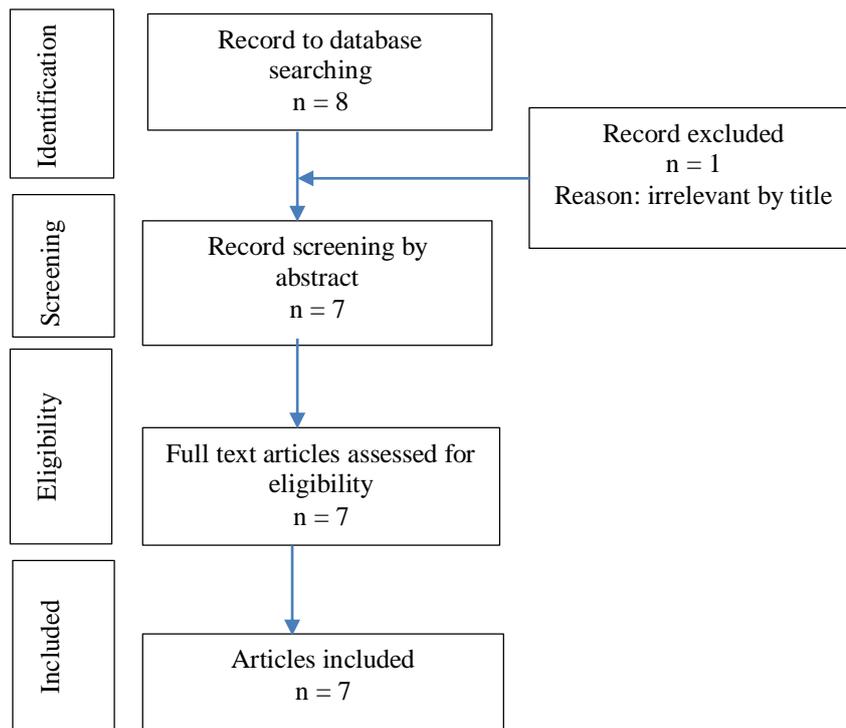

Figure 1. Flowchart of the study selection process

Triglyceride Glucose (TyG) Index

The TyG index was calculated as follows, TyG = Ln [fasting triglycerides (mg/dL) × fasting plasma glucose (mg (dL)/2]. There is a significant correlation between the TyG index and DKD. Li et al studies show the mean of TyG index in the the non-DKD DM group was 9,051±0.757, the DM group with DKD 9,312±0.831 with p<0.001. Lv et al studies show the mean total of TyG is 9.17 (8.73-9.71). Tu et al studies showed, the non-DKD DM group 7.38 (6.89-7.92), DM group with DKD 7.53 (7.07-8.09). Jiang and Lai, 2024 studies show the average TyG of the the non-DKD DM group was 9.77±1.06, the DM group with DKD 10.01±1.02 (p=0.005). Lui et al, 2020 studied that the average TyG of the the non-DKD DM group was 9.10±0.358, the DM group with DKD 9.42±0.74 (p<0.001). While there is evidence linking elevated TyG indices to increased risks of both DM and DKD, specific consensus on cut-off values remains unclear and varies by study. However, all studies show that the mean of the TyG index is higher in the DM group with DKD (table 1).

Table 1. Comparison of TyG index between control and DM+DKD: (mean±SD)

No	Authors	Year	DM	DM+DKD	p
1	Li et al	2023	9,051±0.757	9,312±0.831	p<0.001
2	Lv et al	2021	Mean=9.17 (8.73-9.71)		
3	Tu et al	2024	7.38 (6.89-7.92)	7.53 (7.07-8.09)	
4	Jiang and Lai	2024	9.77±1.06	10.01±1.02	p=0.005
5	Lui et al	2021	9.10±0.358	9.42±0.74	p<0.001

The DKD parameters

Kidney Disease Improving Global Outcomes (KDIGO) states that a decrease in estimated glomerular filtration rate (eGFR < 60 ml/min/1.73 m2) and an increase in urine albumin excretion (≥ 30 mg/g creatinine) over three months is required for the diagnosis of DKD.[10] DKD parameters include a decrease of eGFR and an increase the urine microalbuminuria: creatinine ratio (UACR). Based on journals in this review, eGFR for the non-DKD DM group 90,876±15,442, DM group with DKD 81,017±22,702 (p<0.001); the non-DKD DM group 123.36±25.56, DM group with DKD 108.46±36.90 (p<0.001); eGFR of the non-DKD DM group 94.93 (90.17-108.39), DM group with DKD 35.79 (14.35-53.42) mL/min/1.73m^2 (p<0.001) and eGFR of the non-DKD DM group 128.9 (100.7-157.7), and DM group with DKD 76.1 (38.0-121.8) mL/min/1.73m^2 (p<0.001). Other parameters of DKD are UACR for the non-DKD DM group 11.8 (7.70-18.20), DM group with DKD 88.8 (46.50-215.40). Whereas in other journals, the value of UACR for the non-DKD DM group was 20.65+45.04, DM group with DKD 156.73±438.94 (p<0.001).

Correlation of TyG index with DKD

The correlation between TyG with DKD parameters based on this review, UACR was r=0.172 (p<0.001) and albumin r=0.102 (p<0.008), and correlation between TyG with DKD (OR=1.693; 95% CI=1.002-2.803; p=0.041). After performing a binary logistic regression analysis, another publication demonstrated the relationship between the TyG Index and DKD. The low tertile in this model of the TyG Index is set as a reference, the TyG Index in the upper terminus is associated with a higher OR for microalbuminuria (OR=2.342; 95% CI=1.744–3.144; p< 0.001), eGFR (OR=1.696; 95% CI=1.096–2.625; p=0.018) and DKD (OR=2.728; 95% CI=2.030–3.661; p<0.001) determined by sex and age.

The triglyceride-glucose (TyG) index has been investigated for its association with diabetic kidney

disease (DKD), but consensus on specific cut-off values is still evolving across different studies. A TyG index cut-off value of ≥ 8.31 has been linked to a higher risk of type 2 diabetes, but values between 8.7 and 8.9 indicate a 54% sensitivity and a 71% specificity in predicting the disease.[11] Higher values were associated with higher risk, and a TyG index cut-off of 9.5 was found to be meaningful in categorized risk for ESRD in individuals with T2DM and Chronic kidney Disease (CKD).[12]

Multiple regression analysis based on the evaluation of the included article showed that the occurrence of DKD in patients with T2D was correlated with SBP, DBP, BMI, HbA1c, TG, TyG index (OR=1.57; 95% CI=1.26–1.94; p<0.001), and TyG-BMI after controlling for confounding factors like age and sex. According to other journals, the TyG index has a good correlation with both albuminuria and eGFR, a DKD marker. The TyG index and lnAER had a positive association, per the correlation analysis (r = 0.190, p = 0.003). After adjusting for several factors, such as age, sex, duration of illness, weight, prevalence of hypertension, HbA1C, and serum uric acid, this link persisted (r = 0.173, p = 0.006). There was no correlation between the TyG index and lneGFR (r = -0.095, p = 0.138) or without (r = -0.016, p = 0.805) after confounding factors were considered. Subjects with normoalbuminuria showed a lower TyG index than patients with macro- and microalbuminuria (p < 0.05). Between DKD patients with eGFR <30, 30-59, 60-89, and $\geq$90 mL/min/1.73 m2, there was no difference in the TyG index (p = 0.786).

Table 2. Correlation of TyG index with DKD

No	Author	Results	Main findings
1	Li et al, 2023	UACR r=0.172, p<0.001	The TyG index were independently related to DKD and related metabolic disorders
2	Lv et al, 2021	Microalbuminuria (OR = 2.342, 95% CI =1.744–3.144, p < 0.001), eGFR (1.696, 1.096–2.625, 0.018) and DKD (2.728, 2.030–3.661, <0.001)	The TyG Index is a potential predictor for DKD in T2DM patients.
3	Tu et al, 2024	Univariate logistic regressions: risk of DKD (OR = 1.842, [95% CI] 1.317–2.578, p < 0.01). Multivariable logistic regression: risk of DKD (OR = 1.581, [95% CI] 1.031–2.424, p < 0.05)	Elevated the TyG was significantly associated with an increased risk of DKD in T2D
4	Wang et al, 2024	TyG index was identified as a prominent clinical risk factor for DKD, showing the highest odds ratio (OR 1.57 (1.26 - 1.94), P<0.001).	The DKD risk presented a threshold effect with the increase of TyG index, initially stable at a low level, and then gradually rising when the TyG index is above 9.35.
5	Jiang and Lai, 2024	Logistic regression revealed that TyG index (odds ratio [OR] 1.232, 95% confidence interval [CI] 1.064–1.428, p = 0.005) and TyG-BMI (OR 1.003, 95% CI	Among newly diagnosed T2D patients, the risk of DKD increases with the increase of TyG index and the TyG-BMI, with their respective cut-off values being 9.68 and 243. Both the TyG index and the TyG-BMI

		1.000–1.006, p = 0.021) were risk factors for DKD.	have poor diagnostic values for the risk of DKD.
6	Shang et al, 2019	A non-linear relationship was identified between TyG index and the risk of newly diagnosed biopsy-proven diabetic nephropathy with a potential threshold of TyG at 9.05–9.09.	In people with type 2 diabetes, the TyG index above 9.05–9.09 could be a prognostic threshold to identify individuals at high risk of diabetic nephropathy.
7	Lui et al, 2020	The TyG index positively correlated with lnAER (r = 0.190, p = 0.003).	The TyG index was independently associated with DN in patients with type 2 diabetes and was a better marker than HOMA2-IR for the identification of DN in type 2 diabetes patients.

