Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

NEPHROPATHY IN ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS: SYSTEMATIC REVIEW

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ARTICLE INFO

Received:
18 May 2022
Received in revised form:
10 Aug 2022
Accepted:
22 Aug 2022
Available online:
28 Aug 2022

Keywords: Nephropathy, Renal disease, T1DM, Adolescents

ABSTRACT

Diabetic nephropathy (DN) is an emerging public health and clinical issue linked to heart failure, ESRD, and other negative effects, including renal replacement therapy. A systematic search of five major databases, including PubMed, Web of Science, Science Direct, EBSCO, and Cochrane library, was conducted to comprise eligible literature for research. This systematic review studies the risk factors associated with the development of DN and albuminuria in adolescents suffering from T1DM. A total of 13 study articles with 1489 patients were included in this review. Hypertension in association with albuminuria was found in six studies, high mean HbA1c in association with DN was demonstrated in all the included studies, and dyslipidemia/ high total cholesterol level was reported in three studies. Hypertension, high HbA1C (poor glycemic control), dyslipidemia, high cholesterol levels, and high BMI indicating overweight or obesity are risk factors for the incidence of microalbuminuria and DN in adolescents with T1DM.

To Cite This Article: AlEdeilah RD, AlSulailm AS, AlAnazi SM, AlAnazi MF, AlEnazi NFN, Alanazi RRMSAASAA, et al. Nephropathy in Adolescents with Type 1 Diabetes Mellitus: Systematic Review. Pharmacophore. 2022;13(4):135-41. https://doi.org/10.51847/eC6QibkaX4

Introduction

Type 1 diabetes mellitus (T1DM) is generally believed to be precipitated by immune-mediated destruction of pancreatic β cells that produce insulin [1]. Polydipsia, polyphagia, polyuria (the classic triad of symptoms related to the disease onset), and hyperglycemia are still diagnostic hallmarks of characteristics in adolescents and children and to a lower extent in adults [2]. There were 9 million people with type 1 diabetes worldwide in 2017; the majority of them reside in high-income nations [3]. Adolescence is a challenging period for everyone, especially for young people with T1DM, as they must learn to manage their condition while adjusting to the necessary social, physical, and emotional changes. Adolescents with T1DM experience more anxiety and depression symptoms than peers without the disease [4], and these symptoms are linked to poor glycemic control and impaired diabetic self-management [5].

Significant morbidity, disability, and early mortality are caused by diabetes. Diabetes has been associated with a variety of other serious conditions, including communicable conditions such as cardiovascular disease and kidney disease [6], and non-communicable conditions, including invasive bacterial infections [7].

Diabetic nephropathy (DN) is a significant clinical and public health concern that has been linked to fatal outcomes such as

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end-stage renal disease (ESRD), heart failure, kidney replacement therapy, and related mortality [8] by shortening life expectancy [9].

The renal glomeruli and tubules can develop lesions that lead to the common and serious long-term microvascular complication known as DN. Alongside this, the condition is frequently linked to other atherosclerotic processes that, in people without diabetes, resemble macrovascular morbidity and that manifest earlier in people with DM, particularly in young adults, having an impact on both the affected individuals and society as a whole [10].

According to previous epidemiological studies, between 25% and 40% of those with T1DM would eventually develop DN. Additionally, after an average of 5 to 10 years with diabetes, 20% to 30% of T1DM patients show signs of microalbuminuria [11]. ESRD incidence has been estimated to be 4-17% in 20–30 years from the onset of T1DM. So early in the course of diabetes, DN screening should start [12]. Although non-albuminuric DN is a less well-studied condition, Thorn *et al.* recently revealed that it affected 2% of T1D patients and was frequently linked to cardiovascular morbidity [13].

The pathophysiology causes the advanced glycation end products to be produced and circulated, growth factors to be produced, and hemodynamic and hormonal alterations causing diabetic nephropathy, ensuing end-stage kidney disease. Reactive oxygen species and inflammatory mediators are released as a result of this. Together, these modifications cause altered glomerular composition, renal hypertrophy, glomerular hypertension, and glomerular hyperfiltration, which are clinically expressed as albuminuria and hypertension [14].

