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Type 1 Diabetes as a Risk Factor for Chronic Kidney Diseases and Renal Failure in Adolescents: A Systematic Review

Jawaher Yousef AlRashada[1*], Yasser El. Medany[1], Jamal Khaled S Aljamal[1], Mohammed Abdulrahman Al-Falah[1], Abdullatif Waleed Alarfaj[1], Yasmeen Mohammed Al-Mulhim[1], Mariam Sami Alshehab[1], Mareyah Alshaikh Husain[1], Muneerah Saleh Alhumaidy[1], Ibrahim Hamad Almakhayitah[1], Mohammed Abdullah Alsayed[1], Nawaf Ammash Alsubaie[1]

[1]Family Medicine Department, King Abdulaziz Hospital, MNGHA, Al-Ahsa, Saudi Arabia

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***Corresponding author:** Jawaher Yousef AlRashada
Family Medicine Department, King Abdulaziz Hospital, MNGHA, Al-Ahsa, Saudi Arabia

Abstract

Objectives: The purpose of this systematic review is to investigate the risk factors and association of the incidence of diabetic kidney disease in adolescents with type 1 diabetes (T1D) patients. ***Methods:*** We conducted a thorough search of PubMed, SCOPUS, Web of Science, Google Scholar, and Science Direct to find pertinent literature. Rayyan QRCI was utilized during the entire process. ***Results:*** We included eight studies with a total of 11,468 T2D patients and 4966 (43.3%) were females. The available literature on the association between T1D and CKD among adolescents lacks epidemiological data on the prevalence and sex differences. Higher eGFR, diabetes duration, low C-peptide levels, glycemic control, age at a clinic visit, advanced glycation end products, and BMI were reported as significant risk factors for developing renal impairment in adolescents with T1D. ***Conclusion:*** The results of this research point to the necessity of a standardized screening procedure for the early identification and appropriate treatment of DKD. In order to provide an accurate assessment of this illness, methodological approaches should be taken into account. Furthermore, it's imperative to educate teenagers with T1D about the possibility of DKD, which can result in renal failure and even death. Future improvements in the quality of life for teenagers with T1D are anticipated as a result of this awareness.

Keywords: Chronic kidney disease; Diabetic nephropathy; Type 1 diabetes; Adolescents; Systematic review.

INTRODUCTION

An autoimmune disease known as T1D is typified by the immune system destroying pancreatic beta cells. T1D's precise etiology is yet unknown. Though B cells may also play a part in the pathophysiology of illness, T cells are generally thought to be the ones that destroy β cells [1]. Among T1D patients, diabetic nephropathy (DN) is one of the most dangerous side effects. Even while hyperglycemia is thought to be one of the main risk factors for the development of DN, there are numerous additional variables that are also involved in the pathogenesis process that led to the formation of DN [2].

Risk factors for T1D microvascular problems include age, ethnicity [3, 4], age at onset, duration of diabetes, height, BMI, and puberty [5, 6]. High blood pressure (BP) [5, 7] and sustained glycemic control [8, 9] are two further modifiable risk factors. Numerous investigations have determined that the latter is the primary risk factor for the occurrence of diabetic microangiopathies [8, 9]. Studies on microvascular problems in T1D-affected adolescents in sub-Saharan Africa are scarce. All published African investigations, however, revealed significant incidence rates in young patients with brief durations of illness [10, 11].

Numerous reviews in the literature have added to our understanding of the pathophysiology, diagnosis, and treatment choices for DN and chronic kidney disease (CKD) in adolescents with T1D patients. The purpose of this systematic review is to investigate the risk factors and association of the incidence of CKD in adolescents with T1D patients.

METHODOLOGY

Study Design and Duration

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards were followed in the conduct of this systematic review [8]. March 2024 marked the start of this systematic review.

Search Strategy

PubMed, SCOPUS, Web of Science, Google Scholar, and Science Direct were the four main databases that were thoroughly searched in order to locate pertinent literature. We looked through exclusively English databases, taking into consideration each one's particular needs. We transformed the following keywords to PubMed Mesh terms in order to locate the pertinent studies; "Diabetes mellitus," "Type 1 diabetes," "T1D," "Diabetic nephropathy," "Renal failure," and "Chronic kidney disease." "OR," "AND," and "NOT," three Boolean operators, matched the necessary keywords. Full-text English publications, freely accessible articles, and human trials were among the search results.