Discussion

Based on the seven studies the reseachers reviewed, the biomarker of insulin resistance, the TyG index, relates to DKD parameters such as UACR and eGFR. Insulin resistance has multiple effects on diabetes-related kidney disease (CKD), contributing to the incidence and progression. Hyperinsulinemia can lead to glomerular hyperfiltration, which raises the rate of renal filtration and may eventually cause injury. Moreover, hyperinsulinemia promotes blood vessel permeability, which can lead to renal inflammation and oxidative stress. Insulin resistance affects podocytes as well, and maintaining the structural integrity of the glomerular filtration barrier depends on it. Reduced insulin action can lead to glomerulosclerosis and albuminuria by thickening the base membrane of the glomerulus, removing leg processes, and triggering apoptosis in the podocit. Insulin resistance can be found in various chronic kidney diseases (CKD) in addition to diabetic nephropathy. The impairment of glucose, lipid, and protein metabolism caused by CKD could contribute to systemic insulin resistance, a condition that progressively decreases kidney function.[13,14]

A study conducted by Li et al. showed that the TyG index had a positive correlation with the urinary albumin-creatinine ratio (UACR) and was closely associated with DKD. The risk factor is independent of the DKD increase of 1,699 times on each increase in the TyG index. A TyG index higher than 9.25 showed a significant difference in the eGFR value (60-89.9 mL/min/1.73 m2).[15] Lv et al (2024) reported that an increase in the TyG Index was associated with an increased risk of microalbuminuria and a decrease in eGFR. Longitudinal studies also show that the TyG Index can effectively predict DKD. The TyG index also often interferes with insulin resistance (IR) conditions, so it can be used as a substitute for IR.[16]

After adjusting for confounding factors, Tu et al. (2024) found a strong correlation between TyG and DKD (OR=1.581; 95% CI=1.031–2.424). According to univariate logistic regression, an increase in the TyG index is associated with an increased risk of DKD. Various metabolic conditions can affect the TyG

index. Therefore, some variables associated with TyG can be identified through quantitative regression. These variables include age, gender, SBP, HbA1c, FCP, TC, HDL-C, LDL-C, and drinking habits. In patients with T2D, this indicator is mainly associated with the metabolic impairment associated with TyG and microvascular complications. After confounding is controlled, the risk of diabetic kidney disease (CKD) increases.[17]

Research by Wang et al. (2024) used a cross-sectional design to investigate the threshold between the TyG index and DKD risk. The results showed that even though the confounding factor was removed, the risk of DKD remained stable at a lower level in patients with a TyG index of less than 9.35, but in patients with a TyG index of more than 9.35, an increase of one unit of the TyG index led to a 94% increase in the risk of DKD. The results of this study can be used to place risk and management interventions in DKD patients with type 2 diabetes (T2D). [5]

This review also included the TyG index as a marker of insulin resistance associated with the risk of newly diagnosed DKD in people with type 2 diabetes mellitus. Jiang and Lai's study examined the relationship between the TyG index and the presence of DKD in patients with newly diagnosed T2D. The results show that the TyG index is an important risk factor for DKD. This relationship proved significant after adjusting for confounding variables based on nonlinear correlations. The risk of DKD increases as the TyG index increases greater than 9.68, which indicates that the TyG index is a potential indicator of DKD risk. [8] The research by Shang et al. (2019), the threshold value of the TyG index was obtained 9.07 (9.05–9.09). People with type 2 diabetes who are newly diagnosed with DKD as evidenced by a biopsy have a much higher risk with a TyG index value above 9.07. This conclusion is in line with previous findings, a high TyG index (specifically a TyG index above 9.07) is associated with a high risk of CKD, which is the main cause of end-stage kidney disease in diabetics.[9] These results suggest that the TyG index may be useful for finding and monitoring the risk of DKD in patients with newly diagnosed T2D.

In a study conducted by Liu et al (2021), patients with type 2 diabetes and DKD showed greater insulin resistance compared to patients without DKD, as indicated by the TyG index and higher HOMA2-IR scores. To identify DKD in type 2 diabetic patients, the TyG index showed a higher AUC ROC score (AUC 0.67, p=0.002) compared with HOMA2-IR (AUC 0.61, p=0.029). With a cut-off point of more than 9.66, the TyG index has a sensitivity of 61.7% and a specificity of 76.0%. In addition, the TyG index was positively correlated with levels of metabolic indicators such as weight, HbA1C, triglycerides, total cholesterol, serum uric acid, fasting glucose, and HOMA2-IR (p < 0.05 for each) but not with lneGFR values. According to multiple regression analysis, the TyG index as a marker of insulin resistance substitution is independently associated with the diagnosis of type 2 diabetes complications (OR=1.91; p= 0.001).[18]

The present review demonstrates that the TyG index is a useful tool for detecting DKD in T2D patients. A new indicator that has been proposed recently, the TyG Index, has shown to be a simple and dependable marker to replace IR.[12] This review also showed that in patients with type 2 diabetes, elevated FBG and TG have been linked to the development of DKD. A high TyG index has been linked to an increased risk of type 2 diabetes in the general population.[9]

The etiology of DKD is linked to insulin resistance, however, incompletely understood mechanisms underlie the association.[19] Increased renal vascular permeability and, eventually, glomerular hyperfiltration are linked to insulin resistance and increased glomerular hydrostatic pressure. Additional routes and mechanisms that may connect diabetes-related kidney disease (DKD) with insulin resistance include increased lipotoxicity, oxidative stress, metabolic acidosis, and inflammation, which can result in microangiopathy.[4,20]

This review has some limitations. There are certain restrictions on this review. A broad spectrum of scientific literature is typically included in reviews, which can be obtained via several techniques such as manual searches, electronic databases, internet search engines, and gray literature, among others. Nevertheless, because this review's search techniques were restricted to electronic databases, it is likely that fewer papers were examined than it would have if other search methods had been included.

Conclusion

We concluded that among patients with type 2 diabetes mellitus, TyG and DKD significantly correlated positively in our review. The TyG index has been proposed as a marker of insulin resistance as a simple and clinically reliable substitute for predicting the risk of diabetic kidney disease in type 2 diabetes mellitus.

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Literature Review   **Open Access**

A Comprehensive Review of HLA-DPB1 *05:01 in Hepatitis B: Cases and Sequencing Methods

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ABSTRACT

Introduction: The human leukocyte antigen (HLA) system is critical in mediating immune responses. The HLA-DPB1*05:01 allele, has been associated with various immunological outcomes and disease processes, including hepatitis B virus (HBV) infection. This review seeks to investigate the relationship between HLA-DPB1*05:01 and HBV infection, its role in disease progression, and the response to vaccines, while also examining the techniques used for sequencing this allele.

Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a comprehensive literature search was conducted across PubMed, ScienceDirect, Wiley, and Google Scholar. Studies included in this review focused on HLA-DPB1*05:01 in the context of HBV, encompassing epidemiological research, clinical outcomes, and sequencing techniques.

Results: The HLA-DPB1*05:01 allele plays a significant role in HBV infection, with its effects varying across different populations. In Caucasians, it is associated with spontaneous clearance of HBV, suggesting a protective role. Conversely, in East Asian and Chinese populations, it is linked to increased susceptibility to chronic HBV infection. This allele also influences disease progression, slowing progression to severe liver diseases in some populations but increasing risk in others. Additionally, HLA-DPB1*05:01 affects antiviral treatment efficacy and is associated with a higher likelihood of non-response to the hepatitis B vaccine.

Conclusion: The HLA-DPB1*05:01 allele significantly impacts HBV infection outcomes, highlighting the complex interplay between genetic and environmental factors. While sequencing techniques provide detailed genetic analysis, variability in study methodologies and population-specific effects present challenges. Future research should address these limitations to enhance understanding of HLA-DPB1*05:01 and role in HBV infection

Keywords: HBV genomic; HLA-DPB1; polymorphism; hepatitis B

Introduction

Human leucocyte antigen (HLA) is an essential component of the immune system [1]. Some studies suggest that HLA affects susceptibility to disease, response to vaccination, and transplant reactions [2,3]. Such a major influence on the immune system makes HLA a critical component that must be considered in grafts [3]. HLA is a part of the immune system that has high variability in the population because it is highly polymorphic. [4]. Many loci in HLA are polymorphic and have an important influence on the immune system. One of them is the HLA-DP region. This region is one of three HLA regions that are heterodimer [5]. Domain B in this region is called HLA-DPB. This allele is the parent of many important genes, especially the HLA-DPB1 gene which has been shown to have a major influence on the regulation of the immune system by determining class II antigens [6]. Polymorphism in these alleles affects how strong and fast they respond to antigens.

HLA-DPB1 is located on chromosome 6p21.3 and encodes a protein that forms part of the HLA class II molecule, which presents extracellularly derived peptides to CD4+ T cells [7]. The HLA-DPB1 locus is highly polymorphic, with over 500 alleles identified to date [8]. Among these, the HLA-DPB1*05:01 allele has emerged as particularly noteworthy due to its association with various immunological responses and disease outcomes in Hepatitis B [6].

The role of HLA-DPB1*05:01 in HBV infection is multifaceted. On one hand, this allele may enhance the presentation of HBV-derived peptides to T cells, thereby facilitating a robust immune response that can clear the virus. On the other hand, it may also be associated with an increased risk of chronic infection in certain individuals, potentially due to the persistence of an ineffective immune response [6]. HLA-DPB1*05:01 also has shown varying impacts across different races and populations. A previous study showed the association between HLA alleles and the progression of HBV infection in a cohort of Caucasian patients. Conversely, a study conducted in a Chinese population found that HLA-DPB1*05:01 was more common among chronic HBV carriers, suggesting a higher susceptibility to persistent infection. Another study showed that this allele suggests a protective effect in HBV infection, but the others showed there is no effect. However, none of this study suggests the exact mechanism for this contradictive [1,6,16]. These dual roles underscore the complexity of the interaction between HLA alleles and HBV. Also, it underlines that the true impact is not fully understood.

In addition to its role in natural infection, HLA-DPB1*05:01 also appears to influence the response to HBV vaccination. Vaccination is a critical tool in the prevention of HBV infection, yet not all individuals mount a sufficient immune response to the vaccine [9]. The presence of certain HLA alleles, including HLA-DPB1*05:01, has been linked to variations in vaccine efficacy [1]. When viewed from the high coverage of Hepatitis B vaccination in Indonesia as required since newborns, everyone should have

sufficient anti-HBs titers. In fact, some studies have shown many individuals with low titer, signaling the role of genetic [9]. Recognizing these genetic factors is vital for pinpointing individuals who may be at risk of inadequate vaccine responses and for devising strategies aimed at improving vaccine effectiveness.

The sequencing of HLA alleles, including HLA-DPB1*05:01, is essential for studying their associations with diseases and for identifying the underlying mechanisms of their effects [10]. Traditional sequencing methods, such as Sanger sequencing and PCR-based techniques, have been widely used to characterize HLA alleles [11]. However, the advent of next-generation sequencing (NGS) technologies has revolutionized HLA typing, providing higher resolution and accuracy [12]. NGS allows for comprehensive analysis of HLA alleles, enabling researchers to uncover novel associations and gain deeper insights into the role of HLA in disease [13].

This review aims to provide a comprehensive overview of HLA-DPB1*05:01, focusing on its association with HBV infection and the methodologies used for its sequencing. By examining the current literature and case studies, we seek to elucidate the impact of HLA-DPB1*05:01 on HBV susceptibility, disease progression, and vaccine response. Furthermore, we will explore the sequencing techniques employed to characterize this allele, highlighting their advancements and limitations. Through this review, we hope to contribute to the understanding of the complex interplay between HLA alleles and HBV, aiding in the development of targeted interventions for HBV prevention and treatment.