A variety of risk factors, such as proteinuria, hyperlipidemia, glomerular damage-related hypertension, and genetic susceptibility, have been linked to the development of DN [15]. Most of the previous research on the magnitude of DN is still controversial and imprecise. This systematic review investigates the risk factors associated with the development of DN and albuminuria in adolescents with T1DM.

Materials and Methods

Study Design

This systematic review was implemented following the demonstrated guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA).

Study Condition

This review studies the published literature and risk factors associated with T1DM patients who develop DN and albuminuria.

Search Strategy

A systematic literature search of five major databases, including PubMed, Web of Science, Science Direct, EBSCO, and Cochrane library, was conducted to comprise the eligible literature. Our search was restricted to the English language, and it was customized as needed for each database. The following keywords were used to identify the appropriate studies and were converted into Mesh terms in PubMed; "Type 1 diabetes mellitus," "T1DM," "Insulin-dependent diabetes mellitus," "IDDM," "Juvenile-onset diabetes," "diabetic nephropathy," "DN," "albuminuria," "end-stage renal disease," "ESRD," and "adolescents." The "OR" and "AND" Boolean operators were combined with the relevant keywords. English, full-text publications, freely accessible articles, and human trials were all included in the search results.

Selection Criteria

Our review included the studies with the following criteria:

- Mainly cross-sectional, case-control, cohort studies and study designs that provided qualitative or quantitative data about DN in diabetic patients.
- Patients with T1DM only.
- Adolescents (<18 years old)

Exclusion criteria included the following:

- Studies not conducted in the English language.
- Studies with no free access.

Data Extraction

We utilized Rayyan (QCRI) [16] to detect the duplicate articles of the search strategy outcomes. By filtering the combined search results according to a set of inclusion/exclusion criteria, the researchers assessed the adequacy of the titles and abstracts. The entire texts of the papers that met the criteria for inclusion were evaluated by the reviewers. To resolve any discrepancies, the authors had a discussion. The eligible study was added using a data extraction form that was produced. The authors extracted data about the study titles, authors, study year, study design, study population, participant number, gender, duration of DM, time of onset of DM, diagnostic criteria, HbA1C, and the main findings.

Risk of Bias Assessment

ROBINS-I tool for non-randomized studies [16] was used for qualitative data synthesis to evaluate the included research quality. The authors reviewed any discrepancies in the quality assessment and then took corrective measures.

Strategy for Data Synthesis

Summary tables with the information gathered from the eligible studies were produced to give a qualitative overview of the included study aspects and results in data. Decisions regarding how to make the most of the data from the included study articles were made after the systematic review's data extraction process was complete. Studies that met the full-text inclusion requirements but did not provide any data on the particular patients with DN were excluded.

Results and Discussion

Search Results

A total of 530 study articles were extracted from the systematic search, and then 42 duplicates were removed. Title and abstract screening were conducted on 488 studies, and 380 studies were excluded. One hundred and eight reports were sought for retrieval, and only 8 articles were not retrieved. Finally, 100 studies were screened for full-text assessment; 52 were excluded for wrong study outcomes, 20 for unavailable data on DN, and 15 for the wrong population type. 13 eligible study articles were included in this systematic review. A summary of the study selection process is illustrated in **Figure 1.**