Selection Criteria

We considered the following criteria for inclusion in this review:

- Studies that summarized to investigate the risk factors and association of the incidence of CKD in adolescents with T1D patients.
- Studies conducted within the last 5 years (2019-2024).
- Adults (>18 years old) were not included.
- Only human subjects.
- English language.
- Free accessible articles.

Data Extraction

Two verifications of the search method's output were conducted using Rayyan (QCRI) [9]. By applying inclusion/exclusion criteria to the aggregated search results, the researchers evaluated the relevance of the titles and abstracts. Every paper that met the inclusion requirements was thoroughly scrutinized by the reviewers. The authors talked about methods for resolving disputes. A pre-made data extraction form was used to upload the approved study. The authors extracted data about the study titles, authors, study year, country, participants, gender, duration of diabetes, mean HbA1c, and main outcomes. A separate sheet was created for the risk of bias assessment.

Strategy for Data Synthesis

By assembling summary tables with information from relevant studies, a qualitative assessment of the research's findings and components was given. After gathering the data for the systematic review, the most efficient way to use the information from the included study articles was chosen.

Risk of Bias Assessment

Using the ROBINS-I risk of bias assessment technique for non-randomized trials of treatments, the quality of the included studies was evaluated [10]. The seven examined themes included confounding, study participant selection, intervention classification, deviation from planned interventions, incomplete data, outcome evaluation, and choice of reported result.

RESULTS

Search Results

The systematic search produced 566 study articles in total, of which 223 duplicates were eliminated. After 343 studies had their titles and abstracts screened, 298 were not included. After 45 reports were requested to be retrieved, 2 articles were found. After screening 43 studies for full-text assessment, 19 were rejected due to incorrect study results, 14 were rejected due to incorrect population type, and 2 articles were editor's letters. This systematic review included eight eligible study articles. A synopsis of the procedure for choosing studies is provided in **Figure 1.**

Characteristics of the Included Studies

Table 1 presents the sociodemographic characteristics of the included study articles. Our results included eight studies with a total of 11,468 T2D patients and 4966 (43.3%) were females. Four were cross-sectional studies [15-18], three were case-control studies [19, 20, 22], and one was retrospective in nature [21]. Two studies were conducted in Turkey [19, 20], one in Australia [15], one in Tanzania [16], one in Germany [17], one in Sudan [18], one in Sweden [21], and one in the USA [22]. **Table 2** presents the clinical characteristics. The available literature on the association between T1D and CKD among adolescents lacks epidemiological data on the prevalence and sex differences. Higher eGFR [15], diabetes duration [15, 16, 17, 18, 20], low C-peptide levels [16], glycemic control [16, 18], age at a clinic visit [16], advanced glycation end products [19], and BMI [16, 22] were reported as significant risk factors for developing renal impairment in adolescents with T1D.

Table 1: Sociodemographic characteristics of the included participants

Study	Study design	Country	Participants	Mean age	Gender (Females)
Forbes *et al.*, 2021 [15]	Cross-sectional	Australia	299	20 ± 3	58 (58%)
Majaliwa *et al.*, 2023 [16]	Cross-sectional	Tanzania	281	19 ± 6	144 (51.2%)
Tönnies *et al.*, 2019 [17]	Cross-sectional	Germany	293	11 - 17	146 (49.8%)
Ahmed *et al.*, 2020 [18]	Cross-sectional	Sudan	100	15.6	61 (61%)
Kırkgöz *et al.*, 2024 [19]	Case-control	Turkey	26	14.9 ± 2.5	13 (50%)
Er *et al.*, 2020 [20]	Case-control	Turkey	21	18.1 ± 4.4	6 (28.6%)
Lind *et al.*, 2019 [21]	Retrospective cohort	Sweden	10 398	14.7	4513 (43.4%)
Vinovskis *et al.*, 2020 [22]	Case-control	USA	50	16 ± 3	25 (50%)