Methods

To conduct a comprehensive review of HLA-DPB1 05:01 and its association with hepatitis B, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The literature search strategy was executed across multiple databases, including PubMed, ScienceDirect, Wiley, and Google Scholar. The primary search terms used were "HLA-DPB1 05:01," "HLA-DP," "Hepatitis B," "HBV," "Hepatitis B Virus," "Immunogenetics," "HLA typing," and "Sequencing methods."

The inclusion criteria for the search focused on studies examining the HLA-DPB1 locus and the *05:01 allele with hepatitis B, published in English, including the research articles, review papers, case reports, and clinical trials. The articles needed to provide the data on the association between HLA-DPB1*05:01 and hepatitis B, including the aspects of disease susceptibility, clinical outcomes, and response to vaccination. Exclusion criteria of this studies are not related to HLA-DPB1*05:01, the articles without a focus on hepatitis B, non-peer-reviewed articles, editorials, opinion pieces, and duplicate studies.

The literature search and selection process are illustrated in the PRISMA flow diagram. In the identification phase, records were identified through database searching and additional sources. During

screening, duplicates were removed, and titles and abstracts were screened, leading to the exclusion of irrelevant records. In the eligibility phase, full-text articles were assessed, and those that did not meet the criteria were excluded with reasons documented. Finally, the articles analyzed are those that meet all the criteria.

Data extraction was conducted using a standardized form, capturing essential information such as study design, population characteristics, HLA-DPB1*05:01 allele frequency, association with hepatitis B susceptibility and outcomes, sequencing methods used, and key findings and conclusions.

Result

Study Selection

A total of 11 studies met the inclusion criteria and were included in this review [1,6,14–22] (Table 1). The studies were selected based on their focus on the HLA-DPB1*05:01 allele in the context of hepatitis B virus (HBV) infection, including epidemiological studies, clinical trials, and genetic analyses. The literature search yielded 55 potential articles; after screening for duplicates, title and abstract reviews, and full-text evaluations, 11 articles were included in the final synthesis.

Table 1. Included studies

No	Author (year)	Title	Population
1	Koukoulioti et al. (2019)	Association of HLA-DPA1 and HLA-DPB1 polymorphisms with spontaneous HBsAg seroclearance in Caucasians	Caucasian: 618 chronic HBV infections, 239 spontaneous HBsAg seroclearance, and 254 healthy controls
2	Ou et al. (2021)	Variation and expression of HLA-DPB1 gene in HBV infection	Chinese: 259 HBV infections and 442 healthy controls
3	Huang et al. (2020)	Large-scale genome-wide association study identifies HLA class II variants associated with chronic HBV infection: a study from Taiwan Biobank	Taiwanese: 15352 seropositive for HBV core antibodies
4	Ashouri et al. (2022)	Genome-Wide Association Study for Chronic Hepatitis B Infection in the Thai Population	Thai: 318 chronic HBV and 309 healthy controls
5	Wasityastuti et al. (2016)	Protective effects of HLA-DPA1/DPB1 variants against Hepatitis B virus infection in an Indonesian population	Indonesians: 222 HBV carriers, 228 spontaneously resolved HBV, and 236 healthy controls
6	Brouwer et al. (2014)	Polymorphisms of HLA-DP are associated with response to peginterferon in Caucasian patients with chronic hepatitis B	Caucasian: all chronic HBV with Peginterferon treatment for 1 year
7	Hu et al. (2014)	HLA-DPB1 Variant Effect on Hepatitis B Virus Clearance and Liver Cirrhosis Development Among Southwest Chinese Population	Chinese: 342 persistent HBV infection and 342 age and gender-matched spontaneous resolved of HBV
8	Nishida et al. (2015)	Effects of HLA-DPB1 genotypes on chronic hepatitis B infection in Japanese individuals	Japanese: 761 healthy volunteers, 892 HBV patients, 892 treated patients, and 929 others
9	Cheng et al. (2014)	Effect of HLA-DP and IL28B gene polymorphisms on response to interferon treatment in hepatitis B e-antigen seropositive chronic hepatitis B patients	Chinese: 144 persistent chronic HBV carrier

| 10 | Akcay et al. (2018)* | Host genetic factors affecting hepatitis B infection outcomes: Insights from genome-wide association studies | NA |
| 11 | Jose-Abrego et al. (2023)* | Host and HBV Interactions and Their Potential Impact on Clinical Outcomes | NA |

* Review articles

Study Characteristics

The studies were conducted across a various populations, including Caucasians, East Asians, Chinese, and Indonesian cohorts. Most studies employednext-generationsequencing (NGS) or polymerase chain reaction (PCR) based methods for HLA-DPB1 genotyping. The studies ranged from large genome-wide association studies (GWAS) to focused clinical trials evaluating vaccine response and HBV progression.

*HLA-DPB1*05:01 and Hepatitis B Infection*

Several studies explored the association between HLA-DPB1*05:01 and HBV infection. One study found an association between HLA-DPB1 polymorphisms and spontaneous HBsAg seroclearance in Caucasians [1]. Another study highlighted variations in HLA-DPB1 gene expression linked to HBV infection in Chinese populations [6]. A large Taiwanese cohort identified significant associations between HLA class II variants, including HLA-DPB1*05:01, and chronic HBV infection [14]. Similarly, a GWAS in the Thai population showed an association between HLA-DPB1 variants and chronic HBV infection [15]. An Indonesian cohort study demonstrated the protective effects of HLA-DPA1/DPB1 variants against HBV [16].

*HLA-DPB1*05:01 Affects Disease Progression, Chronicity, and Response to Treatment*

Theterms of disease are progression, chronicity, and treatment response, various studies have shown the role of HLA-DPB1*05:01. Host genetic factors, particularly HLA-DP variants, influence HBV clinical outcomes [21]. HLA-DP polymorphisms were associated with a better response to peginterferon treatment in Caucasian HBV patients [17]. In a Southwest Chinese population, HLA-DPB1*05:01 was linked to HBV clearance and slower progression to liver cirrhosis [18]. A study in Japanese individuals found a significant relationship between HLA-DPB1 genotypes and chronic HBV infection [19]. Another study demonstrated that certain HLA-DPB1 variants affected the efficacy of interferon treatment in HBV patients [20].

Discussion

*HLA-DPB1*05:01 and Hepatitis B infection*

Many epidemiological studies have been conducted to look at the impact of the HLA-DPB1*05:01 allele variant, especially on hepatitis B virus (HBV) infection. This study have a dominant impact on susceptibility to infection, resistance to anti-hepatitis drugs, and disease progression in chronic hepatitis

B [1,6,14,15,21]. The findings from these studies have provided valuable insights into the genetic factors that contributes to the variability in HBV infection outcomes.

HBV infection in a cohort of Caucasian patients. The study found that individuals carrying the HLA-DPB1*05:01 allele had a significantly higher likelihood of spontaneous clearance of the virus compared to those without the allele, suggesting a protective effect [1]. This allele was hypothesized to enhance the presentation of HBV peptides to CD4+ T cells, promoting a robust immune response capable of eliminating the virus.

In contrast, a study conducted in a Chinese population presented a distinct perspective. This large-scale case-control study included patients with chronic hepatitis B and hepatocellular carcinoma. The results indicated that HLA-DPB1*05:01 was more frequent among chronic HBV carriers, implying an increased susceptibility to persistent infection. The authors proposed that the allele might be associated with an ineffective immune response, allowing the virus to evade clearance and establish chronic infection [6].

The studies that show specific population impacts on Indonesians are different from previous results. This study showed there was no significant correlation between the HLA-DPB1*05:01 allele and outcomes from the occurrence of Hepatitis B infection. The study highlighted the complexity of genetic influences on HBV infection and suggested that other genetic or environmental factors might modulate the impact of HLA-DPB1*05:01 in different ethnic groups [16].

Two other studies utilized a genome-wide association study (GWAS) approach to identify genetic variants associated with chronic hepatitis B in the East Asian population. Both studies highlight the significant role of HLA-DPB1 variants in protecting against chronic hepatitis B (CHB) and promoting viral clearance in East Asian populations. Specifically, they emphasize the association of specific SNPs within the HLA-DPB1 gene with protection against CHB and HBV clearance. HLA-DPB1 alleles are crucial in determining susceptibility to CHB and conferring protective effects against HBV infection. Haplotype analysis identified protective and risk-associated haplotypes in the HLA-DPB1 gene, further underlining its involvement in CHB susceptibility. Both studies confirmed that HLA-DPB1*05:01 is associated with a heightened risk of chronic HBV infection, mirroring results from the Chinese cohort. This extensive genetic analysis offered convincing evidence supporting the role of HLA-DPB1*05:01 in influencing HBV persistence [15,21]. The importance of HLA-DPB1 in protecting against chronic HBV infection and promoting viral clearance is reiterated in both studies.

Moreover, a meta-analysis compiling data from multiple studies assessed the broader influence of HLA-DPB1*05:01 on HBV infection. The findings revealed that HLA-DPB1*05:01 was linked to both a greater susceptibility to chronic HBV infection and a higher chance of vaccine non-response. This dual

effect highlights the complex role of this allele in shaping the immune response to HBV [22].

In summary, epidemiological studies have demonstrated that the HLA-DPB1*05:01 allele plays a significant role in HBV infection, although its effects vary across different populations.

*HLA-DPB1*05:01 Affects Disease Progression, Chronicity, and Response to Treatment*

Previous research in the Caucasian population investigates the association of HLA-DP polymorphisms with the response to peginterferon (PEG-IFN) therapy in patients with chronic hepatitis B (CHB). The research included 262 Caucasian CHB patients infected with HBV genotypes A or D, and treated with PEG-IFN for one year. The study found that HLA-DPB1 polymorphisms were independently associated with virological response, with an adjusted odds ratio (OR) of 1.8. Additionally, HLA-DPB1 was linked to undetectable HBV DNA levels, with an adjusted OR of 2.4. HLA-DPA1 and HLA-DPB1 haplotype block GG also showed a significant associations with virological and combined responses. The findings suggests that individuals carrying the HLA-DPB1*05:01 allele experienced a slower progression to liver cirrhosis and hepatocellular carcinoma [17].

Conversely, a study in a Chinese cohort found that HLA-DPB1*05:01 was associated with an increased risk of developing severe liver disease, including cirrhosis and liver cancer. The study hypothesized that in this population, the allele might contribute to a chronic inflammatory response, exacerbating liver injury and facilitating disease progression [18].