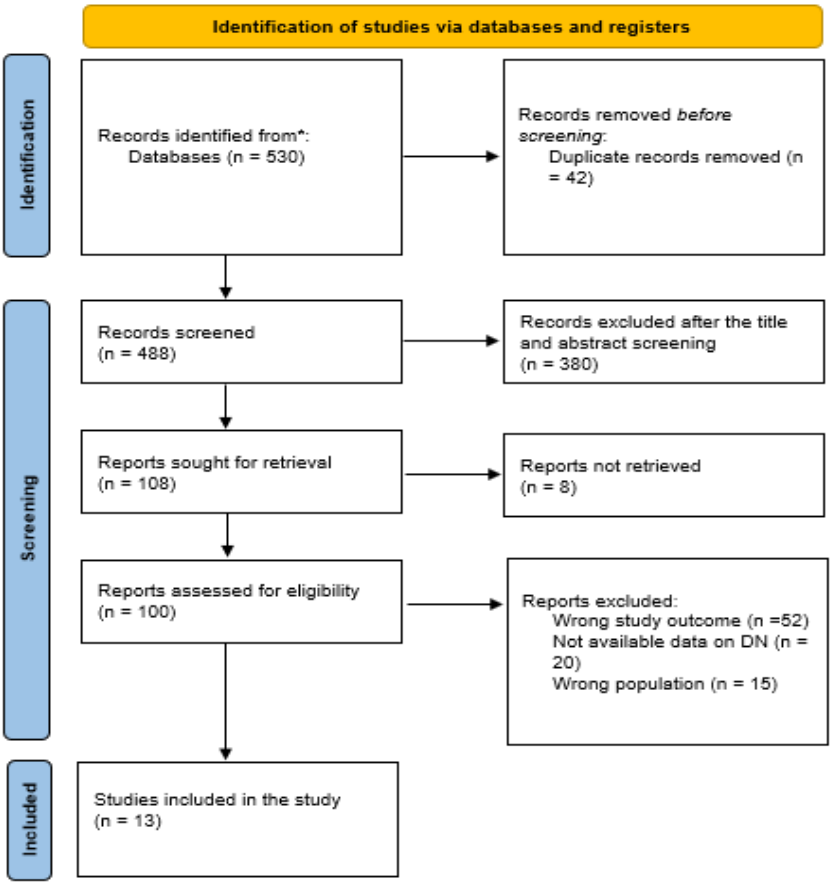

Figure 1. PRISMA flow chart presenting the study selection results.

Characteristics of the Included Studies

A total of 13 studies were included in this review, with 1489 adolescent patients diagnosed with DN as a microvascular complication of T1DM. Less than half of them (48.2%) were males. As shown in **Table 1**; four studies were conducted in Egypt [17-20], two in Canada [21, 22], one in Ukraine [23], one in Australia [24], one in Russia [25], one in Germany [26], one in Sudan [27], one in Italy [28], and one in Sweden [29].

Hypertension in association with albuminuria was found in six studies [20, 23, 26-29], normal BP was reported in three studies [17, 18, 21], while the rest of them did not report adequate data on hypertension. Seyed Ahmadi *et al.* reported that a blood pressure greater than 140/70 mmHg was linked to increased albuminuria in people with poor glycemic control [29].

High mean HbA1c in association with DN was demonstrated in all the included studies. One study reported that more than half of the patients (59.7%) had dyslipidemia [26]. Dyslipidemia/ high total cholesterol level was reported in three studies [19, 26, 29]. One study reported that 8.3% of the patients were obese or overweight [27]. Two studies reported high mean BMI [28, 29].

Genetic predisposition was documented in three studies, including the AGT 235T variant [24], APOE gene [25], and the AA genotype and the A allele of the IL-10 rs1518111 SNP [17]. Another study reported that serum MK is a valuable, new, and helpful marker for assessing renal dysfunction in children with T1DM [19].