*NM=Not-mentioned

Table 2: Clinical characteristics and outcomes of the included studies

Study	Mean Diabetes duration (years)	Mean HbA1c	Main outcomes	ROBIN-I
Forbes *et al.*, 2021 [15]	10.0 ± 7.5	8.2 ± 1.3	The risk of diabetic kidney disease in young people with T1D who have not yet been diagnosed with complications is increased by higher eGFR and diabetes duration.	High
Majaliwa *et al.*, 2023 [16]	NM	175 (62.3%) had poor glycemic control (HbA1c) >10%	Given that the risk of nephropathy was 41.3%, the prevalence of microvascular problems overall is quite high. The majority of patients exhibited low C-peptide levels, which supported the severe insulin insufficiency associated with T1D. There was a weak correlation found between problems and low C-peptide levels. Potential predictors of diabetic microvascular problems included glycemic control, age at a clinic visit, BMI centiles, and length of diabetes.	Moderate
Tönnies *et al.*, 2019 [17]	11.1-12.6	7.1-8.7	In young people with early-onset T1D, the early phases of DN may already have an impact on QOL. It should be highlighted that even though the differences were rather minor, they only applied to DN phases where there were no symptoms. Additionally, these discrepancies grew as the length of diabetes increased, which may indicate that early stages of DN in childhood serve as a precursor to bigger variations in QOL in adult T1D.	High
Ahmed *et al.*, 2020 [18]	7 o 11.4	9 to 14	36% of cases were microalbuminuria. This study found a high frequency of early stages of DR and incipient DN. Diabetic retinopathy was found to be more common in patients with longer-term diabetes and greater HbA1c. High blood pressure was one of the DN risk factors.	Moderate
Kırkgöz *et al.*, 2024 [19]	7.4 ± 3.6	8.6 ± 1.5	There is a substantial correlation between blood levels of advanced glycation end products and nephropathy, but not with retinopathy or neuropathy.	Moderate
Er *et al.*, 2020 [20]	12.2 ± 4.1	8.6 ± 0.63	Even at comparable mean HbA1c levels, long-term variations in HbA1c are linked to the emergence of microvascular problems in T1D, including nephropathy, which was found in 17 cases (80.9%).	Moderate
Lind *et al.*, 2019 [21]	1.3	8	Nephropathy risk was higher for severe hypoglycemia relative to HbA1c levels 6.5–6.9%, but it did not change for HbA1c levels less than 6.5%. Milder problems were more likely to occur at HbA1c levels >7.0%, whereas the risk of severe consequences was higher at HbA1c levels >8.6%.	Moderate
Vinovskis *et al.*, 2020 [22]	5.7 ± 2.6	8.7 ± 1.3	Adolescents diagnosed with T1D have relative renal hypoxia, which has been linked to normal-range albuminuria, high blood pressure, obesity, and insulin resistance.	Moderate