Another study investigates the association between genetic variants in the HLA-DP locus and persistent chronic hepatitis B virus (HBV) infection in the Japanese population. This study involved 2582 Japanese genomic DNA samples. Haplotype analysis revealed that specific combinations of protective and risk alleles significantly affect HBV infection risk. The HLA-DPB1*05:01 allele with a combination of HLA-DPB1*09:01 has been associated with an increased risk of chronic hepatitis B virus (HBV) persistence [19]. The study suggested that HLA-DPB1*05:01 might impair the effective clearance of the virus, leading to persistent infection.

A meta-analysis consolidated data from multiple studies and confirmed that HLA-DPB1*05:01 is a significant genetic risk factor for chronic HBV infection. The analysis revealed that this allele was consistently associated with higher rates of chronicity across different ethnic groups, reinforcing the allele's role in influencing HBV infection outcomes [21].

HLA-DPB1*05:01 also affects the response to HBV treatment, particularly antiviral therapy, and vaccination. A study explored the impact of HLA-DPB1*05:01 on the efficacy of antiviral treatment in patients with chronic HBV. The study found that carriers of the allele responded less favorably to nucleos(t)ide analog therapy, exhibiting slower viral clearance and higher rates of drug resistance [17]. Another study also supports this and suggests that the allele may influence the effectiveness of antiviral mechanisms, through altered immune modulation [20].

Regarding HBV vaccination, previous research indicated that individuals with HLA-DPB1*05:01 were more likely to be non-responders to the hepatitis B vaccine [9]. This study, conducted in 152 adolescents with undetectable anti-HBs titer, found that the presence of the allele correlated with lower protection in post-vaccination. The authors proposed that HLA-DPB1*05:01 might affect antigen presentation and immune activation, resulting in a suboptimal vaccine-induced immune response.

*Detecting HLA-DPB1*05:01 Using Sequencing Methods*

The allele for HLA-DPB1*05:01 is NM_002121.5:c.[190T>C; 194C>T; 251C>A; 252T>G; 338G>A; 341G>A; 343C>G; 346A>G; 374G>A; 381T>C; 406T>C; 441G>A; 588T>C; 596C>T; 624T>C; 700G>A] [23].

However, the sequence for NM_002121.5 which the mutation covered is:

GTCACAGAAGACTACTTGGGTTCATGGTCTCTAATATTTCAAACAGGAGCTCCCTTTAG
CGAGTCCTTCTTTTCCTGACTGCAGCTCTTTTCATTTTGCCATCCTTTTCCAGCTCCATGATG
GTTCTGCAGGTTTCTGCGGCCCCCCGGACAGTGGCTCTGACGGCGTTACTGATGGTGCTGCT
CACATCTGTGGTCCAGGGCAGGGCCACTCCAGAGAATTACCTTTTCCAGGGACGGCAGGAA
TGCTACGCGTTTAATGGGACACAGCGCTTCCTGGAGAGATACATCTACAACCGGGAGGAGT
TCGCGCGCTTCGACAGCGACGTGGGGGAGTTCCGGGCGGTGACGGAGCTGGGGCGGCCTG
CTGCGGAGTACTGGAACAGCCAGAAGGACATCCTGGAGGAGAAGCGGGCAGTGCCGGACA
GGATGTGCAGACACAACTACGAGCTGGGCGGGCCCATGACCCTGCAGCGCCGAGTCCAGC
CTAGGGTGAATGTTTCCCCCTCCAAGAAGGGGCCCTTGCAGCACCACAACCTGCTTGTCTG
CCACGTGACGGATTTCTACCCAGGCAGCATTCAAGTCCGATGGTTCCTGAATGGACAGGAG
GAAACAGCTGGGGTCGTGTCCACCAACCTGATCCGTAATGGAGACTGGACCTTCCAGATCC
TGGTGATGCTGGAAATGACCCCCCAGCAGGG (600 bp) [24].

Then the primer should be used between1-600. The primers used for PCR amplification were designed to target the HLA-DPB1 gene, with the forward primer sequence 5′-TCCCTTTAGCGAGTCCTTCTTT-3′ and reverse primers 5′-TGCTGCCTGGGTAGAAATCC-3′. The product length for this pair is 526. Tm, GC%, Self-complementarity, Self 3' complementarity is acceptable for both primer (forward: 59.10; 45.45; 4.00; 0.00 and reverse: 59.74; 55.00; 4.00; 1.00) [25].

Conclusion

This review underscores the significant role of the HLA-DPB1 especially for the *05:01 allele in hepatitis B virus (HBV) infection, disease progression, and treatment response. The HLA-DPB1 gene, a key component of the human leukocyte antigen (HLA) system, facilitates immune responses by presenting

peptides to T cells. HLA-DPB1*05:01 influences HBV infection outcomes, with its effects varying across populations. In Caucasians, HLA-DPB1*05:01 is linked to spontaneous HBV clearance, suggesting a protective effect through enhanced peptide presentation to CD4+ T cells. Conversely, in East Asian and Chinese populations, the allele increases susceptibility to chronic HBV infection due to a potentially ineffective immune response. The allele's influence on disease progression also varies it slows progression to severe liver diseases like cirrhosis and hepatocellular carcinoma in some populations but increases the risk in others.

HLA-DPB1*05:01 affects antiviral treatment efficacy, with carriers showing slower viral clearance and higher drug resistance rates. Furthermore, the HLA-DPB1*05:01 allele has been linked to an increased chance of non-responsiveness to the hepatitis B vaccine, leading to reduced antibody titers after vaccination. Sequencing of HLA alleles, including HLA-DPB1*05:01, is crucial for understanding their disease associations and underlying mechanisms. Using specifically designed primers, a 526 bp product was generated for detailed genetic analysis. The findings highlight the complex interplay between HLA alleles and HBV, influenced by genetic and environmental factors. Further research is needed to elucidate these mechanisms, especially the variability in HLA-DPB1*05:01 alleles impact across populations.

Several limitations should be noted. The reviewed studies show considerable heterogeneity in methodologies, populations, and clinical outcome definitions, affecting the generalizability of the findings. Many studies focus on specific ethnic groups, limiting broader applicability. The complex nature of HBV infection involves multiple genetic and environmental factors, meaning the observed associations may not fully capture HLA-DPB1*05:01's role. Longitudinal studies tracking individuals over time are lacking, which would provide a more dynamic understanding of the allele's influence on HBV infection and progression. Finally, while next-generation sequencing offers high accuracy, its cost and accessibility may limit widespread application, potentially biasing research towards well-funded studies or institutions. Addressing these limitations in future research is crucial for advancing the understanding of HLA-DPB1*05:01 and its impact on HBV infection.

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Original Article   **Open Access**

Satisfaction with Online and Offline Learning among 2020 Medical Students at Universitas Muslim Indonesia

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ABSTRACT

Introduction: In recent years, Indonesian education has undergone drastic changes to respond to the world's digital challenges. When learning online, education components make many preparations while offline learning tends to require higher tuition fees. The lecturer needs to adjust the curriculum and lesson planning, learning practices and learning assessment, online and offline learning are different, so the level of student satisfaction will be very different. Knowing the level of satisfaction of online learning and offline learning in 2020 batch students of the Faculty of Medicine, Universitas Muslim Indonesia.

Methods: This study used a descriptive method with a cross-sectional research design.

Results: 252 samples who filled out the questionnaire, the level of online learning satisfaction of the class A sample, the satisfied category was 120 respondents (94.5%) and dissatisfied as many as 7 respondents (5.5%), while the level of offline learning satisfaction of the class A sample, the satisfied category was 121 respondents (95.3%) and dissatisfied as many as 6 respondents (4.7%). The level of online learning satisfaction of the class B sample, the satisfied category was 117 respondents (93.6%) and dissatisfied as many as 8 respondents (6.4%), the level of offline learning satisfaction of the class A sample, the satisfied category was 123 respondents (98.4%) and dissatisfied as many as 2 respondents (1.6%).

Conclusion: The students of the medical faculty class of 2020 at Universitas Muslim Indonesia are satisfied with both online and offline learning methods.

Keywords: Satisfaction level; online; offline; student

Introduction

The COVID-19 outbreak forced a rapid shift to online learning, as outlined in the Circular Letter of the Minister of Education and Culture (No: 36962 / MPK. A/MK/2020). This policy encouraged schools and universities to adopt online learning while emphasizing health protocols to prevent the spread of COVID-19.[1] Online learning has changed the way people perceives learning so far.[2] This sudden transition changed the perception of learning, requiring adjustments in curriculum, lesson plans, teaching practices, and assessments[3].

The purpose of this study is compare the online and offline learning, focusing on student satisfaction, particularly among medical students, during the pandemic. Online learning relies on internet technology, making it suitable for lecture-based content but less effective for hands-on subjects. Network and technical issues also pose challenges. The Ministry of Education allowed flexibility for institutions to adjust their implementation.[4]

The government's policies significantly impacted higher education, requiring both public and private universities to adapt. While we are becoming accustomed to online learning, it differs greatly from offline learning, which affects students' psychology.[5] According to Karwati (2014), the quality and satisfaction of online learning vary from offline, as do academic services, which had to transition to digital formats. Student satisfaction is crucial for universities to remain competitive.[6]

Face-to-face learning allows spontaneous interaction in a physical environment, which enhances psychological and emotional engagement. However, it comes with higher tuition fees, especially at prestigious institutions (Norman, 2016). Experts agree that the interactive experiences in traditional classrooms are hard to replicate online.[7]

Few studies have investigated satisfaction levels in online versus offline learning, particularly among medical students.[8] Sriwahyuni (2018) found that higher teacher professionalism leads to increased student satisfaction.[9] Research by Achmad C. (2020) indicated that online learning helped maintain stable student outcomes during the COVID-19 pandemic.[10]

Methods

The methods use descriptive research. The design of this study is *cross-sectional*, meaning that in this study the form of data collection is carried out within a certain period of time, research only once and observation throughout the research process, which is only once and there is no repetition.

Total sampling is a sampling technique, where the number of samples is equal to the number of populations. The total research sample is the total number of students of the Faculty of Medicine, Universitas Muslim Indonesia who attended online and offline lectures in the class of 2020.

Result

The data collection was carried out on medical education students of the Faculty of Medicine, Universitas Muslim Indonesia. This research was conducted by taking secondary data in the form of questionnaires distributed to the class of 2020 to assess the level of student satisfaction in participating in online and offline lectures. The sample 252 students from the class of 2020 of the Faculty of Medicine UMI , consisting of 127 samples from class A and 125 samples from class B.