Table 1. Summary of characteristics of the included studies

Study	Study design	Country	Total Participants	Male (%)	Mean age (y)	Mean duration of diabetes (y)	HbA1C (mg/dL)	Diagnostic criteria	Key findings	ROBINS-I
Burlaka *et al.*, 2022 [23]	-	Ukraine	47	33 (70.2)	13.3±0.6	6.0±0.51	10.2±9.6	Albuminuria	The DN group had a high frequency of DKA episodes per year, and high microalbuminuria. They also had a high mean SBP (126.4±1.34 mmHg) and high HbA1C.	Moderate
Cook *et al.*, 1990 [21]	A double-blind, placebo-controlled study	Canada	12	4 (33.3)	14.4±1.7	5.1±2.5	8.6 ± 1.3	Albuminuria	Normotensive patients with microalbuminuria and high HbA1C.	High
Gallego *et al.*, 2008 [24]		Australia	41	NA	13.6–17.1 (range)	5.5–11.8 (range)	9.9±1.8	Albuminuria	There is a link between chronic microalbuminuria in the T1DM pediatric population and genetic variation at the RAS, particularly the AGT 235T variant.	Moderate
Shcherbak *et al.*, 2001 [25]	Case-control study	Russia	74	40 (54.1)	25.1±11.9	14.8±8.8	10.5±2.2	Albuminuria	Although not strongly linked, there may be a mild or moderate association between APOE gene polymorphism and diabetic nephropathy.	High
Tönnies *et al.*, 2019 [26]	Population-based cross-sectional study	Germany	293	147 (50.2)	14-16.2 (range)	11.1-12.6 (range)	7.1-8.7 (range)	Albuminuria	There is hypertension and dyslipidemia in (59.7%) and (41%) of the patients, respectively. It also reported that diabetic microvascular complications greatly impair the patient's quality of life.	Moderate
Ahmed *et al.*, 2020 [27]	Cohort study	Sudan	36	17 (47.2)	14.4-17.2 (range)	4– 9 (range)	9 -14 (range)	Albuminuria	High blood pressure was a risk factor for DN (13.9%), 8.3% were obese or overweight, and relatively high HbA1C. Therefore, it's necessary to regularly check for these problems and improve glycemic control.	High
El Helaly *et al.*, 2021 [17]	Cross-sectional	Egypt	74	34 (46)	13.3±2.8	2.0–14 (range)	8.3±0.9	Albuminuria	No hypertension was demonstrated among diabetic patients in this study. Children in Egypt may be at higher risk for T1DM and DN if they have the AA genotype and the A allele of the IL-10 rs1518111 SNP.	High
Abdelghaffar *et al.*, 2021 [18]	Cross-sectional	Egypt	45	19 (42.2)	13.2±3.6	8.37±3.70	10.64	Albuminuria	While miRNA-25 may play a reno-protective role, miRNA-377, miRNA-93, miRNA-216a, and miRNA-21 may be involved in the pathogenesis of DN. The mean BP was normal, while a high cholesterol level was noticed (178.7±37.2)	High
Metwalley *et al.*, 2021 [19]	Case-control	Egypt	60	32 (53.3)	16.5±2.7	9.3±26	9.2±1.3	Albuminuria	The findings of this study indicate that serum MK is a valuable, new, and helpful marker for assessing renal dysfunction in children with T1D. A high cholesterol level was noticed (198.7±37.3)	Moderate

Chiarelli *et al.*, 2002 [28]	Cross-sectional	Italy	15	5 (53.3)	18.6±4.1	12.5±2.5	9.6±1.4	Albuminuria	Compared to diabetic patients with normoalbuminuria, those with microalbuminuria had considerably higher mean HbA1c values and BMI (24.2 ± 3.9).	High
Seyed Ahmadi *et al.*, 2022 [29]	Cross-sectional	Sweden	737	361 (49)	15.3±7.9	1.4±1.7	8.5±1.3	Albuminuria	The greatest risk factor for albuminuria was HbA1c, followed by blood pressure (118.2 ± 10.0), blood lipids, and BMI (23.6 ± 4.9). Smoking was not associated with anything. Blood pressure greater than 140/70 mmHg was linked to an increased incidence of albuminuria in people with poor glycemic management (mean HbA1c>8.1%).	High
Gorman *et al.*, 1999 [22]	Retrospective cohort	Canada	28	11 (39.1)	14.3±1.7	6.1±3.1	9.0±1.1	Albuminuria	the mean HbA1c in the first five years of diabetes and the baseline AER were independent predictors for advancement. Starting early in the course of their disease, T1D in teenagers should be checked for AER.	Moderate
Metwalley *et al.*, 2013 [20]	Cross-sectional controlled study	Egypt	27	18 (66.7)	16.9±5.2	10.2 ± 4.3	11.2	Albuminuria	Patients with microalbuminuria had significantly higher mean systolic and diastolic blood pressures. The current investigation showed that, in comparison to patients with normal albuminuria, those with microalbuminuria had significantly higher mean cholesterol (183.7 ± 18.6) and TG levels and required higher insulin dosages.	Moderate

DN is becoming a global cause of ESRD and is established as an independent hazardous factor for cardiovascular disease. Even while it may be feasible to significantly delay the onset of nephropathy in the early stages of the disease, high urine albumin excretion may eventually lead to its development. Here, the roles of blood pressure, cholesterol level, BMI, and glucose regulation may be sufficient [30].