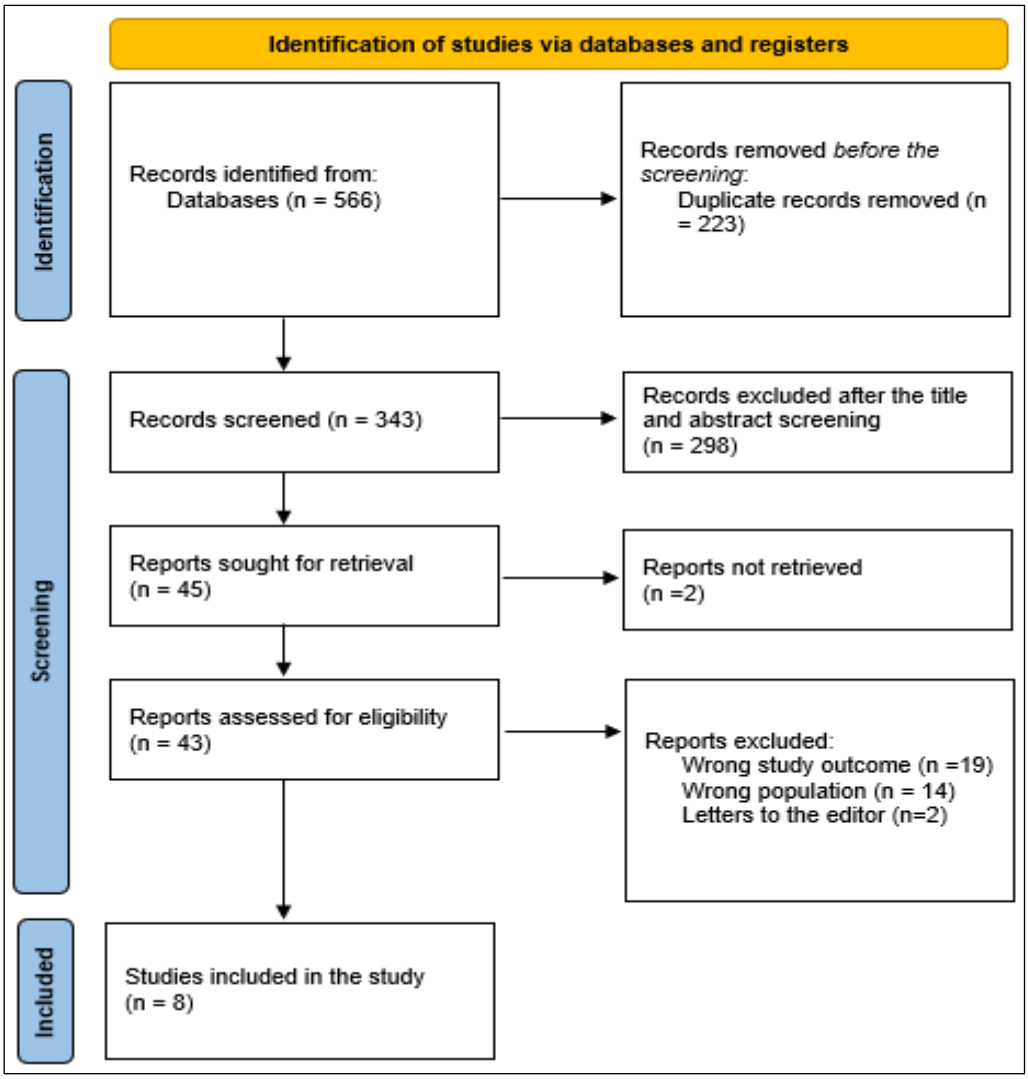

Figure 1: Study selection is summed up in a PRISMA flowchart

DISCUSSION

Our review focused mainly on adolescents as a specific group of T1D patients at risk of CKD. This focus limited our search and findings due to the lack of relevant literature on our objective.

Both macrovascular problems (cardiovascular disease) and diabetic nephropathy are brought on by persistent hyperglycemia [23]. Four main pathogenic processes are identified in diabetic kidney disease (DKD): oxidative stress, inflammation, tubular damage, and glomerular damage [24]. Patients with DKD exhibit significant changes in both the interstitium and tubules. These results could lead the way or show up simultaneously with glomerular changes [25].

Tubular hypertrophy, which is seen right after hyperglycemia, maintains this. It was also discovered that even in diabetic patients with normoalbuminuria, there was a rise in tubular basement membrane thickness. One of the earliest structural modifications is located in the tubular basement membrane. As a result, it might serve as a more accurate indicator of DKD severity than glomerular basement membrane alteration [25]. Pathological glomerular alterations include podocyte foot process broadening, endothelial fenestration loss, glomerular basement membrane thickening, and mesangial matrix enlargement that are diagnostic of DKD [26].

Interestingly **Zhao *et al.*** reported that youths with T2D are more likely to experience complications than adults with T1D and T2D [27]. Diabetes causes a number of microvascular complications, the most notable of which are DKD and diabetic nephropathy, which ultimately result in ESRD. Changes in biology and clinical presentation will be seen as diabetes progresses. One of the most significant and common DM complications, DKD is associated with a variety of risk variables, some of which are adjustable. Therefore, thorough control of these factors may have a significant impact on the occurrence or evolution of DKD [27]. In the context of these risk factors, our study reported that higher eGFR [15], diabetes duration [15-17, 18, 20], low C-peptide levels [16], glycemic control [16, 18], age at a clinic visit [16], advanced glycation end products [19],

and BMI [16, 22] were reported as significant risk factors for developing renal impairment in adolescents with T1D.

Individuals with T1D are known to exert more effort in order to achieve lower HbA1c targets [28, 29], and caregivers of diabetic children are more likely to do so. Regular glucose testing, regular insulin administration, and adherence to certain measures, like eating a healthy diet or making sure you get enough exercise, are all necessary. To meet HbA1c standards, children and their parents frequently have to put in a lot of effort in their daily lives. This may involve taking extra insulin doses and monitoring blood sugar levels overnight. Diabetes is linked to higher levels of stress, and people with T1D may find it frustrating to have to manage their condition [28, 29]. Because treatment is linked to a high quality of life at HbA1c levels, the current findings imply that doctors should exercise extra caution to ensure that persons with diabetes do not spend a significant amount of time in hypoglycemia.

The most effective methods for preventing and delaying the development of diabetic nephropathy and the decline in renal function are still the well-known tactics of tight glucose control, vigilant blood pressure management, and obesity modification. These treatments have shown promise primarily because they address the modifiable risk factors associated with diabetic nephropathy.

CONCLUSION

The results of this research point to the necessity of a standardized screening procedure for the early identification and appropriate treatment of DKD. In order to provide an accurate assessment of this illness, methodological approaches should be taken into account. Furthermore, it's imperative to educate teenagers with T1D about the possibility of DKD, which can result in renal failure and even death. Future improvements in the quality of life for teenagers with T1D are anticipated as a result of this awareness.

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