Table. 1 Distribution frequency of online and offline learning satisfaction levels in class of 2020 class, faculty of medicine, Universitas Muslim Indonesia

Satisfaction Level	Learn Online		Learn Offline	
	Amount (N)	Percentage (%)	Amount (N)	Percentage (%)
Satisfied	120	94,5	121	95,3
Not satisfied	7	5,5	6	4,7
Total	127	100,0	127	100,0

Source: Primary Data Analysis, 2023

Based on **Tabel. 1**, out of 127 respondents with a level of satisfaction with online learning in class A students of the Faculty of Medicine, Universitas Muslim Indonesia in the satisfied category as many as 120 respondents (94.5%) and dissatisfied as many as 7 respondents (5.5%) and it can also be known that from 127 respondents with a level of satisfaction with learning satisfaction in class A students of the Faculty of Medicine, Universitas Muslim Indonesia in the satisfied category as many as 121 respondents (95.3%) and dissatisfied as many as 6 respondents (4.7%)

Table. 2 Distribution frequency of online and offline learning satisfaction levels in class of 2020 class b students faculty of medicine, Universitas Muslim Indonesia

Satisfaction Level	Learn Online		Learn Offline	
	Amount (N)	Percentage (%)	Amount (N)	Percentage (%)
Satisfied	117	93,6	123	98,4
Not satisfied	8	8	2	1,6
Total	125	100,0	125	100,0

Source: Primary Data Analysis, 2023

Based on **Tabel. 2**, 125 respondents with the level of online learning satisfaction in class B students of the Faculty of Medicine, Universitas Muslim Indonesia in the satisfied category as many as 117 respondents (93.6%) and dissatisfied as many as 8 respondents (6.4%) and it can also be known that from 125 respondents with the level of offlinelearning satisfaction in class A students of the Faculty of Medicine, Universitas Muslim Indonesia in the satisfied category as many as 123 respondents (98.4%)

and dissatisfied as many as 2 respondents (1.6%).

Table. 3 Distribution of offline and online learning satisfaction frequency based on the type of learning in class a class 2020 faculty of medicine, Universitas Muslim Indonesia

Types of Learning	Satisfaction Category		Method	
			Offline	Online
Lecture	Satisfied	n	123	117
		%	96,9	92,1
Practicum	Satisfied	n	123	114
		%	96,9	89,8
PBL	Satisfied	n	117	115
		%	93,7	92,1
CSL	Satisfied	n	123	113
		%	96,9	89,0
Pleno	Satisfied	n	121	117
		%	95,3	92,1

Source: Primary Data Analysis, 2023

Based on **Table. 3**, the level of class satisfaction A learning aspects of lectures that answered satisfied in the offline method was 123 respondents (96.9) and the online method was 117 respondents (92.1). In the practicum aspect, 123 respondents were satisfied with the offline method (96.9) and the online method as many as 114 respondents (89.8). In the PBL aspect, 117 respondents were satisfied with the offline method (93.7) and the online method as many as 115 respondents (92.1). In the CSL aspect, 123 respondents (96.9) answered satisfied with the offline method (96.9) and 113 respondents with the online method (89.0). In the plenary aspect, 121 respondents were satisfied with the offline method (95.3) and the online method as many as 117 respondents (92.1).

Table 4. Distribution of offline and online learning satisfaction frequency based on the type of learning in class a class 2020 faculty of medicine, Universitas Muslim Indonesia

Types of Learning	Satisfaction Category		Method	
			Offline	Online
Lecture	Satisfied	n	4	10
		%	3,1	7,9
Practicum	Satisfied	n	4	13
		%	3,1	10,2

			Offline	Online
PBL	Satisfied	n	8	10
		%	6,3	7,9
CSL	Satisfied	n	4	14
		%	3,1	11,0
Pleno	Satisfied	n	6	10
		%	4,7	7,9

Source: Primary Data Analysis, 2023

Based on **Table. 4,** the level of satisfaction with class A learning aspects of lectures that answered dissatisfaction in the offline method was 4 respondents (3.1) and the online method was 10 respondents (7.9). In the practicum aspect, 4 respondents (3.1) answered dissatisfaction with the offline method (3.1) and the online method as many as 13 respondents (10.2). In the PBL aspect, 8 respondents (6.3) were dissatisfied with the offline method (6.3) and the online method as many as 10 respondents (7.9). In the CSL aspect, 4 respondents (3.1) were dissatisfied with the offline method (3.1) and the online method was 14 respondents (11.0). In the plenary aspect, 6 respondents (4.7) were dissatisfied with the offline method (4.7) and the online method as many as 10 respondents (7.9).

Table 5. Distribution frequency of offline and online learning satisfaction levels based on the type of learning in class of 2020 students class b faculty of medicine, Universitas Muslim Indonesia

Types of Learning	Satisfaction Category		Method	
			Offline	Online
Lecture	Satisfied	n	123	120
		%	98,4	96,0
Practicum	Satisfied	n	120	115
		%	96,0	92,0
PBL	Satisfied	n	117	115
		%	93,6	92,0
CSL	Satisfied	n	121	116
		%	96,8	92,8
Pleno	Satisfied	n	124	118
		%	99,2	94,4

Source: Primary Data Analysis, 2023

Based on **Table 5**, the level of satisfaction with class A learning aspects of lectures that answered satisfied in the offline method was 123 respondents (96.9) and the online method was 120 respondents (96.0). In the practicum aspect, 120 respondents were satisfied with the offline method (96.0) and the

online method as many as 115 respondents (92.0). In the PBL aspect, 117 respondents were satisfied with the offline method (93.6) and the online method as many as 115 respondents (92.0). In the CSL aspect, 121 respondents were satisfied with the offline method (96.8) and the online method as many as 116 respondents (92.8). In the plenary aspect, 124 respondents were satisfied with the offline method (99.2) and the online method as many as 118 respondents (94.4).

Table 6. Distribution frequency of offline and online learning satisfaction levels based on the type of learning in class of 2020 students class b faculty of medicine, Universitas Muslim Indonesia

Types of Learning	Satisfaction Category		Method	
			Offline	Online
Lecture	Not Satisfied	n	2	5
		%	1,6	4,0
Practicum	Not Satisfied	n	5	10
		%	4,0	8,0
PBL	Not Satisfied	n	8	10
		%	6,4	8,0
CSL	Not Satisfied	n	4	9
		%	3,2	7,2
Pleno	Not Satisfied	%	99,2	94,4
		n	1	7

Source: Primary Data Analysis, 2023

Based on **Table 6**, the level of satisfaction with class A learning aspects of lectures that answered dissatisfaction in the offline method was 2 respondents (1.6) and the online method was 5 respondents (4.0). In the practicum aspect, 5 respondents (4.0) answered dissatisfaction with the offline method (4.0) and the online method as many as 10 respondents (8.0). In the PBL aspect, 8 respondents (6.4) answered dissatisfaction with the offline method (6.4) and 10 respondents (8.0) in the online method. In the CSL aspect, 4 respondents (3.2) were dissatisfied with the offline method (3.2) and the online method as many as 9 respondents (7.2). In the plenary aspect, those who answered dissatisfaction with the offline method were 1 respondent (0.8) and the online method as many as 7 respondents (5.6).

Discussion

Based on data analysis and findings in the field further contributing to knowing the analysis of the level of satisfaction with online learning and offline learning in students of the class of 2020 Faculty of Medicine, Universitas Muslim Indonesia.

Based on the results of the study, showed that of 252 respondents with the level of online learning satisfaction in students of the class of 2020 Faculty of Medicine, Universitas Muslim Indonesia class A in the satisfied category, there were 120 respondents (94.5%) and 7 respondents (5.5%) dissatisfied in the class of 2020 students of the Faculty of Medicine, Universitas Muslim Indonesia class B in the satisfied category as many as 117 respondents (93.6%) and dissatisfied as many as 8 respondents (6.4%).

Research by Susilawati, S. et al (2022) entitled online learning satisfaction during the *COVID-19* pandemic in terms of: class, gender and age. This shows the results of the assessment of attitudes and responses through discussion activities, namely overall that students are satisfied with the online learning process that has been carried out by educational institutions and this is also in line with our research.[11] Several previous studies have also stated that online learning is effective when the emergency conditions such as during the *COVID-19* pandemic outbreak. However, educational institutions are expected to improve online learning services such as the internet network and the intention to participate in the online learning process to achieve the expectations of students.[12]

Online learning is considered the best solution because it can provide opportunities for students to take certain courses that are difficult to reach offline and can provide massive and open learning services so that they have a wide and large range of enthusiasts and provide good learning outcomes.[12] This is also in line with research conducted by Fitria, N. M and Sukmawati, W. (2022) which states that there are significantly higher results in the learning outcomes of mathematics subjects building learning spaces carried out online compared to offline learning. Effectiveness is the key to successful online learning so that students are honed in their ability to see reality in the real world then analyze and share it with the public through online media.[13]

Based on the results of the study, showed that of 252 respondents with a level of offline learning satisfaction in students of the class of 2020 Faculty of Medicine, Universitas Muslim Indonesia class A in the satisfied category as many as 121 respondents (95.3%) and dissatisfied as many as 6 respondents (4.7%) and the level of offline learning satisfaction in the class of 2020 students of the Faculty of Medicine, Universitas Muslim Indonesia class B in the satisfied category as many as 123 respondents (98.4%) and dissatisfied as many as 2 respondents (1.6%).