Our review noticed an association between hypertension and the development of DN in patients with T1DM. A study conducted by Seyed Ahmadi *et al.* reported that blood pressure greater than 140/70 mmHg was linked to an increased incidence of albuminuria in people with poor glycemic control [29]. The emergence of clinical proteinuria in IDDM is highly correlated with arterial hypertension [31]. Early in the disease, hypertension is rarely seen, and newly diagnosed diabetics' mean arterial blood pressure is not much higher than that of the general population. The subject of intense debate is whether there is a connection between blood pressure levels early in the disease and the eventual emergence of clinical diabetic nephropathy [32].

Patients with microalbuminuria have shown minor but significant increases in blood pressure. Blood pressure is also considerably greater in patients with overt proteinuria but normal serum creatinine levels compared to otherwise comparable patients without proteinuria [31]. Thus, it can be said that hypertension is a very early symptom of diabetic nephropathy. However, it is still unknown whether an increase in blood pressure is what triggers the development of microalbuminuria and nephropathy in the first place or whether an increase in urinary albumin excretion and an increase in blood pressure are both the results of a series of intra- and extra-renal vascular events [32].

We found that many studies reported an association between high HbA1c and DN as an indication of poor glycemic control. In 1993, DCCT demonstrated the advantages of intensive therapy over standard therapy in terms of lowering HbA1c and reducing the risk of nephropathy [33]. Fares *et al.* reported that in type 1 diabetic patients, the mean HbA1C is still the only reliable indicator of the onset of diabetic nephropathy [34]. Another Chinese study demonstrated a significant and independent association between HbA1c≥5.5% and ACR. When risk factors were taken into account, the connection remained steady and substantial. The relevance of early glucose management and the requirement for assessing renal function in at-risk populations are highlighted by this discovery, which also highlights the need to prevent the development of renal problems from diabetes [35].

Dyslipidemia and high cholesterol levels were reported in association with DN development in many studies in this review. Previous research has demonstrated that in diabetic patients, dyslipidemia promotes glomerulosclerosis. It has been established that dyslipidemia made worse by diabetes contributes to the onset of DN. They have previously shown that diabetic rats' albuminuria is exacerbated by hypercholesterolemia [36].

Three phases are thought to link this pathophysiologic process of renal damage to dyslipidemia. First, exposure to oxidized lipoproteins enhances the release of chemotactic and adhesion molecules by mesangial cells, which further increases the attraction of macrophages. Tubular fibrosis and glomerulosclerosis are the outcomes of the monocyte invasion. Moreover, the ingestion of oxidizing LDLC by recruited macrophages promotes the production of reactive oxygen species and the expression of pro-sclerotic and proliferative cytokines (transforming growth factor [TGF]-1 and platelet-derived growth factor-AB). [These cytokines also promote the expansion of mesangial cells by stimulating the synthesis of extracellular matrix proteins [37, 38].

Obese and overweight diabetic patients are at higher risk for developing DN. According to data from the European Diabetes Prospective Complications Study, smoking, poor glycaemic management, albuminuria frequency, central obesity, and high BMI were all significant predictors of microalbuminuria in T1DM with a childhood onset [39].

Conclusion

There is an association between hypertension and the incidence of microalbuminuria and DN in adolescents with T1DM. Many studies established that high HbA1C and poor glycemic control are the most important risk factor for DN. Dyslipidemia, high cholesterol levels, and high BMI indicating overweight or obesity are also reported as risk factors for the development of DN.

Acknowledgments: Many thanks to Dr. Rawan Deham Aledeilah; Senior Registrar, Family Medicine, Aziziayah Primary health care center, Arar, Saudi Arabia, for her continuous help, support and encouragement to complete this work.

Conflict of interest: None

Financial support: None

Ethics statement: None

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