Based on research conducted by Rosari, B. E. et al (2022) entitled The Effect of Online Learning Changes to Offline Learning on the Learning Interests of Grade VII Students of Wesley Marindal II Junior High School, stated that student interest in learning is higher in offline learning because offline learning is considered more effective by students due to several things such as direct interaction, Save quota, do not worry about bad internet network, improve concentration and better understand the material delivered by the teacher directly.[13] In line with research conducted by Tullah, H. (2022) which states that the

difference in offline and online learning patterns is that when offline learning students read books more often before learning begins, more often make their own study schedules, study according to pre-made schedules, make summaries of material before and have studied while during online learning students rarely do these activities.[14]

The level of satisfaction with class A learning aspects of lectures that answered satisfied in the offline method was 96.9% and the online method was 92.1%. Then the level of satisfaction with learning class B aspects of lectures that answered were satisfied in the offline method as much as 98.4% and online methods as much as 96.0%. The level of satisfaction with online and offline learning methods in the lecture aspect generally same. However, the offline learning method is slightly higher than the online method, this is because the offline lectures applied can form emotional discipline and students can create a good learning environment so the students will be more enthusiastic about learning which will have an impact on better learning outcomes (9). Several studies agree with offline learning can use cause meaning full and real interactions between students and lecturers, while online lecturers often encounter passive interactions.[15]

The level of satisfaction with learning class A in practicum aspects that answered satisfied in offline methods was 96.9% and online methods were 89.8%, while the level of satisfaction in learning class B practicum aspects who answered satisfied in offline methods was 96.0% and online methods as much as 92.0%. The level of satisfaction with online and offline learning methods in the practicum aspect in general is almost the same. However, the offline learning method is slightly higher than the online method. Face-to-face practicum skills can develop basic scientific skills through the process of observing, measuring, analyzing data and using tools directly.[16] Practicum can make students easier to practice the skills according to procedures, and students can learn to interpret the results of a test.[14] Practicum also helps students in compiling learning concepts, in contrast to online practicum which usually relies on understanding knowledge through online media by watching videos from the media platforms provided or even using makeshift tools at home which causes students to lack understanding of skills because they can only imagine skills through prepared videos [17].[17]

The level of satisfaction with learning class A aspects of PBL who answered satisfied in the offline method was 93.7% and the online method was 92.1%, while the level of satisfaction in learning class B aspects of PBL who answered satisfied in the offline method was 93.6% and the online method was 92.0%. The level of satisfaction with online and offline learning methods in the PBL aspect in general is almost the same. However, the offline learning method is slightly higher than the online method. In principle, a good PBL will provide quality educational output which is largely determined by a structured discussion process using the *seven jump method* that occurs during the tutorial, the role of the tutor greatly determines the success of this program then students become self-directed learning individuals[18][18]. This

PBL strongly supports open, reflective, critical and active learning, so that learners have a high level of confidence.[19] When PBL is carried out with online methods students tend to follow directions, less active and less critical, throughPBL students must be able to become core actors in tutorials that will be reviewed and assessed objectively ability in critical thinking, ability to explain, leadership attitude and cooperation of students both in tutorial discussions and outside.[20]

The level of satisfaction with learning class A in the CSL aspect who answered satisfied in the offline method was 96.9% and the online method was 89.0%, while the level of satisfaction in class B learning in the CSL aspect who answered satisfied in the offline method was 96.8% and the online method was 92.8%. The level of satisfaction with online and offline learning methods in the CSL aspect in general is almost the same. However, the offline learning method is slightly higher than the online method, this is because in online CSL students can only listen to explanations without directly practicing it, because there is no or lack of tools and materials where students are, besides that online CSL activities are greatly influenced by the quality of the internet network, so it greatly impacts the quality of learning and affects students' ability to understand the material taught and satisfaction students in doing CSL online.[21] Other factors that make students feels that there is a lack of interaction between the instructor and students, making it difficult for students to understand the skills learned. In offline CSL instructors can provide information well, and become a facilitators, designers and developers of learning resources. CSL really needs the lecturers who act as observers who provide feedback at the *correction* and *reinforcement* stages, and provide direction to students in learning correct and appropriate procedural techniques from the demonstration stage to performance[17].[17]

The satisfaction level of class A learning in the plenary aspect that answered satisfied in the offline method was 95.3% and the online method was 92.1%. The level of satisfaction with class B learning plenary aspects that answered satisfied in the offline method as much as 99.2% and the online method as much as 94.4%. The level of satisfaction with online and offline learning methods in the plenary aspect is generally almost the same. However, the offline learning method is slightly higher than the online method, this is because the panel discussion should have a massive and active discussion between the speaker and the *audience*, this will happen when these two parties can participate well in the panel/plenary discussion.[14] Unlike when plenary discussions with online methods are very difficult for active interaction to occur because they are still constrained by several problems such as uneven internet networks, while in plenary with offline methods it is very supportive of active interaction and the discussion process is more focused. In addition, the presence of tutors or speakers is the key to successful active discussions because plenary not only facilitates students in gaining knowledge, but also general attitudes and expertise that medical students should have (22[22]).

Conclusion

This study concludes that the students of the class of 2020 fakultas kedokteran Universitas Muslim Indonesia are satisfied with the online and offline learning methods. The author suggests that by reviewing the data of research results that are less significant between online learning and offline learning, researchers should then be able to compile questionnaires properly in order to get better and more significant results. Inovasi learning really needs to be developed to increase satisfaction in student learning. The need for interesting and fun learning is not only monotonous by using one method but trying various methods to create a learning experience for students that is able to increase their understanding of deeper material concepts.

Conflicts of Interest

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Original Article   **Open Access**

Relationship of Fruits and Vegetables Consumption with Children's Cognitive Function in Elementary School Makassar

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ABSTRACT

Introduction: Based on 2018 Basic Health Research data, the proportion of fruits and vegetables consumption among the Indonesian population ≥ 5 years old is still less, namely 95.5%. Eating fruits and vegetables can maintain cognitive function and repair damaged brain cells. The research aimed to determine the relationship between fruits and vegetables consumption and cognitive function in elementary school children in Makassar.

Methods: The research methodology is descriptive observational. The study sample size was 37 participants selected using a simple random sampling technique at SDN Borong Raya Makassar from September 2023 to October 2023. The independent variable was fruits and vegetables consumption, while the dependent variable in this study was cognitive function.

Results: Data analysis used the SPSS statistical Chi-square test where $p < 0.05$. The research results show that children who consume enough fruits and vegetables have good cognitive development (71.43%).

Conclusion: There is a relationship between fruits and vegetables consumption and cognitive function. Adequate consumption of fruits and vegetables can optimize children's cognitive development.

Keywords: Fruits; vegetable; cognitive function; children

Introduction

The average fiber intake of the Indonesian population is only a third of what is recommended by the World Health Organization (WHO).[1] People can implement this by consuming fruits and vegetables. Vegetables and fruits contain various nutrients that are good for the body, such as vitamins, minerals, and dietary fiber. Vegetables and fruit must be consumed every day to meet the intake of vitamins and minerals that the body needs to achieve a healthy diet, which by the recommendations of balanced nutrition guidelines for optimal health.[2]

Based on 2018 Basic Health Research data, the proportion of fruits and vegetables consumption among the Indonesian population ≥ 5 years old is still less, namely 95.5%. The prevalence of under consumption of fruits and vegetables in South Sulawesi province is 94.7%, which is lower than the national prevalence of under consumption of vegetables and fruit, namely 95.5%.[3]

Low fruits and vegetables consumption is the most common behavioral problem, especially for school-aged children. Therefore, it is necessary to change children's behavior in consuming fruits and vegetables through increasing knowledge.[4] Consuming fruits and vegetables can affect cognitive function.[5] This is because fruits and vegetables contain the vitamin B group (6.9, 12), vitamin C, polyphenols and minerals which play a role in improving a person's cognitive status.[6]

The ingredients contained in fruits that can affect cognitive function are flavonoids. Flavonoids are polyphenolic compounds with a carbon chain in the form of C6C3C6, found in different amounts in each plant food. There are several subclasses of flavonoids, including anthocyanidins, which have the ability to interact in intercellular neuron signaling pathways which influence neurodegenerative and neuroinflammatory processes that are responsible for memory, learning and cognitive function.[7] Parents are required to provide a good nutritious food for their children, especially those that contain lots of fiber and are found in fruits and vegetables.[8]

Apart from being able to prevent degenerative diseases, consuming fruits and vegetables can also have a positive effect on reducing stress, maintaining cognitive function and repairing damaged brain cells.[9] Fruits and vegetables are a food group that contains various sources of micronutrients that the body needs in metabolic processes.[10]

Cognitive is the ability to learn or think to learn a new skills and concepts. People needs a skills to understand what is happening in the environment and skills to use a memory and problem solving.[11]

Methods

This research is quantitative research using a descriptive observational research design. Descriptive observational research is research that describes a situation or problem that is explored through

observations that occur in the field. This research was conducted in July – August 2023 at SDN Borong Raya Makassar District. Manggala, Makassar City, South Sulawesi. The population in this study were students at Borong Raya Makassar Elementary School with a sample of 3rd-grade elementary school students, used a simple random sampling technique, with a sample size of 37. The tools and materials in this research used the Semi-quantitative FFQ (Semi-Quantitative Food Frequency) as a method for collecting data about the frequency of food consumption during a certain period. The data obtained from this method includes meal frequency per day, per week and month, food portion sizes, a food photo book by the Individual Food Consumption Survey Team and the SYSTEM-R Cognitive Screening. The data analyzed was processed used IBM SPSS Statistics.

Result

In this research, it is classified based on the variables selected in the table in the form of:

Univariate Analysis

Table. 1 Sample of Gender Frequency Distribution

Gender	n	%
Male	13	35,13
Female	24	64,87
Total	37	100,00

Source: Primary Data Analysis, 2023

Table. 1 The sample of gender distribution frequency, where the majority of the sample is female, namely 64.87%.

Table. 2 Sample of Age Frequency Distribution

Age (Year)	n	%
8	21	56,76
9	16	43,24
Total	Total	37

Source: Primary Data Analysis, 2023

Table. 2 The frequency distribution of the age of the sample, where the majority of the sample is 8 years old, namely 56.76%.

Table. 3 Frequency Distribution of Sample Fruits and vegetables Consumption Categories

Consumption	n	%
Enough	21	56,76
Deficient	16	43,24
Total	Total	37

Source: Primary Data Analysis, 2023

Table. 3 The distribution of sample fruits and vegetables consumption categories, where the majority of sample fruits and vegetables consumption is in the sufficient category, namely 56.76%.

Table. 4 Sample of Cognitive Frequency Distribution

Cognitive	n	%
Good	20	54,05
Deficient	17	45,95
Total	Total	37

Source: Primary Data Analysis, 2023

Table. 4 The distribution of sample environmental categories, where the majority of the sample has a good cognitive function, namely 54.05%.

Bivariate Analysis

Table. 5 Analysis of the Relationship between Fruits and vegetables Consumption and the Sample's Cognitive Function

			Cognitive function		Total	Mark-p
			Good	Poor		
Fruits and Vegetables Consumption	Enough	n	15	6	21	
		%	71,43	28,57	100,0	0,036
	Not enough	n	5	11	16	
		%	31,5	68,75	100,00	
Total		n	20	17	37	
		%	50,05	45,95	100,00	

Source: Primary Data Analysis, 2023

Table. 5 The result of the chi-square test which analyzes the relationship between fruits and vegetables consumption and cognitive function in the sample, where a p-value of 0.036 (<0.005) was obtained, which means there is a significant relationship between fruits and vegetables consumption and cognitive function.

Discussion

The respondents who consume sufficient fruits and vegetables tend to have good cognitive function, whereas respondents who do not consume enough fruits and vegetables tend to have poor cognitive function, which means there is a relationship between adequate consumption of fruits and vegetables and cognitive function.

Adequate fruits and vegetables intake is necessary to maintain normal cognitive function. Further cognitive decline can be avoided in the early stages of cognitive decline by consuming polyphenolic foods regularly. Flavonoid mechanisms have been shown to inhibit free radicals and modulate signaling pathways related to cognitive function and neuroprotection.[12]

According to experts, nutrition is the most important factor influencing children's cognitive development. Children who have good nutritional status will have optimal cognitive development and vice versa, children who lack nutrition will disrupt brain development and cause delays in cognitive development and ultimately lead to poor academic performance.[13]

This research is in line with Putu Ayu (2021) who stated that children who have a poor nutritional intake of vegetables and fruit have higher suspicions of impaired cognitive development than children who have good nutritional status, namely 85.7%.[14]

Similar results were also found by Indri Nurfadhilah (2019) in Banyumas district that there was a significant relationship between fruits and vegetables consumption and cognitive function of 64.5% and 35.5% was influenced by other factors outside those studied.[15]

Conclusion

The researcher concluded from this research is about 15 out of 21 children with adequate consumption of fruits and vegetables have good cognitive function so there is a significant relationship between adequate consumption of fruits and vegetables and cognitive function. The author suggests that parents needs more attention to educate the consumption of fruits and vegetables for their children, so the children consumption of fruits and vegetables can be sufficient, and also Borong Raya Elementary School to introduce more about the benefits of consuming fruitds and vegetables to its students, so the students likes to consume the fruits and vegetables, and also for future researchers it is best to conduct outreach regarding the benefits of consuming fruits and vegetables before conducting research

Conflicts of Interest

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Reducing Soil-Transmitted Helminths Infection in Children: The Best Outcome of The COVID-19 Pandemic

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ABSTRACT

Introduction: Soil-transmitted helminths (STH) infection remains a significant health challenge in developing countries, including Indonesia, with an incidence of around 28.9%. During the COVID-19 pandemic, there have been some changes in society's habits. Therefore, this study aimed to confirm how the pandemic affects the STH infection prevalence in high-risk children.

Methods: This study, designed as a cross-sectional analysis, was conducted across multiple orphanages in Makassar, Indonesia. The sample population was healthy children aged 1–18 years old diagnosed with iron deficiency. Stool samples were collected and analyzed using the Kato-Katz technique to detect STH infection. The data was analysed with SPSS version 26 and presented in diagrams and tabulations.

Results: A total of 545 children 1-18 years old participated in this study, with 144 (26%) suffering from iron deficiency; 89 (61.4%) girls, and 56 boys (38.6%). The soil-transmitted helminth's prevalence in children with iron deficiency was 6.9%, with A lumbricoides infection at 2.06% (3/144), *T. trichiura* infection at 2.7% (4/144), and both infections at 2.06% (3/144).

Conclusion: The prevalence of soil-transmitted helminth infections among children in Indonesia significantly decreased during the COVID-19 pandemic.

Keywords: Soil-transmitted helminthes; COVID-19; children

Introduction

Soil-transmitted helminths (STH) infection is considered a neglected disease, characterized by being overlooked and persistent, often lacking noticeable clinical symptoms[1]. More than one billion people globally are affected by one or more species of STH, with these infections being widespread, especially in less developed regions. Within this population, there are specific groups at higher risk of morbidity due to STH infections. This affects over 267 million children in preschool and more than 568 million children in school[2]. STH infection major health problem, not only on a global scale but specifically in Indonesia. STH infection prevalence in Indonesia nationwide is estimated at 28.9%[3,4]. Efforts to eradicate the disease are ongoing, but progress is slower than anticipated[4].

There was a close relation between STH infection in children and iron deficiency[5–7]. Helminthiasis caused by STH can lead to various problems, including anemia from intestinal bleeding and malnutrition, particularly in children. The condition exacerbates nutritional deficiencies in multiple ways and, over time, it affects growth and development, including psychomotor performance and stunting. Among the effects of STH, anemia is probably the most common, compared to other related symptoms[4]. Most of the study on STH infection in Indonesia reported that anemia developed during the disease, with the clinical spectrum ranging from asymptomatic to severe form[4].

The COVID-19 pandemic has deeply affected many areas of human life, including the psychosocial well-being of children. Just as adults have experienced disruptions, children have also faced challenges due to interruptions in their daily routines and social activities. Prolonged periods of isolation, limited physical activity, and disrupted routines can lead to increased levels of stress, anxiety, and depression among children[8,9].

On the other hand, the decision of the World Health Organization (WHO) to issue a general recommendation to halt neglected tropical disease (NTD) programs in April 2020 was indeed a challenging one, and it had significant implications for the control of NTDs, include parasitic infections. There are many achievements in the fight against NTDs were compromised or lost due to the suspension of programs.

Furthermore, Parasitic diseases and other NTDs may have been deprioritized at local, national, and regional levels during this time, further complicating efforts to combat these diseases[10,11]. The prevalence of soil-transmitted helminth (STH) infections can be influenced by multiple factors. It can be decreased due to social distancing activity, but it is increased the NTD program's interruption. Therefore, this study aimed to confirm how the pandemic affects the helminth infection prevalence in high-risk children.

Methods

This study was conducted from July to September 2021. This study is part of the Iron Deficiency Study in Makassar (IDeM) which subjects are children at several orphanages in Makassar. The study protocol received approval from the Health Research Ethics Review Committee at the Faculty of Medicine, Hasanuddin University (UH21120764). Informed consent was obtained from the parents or guardians of the participants on the day of their inclusion in the study. The child who was diagnosed as positive for intestinal STH was treated following the study.

The Subjects of this study were healthy children aged 1-18 years old who had been screened through several criteria such as, the child had no infection disease, the child with no immunocompromise and did not get blood transfusion nor iron supplementation. Data on age, sex, and nutritional levels were collected using a questionnaire. Height and weight were measured with a standing scale and a stadiometer mounted on a straight wall, while nutritional status was assessed using the WHO Z-score. for children <5 years old and the CDC curve for children >5 years old.

Sampling and laboratory methods

With the assistance of the guardian, one stool sample per child was collected, and their personal data including their name, gender, and age, were recorded when the stool sample was delivered the following day. Stool sample analysis was performed at the Department of Parasitology using the Kato-Katz method. This technique helps in quantifying the eggs, providing the information about the intensity of infection. Ova parasites examined under the microscope using 10 then 40 times of objectives lenses.

The children with iron deficiency were identified based on three key parameters: hemoglobin levels, mean erythrocyte volume (MCV), and serum ferritin levels. These parameters help in assessing the iron status of the children. The subjects were classified into iron depletion (normal hemoglobin, normal MCV, low ferritin), iron deficient erythropoiesis (normal hemoglobin, low MCV, low ferritin), and iron deficiency anemia (low hemoglobin, low MCV, low ferritin). Low ferritin is determined if serum ferritin level <30 ug/dL, low MCV is determined if MCV level <80 pg, and anemia determined if hemoglobin below the normal limit according to aged (children aged 1-6 years; Hb level is < 11.0 g/dL, children aged 6-12 years; Hb level is < 12 g/dL, boys aged 12-18 years; Hb level is <13 g /dL, girls; Hb level < 12 g/dL).

Statistical Analysis

The data were coded and analyzed using SPSS Statistics 26.0 software. Categorical data were assessed using descriptive statistics, such as frequency and percentage, with results displayed in both graphical and tabular form**.**

Result

Out of the 545 children enrolled in this study, 144 (26%) were found to have iron deficiency. The prevalence of helminthiasis among these iron-deficient children is presented in Table 1.

Table 1. Prevalence of STH infection

	A. Lumbricoides	*T. trichiura*	*A. lumbricoides and T. trichiura*	**Not Infected**
Male	2 (3.6%)	2 (3.6%)	2 (3.6%)	50 (89.3%)
Female	1 (1.1%)	2 (2.3%)	1 (1.1%)	84 (95.5%)
Age	5 (-3.96-13.96)	11.25 (8.53-13.97)	9 (-4.14-22.14)	12.25 (11.57-12.92)

Soil-transmitted helminth prevalence

The STH infection's prevalence in children with iron deficiency was 6.9% (10/144). Diagram 1 depicts the prevalence of *A. lumbricoides* 2.06% (3/144), *T. trichiura* 2.7% (4/144), and both *A. lumbricoides* and *T. trichiura* 2.06% (3/145). (Figure 1)
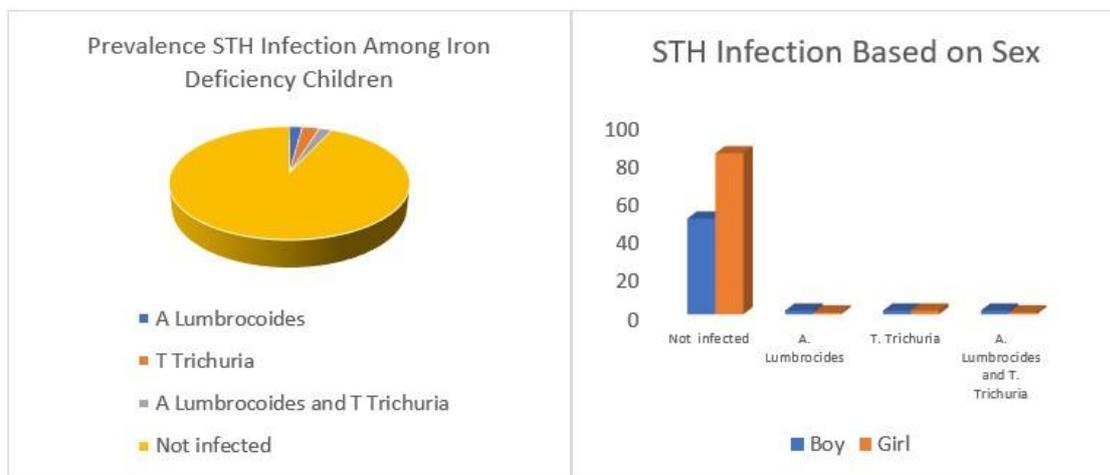

Figure 1. Prevalence STH Infection

Soil-transmitted and Nutritional States

Children infected with *A. lumbricoides* were all well-nourished, whereas children infected with *T. trichiura* consisted of three well-nourished children and one overweight child. Children with both infections consist of two well-nourished children and one overweight child. (Figure 2)
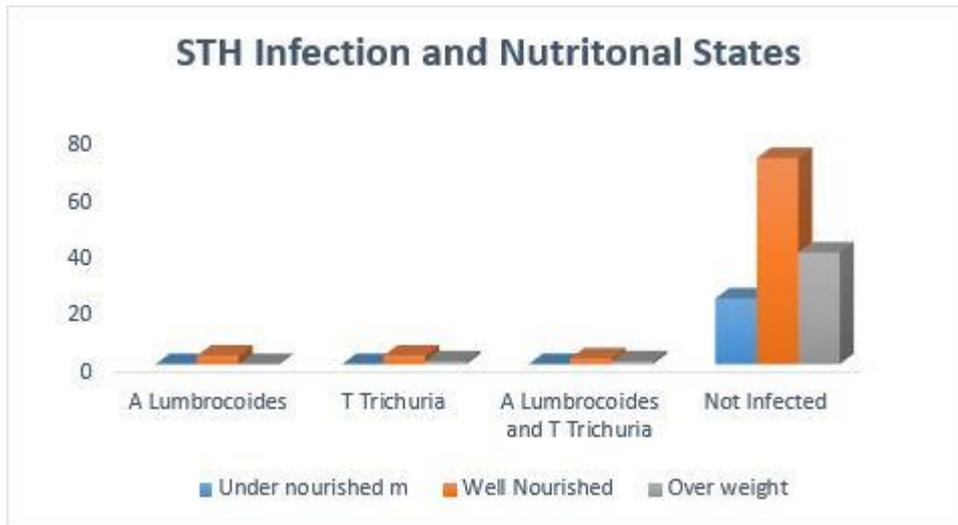
Figure 2. STH Infection and Nutritional States

STH infections and Hemoglobin Level

Hemoglobin concentration in children with STH infection was 12.60 g/dL, while the mean Hb concentration in children without STH infection was 12.95 gr/dl. Hemoglobin level in children with *A. lumbricoides* infection was 12.20 gr/dl, in children with *T. trichiura* was infection 13.10 g/dl, and the children with infection both infection was 11.80 g/dl.

STH infections and Ferritin Level

Children with STH infection had a mean ferritin level of 22.92 ng/ml, compared to 16.42 ng/ml in those without STH infection. Specifically, ferritin levels were 25.69 ng/ml in children with *A. lumbricoides* infection, 20.79 ng/ml (range 2.81-40.19 ng/ml) in those with *T. trichiura* infection, and 24.58 ng/ml in children with both infections." (Figure 3)
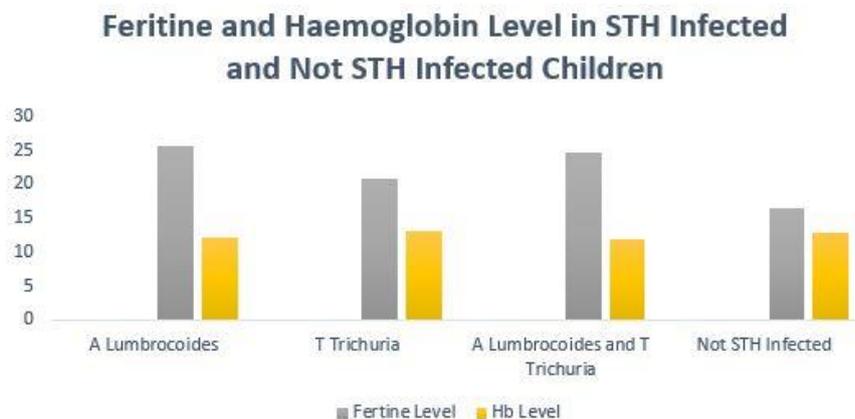

Figure 3. Hemoglobin and Ferritin Level in STH Children

STH infections and Level of Iron Deficiency

Among children with *A. lumbricoides* infection, 1 child (1.5%) had iron depletion, 1 child (1.9%) had iron-deficient erythropoiesis, and 1 child (3.8%) had iron deficiency anemia. Among Children with *T. trichiura* infection, 1 child (1.5%) had iron depletion, 3 children (5.7%) had iron-deficient erythropoiesis, and there were no cases of iron deficiency anemia. Among Children with both *A. lumbricoides* and *T. trichiura* infection, there were no cases of iron depletion, 1 child (1.9%) had iron-deficient erythropoiesis, and 2 children (7.7%) had iron deficiency anemia.

Discussion

Helminth infections, including ascariasis and trichuriasis, remain significant public health concerns in Indonesia (more than 90 million cases of each)[12]. A systematic study by Siagian and Maryanti on the condition of anemia-related STH conducted in Indonesia from 2001 to 2020 found that anemia was quite high among STH infection sample [4]. Meanwhile, our study found the helminth infection prevalence among children diagnosed with iron deficiency during covid 19's pandemic among iron deficiency's children was 6.9%. The prevalence was lower compared to national data from Indonesia, which estimates that 28.9% of children are affected by helminth infections[3]. In Indonesia, the prevalence of helminth infections varies across provinces and is influenced by factors such as demographics, culture, parental education, and socio-economic conditions. Previous studies have reported prevalence rates in different regions: Palembang 22% [13], Semarang 33%[14], Medan 40.2% [15] East Nusa Tenggara 58.8%[10]. The most recent report from Makassar indicates a prevalence of 24%.[16] Based on our study, it appears that the prevalence of this infection was significantly lower during the COVID-19 pandemic.

The children are particularly susceptible to infections due to limited self-protection capabilities, which include both inadequate immune responses and insufficient hygiene awareness[17]. Low education levels, poor quality of drinking water and sanitation, and overcrowded living conditions are well-established risk factors for helminth infections in children[18,19]. Personal hygiene consisting of hand-washing and outdoor play habits are known to be significant factors in the incidence of STH. Another risk factor for helminth infection is poor nail hygiene, as worm eggs can enter the human body through it. The finger nails can hide soil that contains microorganisms or eggs, and it is difficult to clean[20,21].

During the pandemic, there have been several changes in living behavior in a society. The physical distancing limits the movement of people. The community has also begun to implementing the health protocol by diligently washing hands using a soap or antiseptic alcohol. Besides, children are doing school

activities at home. These conditions could be the reason for the decrease in helminthiasis prevalence in children. Both *Ascaris lumbricoides (A. lumbricoides)* and *Trichuris trichiura (T. trichiura)* are transmitted through the fecal-oral route. This means that the transmission of these helminths typically occurs when individuals inadvertently ingest infective eggs, either through contaminated food, water, utensils, or improperly washed hands[14,21]. Water, sanitation, and hygiene (WASH) is a predominant factor in reducing the risk of infection. WASH is an important intervention for infection prevention. The decrease in helminth prevalence in this study may be due to changes in hand-washing behavior that were implemented during the pandemic era, despite the study participants was a high-risk group, in which the children lived in orphanages with low socioeconomic conditions.

WHO has suspended several Healthcare programs to control Neglected Tropical Diseases (NTD) programs during the pandemic, including the helminth infection prevention program[11]. Indonesia's Mass Drug Administration (MDA) program, which includes biannual albendazole treatment for schoolchildren, has effectively lowered the prevalence of STH infections. While education is recognized as fundamental in changing behavior and promoting better hygiene practices, achieving effective education in poor and remote areas can be challenging. Factors such as limited access to educational resources, low literacy rates, and cultural barriers may hinder the implementation of educational programs[12]. The Health Service has a worm eradication program in Makassar that administers anti-helminth drugs twice a year. During the pandemic, however, this program was temporarily postponed in order to focus on the COVID-19 improvement program. Despite the fact that this infection control program was not as effective as usual, this study showed a much lower helminthiasis' prevalence. It could be related to the community's increased emphasis on hand hygiene.

The observed age-related differences in helminth showed a significant difference in helminth prevalence. *Ascaris* infections were found to be more common in children under 5 years, and *Trichuris* infection was found in the children under 10 years.This finding was similar to Osazuwa's study, which discovered that the prevalence of ascariasis decreased gradually as children's ages increased. The widespread parasitemia across nearly all age groups indicates a widespread lack of awareness and/or intentional disregard for basic hygiene rules among children[7,22].

Iron deficiency is globally recognized as one of the leading causes of anemia. Several factors such as insufficient dietary iron intake, physiologic demands of pregnancy, rapid growth, and parasitic infections contribute to iron deficiency, leading to inadequate iron reserves in the body and, subsequently, anemia[5,18]. *T. trichiura* and *A. lumbricoides* are the most caused helminth infections in a children and both of them lead to be iron deficiency[7,18,23,24]. This study found no significant differences in hemoglobin and ferritin levels between the children with and without helminth infections, nor among those infected with *A. lumbricoides*, *T. trichiura*, or both types of helminthiasis, suggests that the helminth infections may not

be having a substantial impact on these particular hematological parameters in the studied population. This finding was consistent with previous studies, which discovered that children with positive STH infections had a positive relationship with low serum iron levels and iron deficiency anemia[5,6,14,15]. Meanwhile, some other studies explained that soil-transmitted helminths are associated with anemia[5,7,10,25]. *Trichuris* directly invades the large intestine, it can attach to the mucosa and cause damage. This damage may lead to blood loss, contributing to anemia. It can also suck micronutrients, including iron, from the intestine. People with trichiuriasis infection usually have anorexia, which can result in reduced food intake. Another helminth, *Ascaris lumbricoides*, can impair the absorption of essential nutrients, from the gastrointestinal tract. It also competes with the host for nutrients, and further compromises the absorption of micronutrients like iron, further causes iron deficiency anemia[15]. Therefore, it is possible that helminth infection was not the cause of iron deficiency in the sample study.

This study did not identify a significant association between helminth infection and nutritional status. Almost every subject studied received adequate nutrition. A study in Molla, Ethiopia, reported a similar result among school-age children. The presence of STH infection in children did not appear to be associated with undernutrition[25]. However, several previous studies found that helminth infection contributes to malnutrition[10,14,24]. Helminth infection affects the small intestine mucous and causes villous atrophy to varying degrees, as well as crypt hypertrophy and inflammatory infiltrate. These changes damage enterocytes and disrupt bile acid metabolism, leading to inadequate absorption of essential macro- and micronutrients, including, iron, zinc, vitamin, and folic acid[15]. The differences in this study explain how helminth infection in children may contribute to nutrition based on the severity and duration of the infection.

The limitation of this study is the small sample size, as we only analyzed children with iron deficiency, targeting a high-risk population. Due to the limited data, the results are not fully detailed but are instead presented in diagram and table formats.

Conclusion

This study concludes that the soil-transmitted helminth infection prevalence of children in Indonesia was significantly decreased during the COVID-19 pandemic. This could be caused by the change of behavior in personal hygiene. This study suggested that primary schools and parents should focus more on maintaining these good habits to prevent the spreading and development of soil helminth infection.

Conflicts of Interest

Funding sources

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