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# A Review: Diabetic Nephropathy in Children and Adolescence

**Ms. Sowjanya A[1], Dr. Satish Kumar B.P[2], Ms. Saniya Shaikh[3], Mr. Amarmani Shivapur[4]**

[1, 2, 3, 4]M Pharmacy
[1, 2, 3,] 4Pharmacy Practice
Sri Adichunchanagiri College of Pharmacy, B.G. Nagar

**Abstract**

**In children and young adults, diabetes is a primary cause of kidney impairment, which frequently results in dangerous consequences like heart enlargement and early death. Particularly in light of the growing prevalence of type 2 diabetes in children associated with obesity, microalbuminuria (MA) is an early indicator of diabetic kidney disease (DKD). To stop the development of end-stage renal disease (ESRD), MA must be identified early during adolescence. Among the risk factors for DKD are genetics, age, blood pressure, and glycemic management. Although ACE inhibitors and renoprotective medications can slow the progression of DKD, early diagnosis is still difficult since symptoms can overlap with those of other illnesses. Early DKD management might lessen catastrophic results, emphasizing the need for improved diagnostics, genetic component studies, and innovative therapies like stem cell.**

## Introduction:

Diabetic nephropathy is important because it kills people affected by type 1 diabetes prematurely and contributes to cardiovascular complications [1]. Additionally, it leads to end-stage renal failure. Therefore, early identification of diabetic nephropathy is critical for persons who are diagnosed with type 1 diabetes during childhood or adolescence. This underlines the significance of performing recommended regular screened urine tests for albumin to track kidney function. The multifaceted nature of type 1 diabetes has once more been illustrated in its complexity concerning age, body weight, blood pressure, HbA1c levels, and gender (all factors set conditions at risk). Hence, for those with type 1 diabetes, sustained microalbuminuria remains a major indicator of nephropathy risk, especially with the start of adolescence, reflecting on the significance of early recognition and timely management [3]. From 2002 through 2015, the annual increase for type 1 diabetes (T1D) and type 2 diabetes (T2D) was 1.9% and 4.8%, respectively. This serves as an indication that diabetes and its insulin-resistant phenotype are becoming a concern among children and adolescents alike. While a rise in T2D has paralleled the obesity epidemic, this rise is more pronounced among racial and ethnic minorities. Diabetes in young people is a much more vicious process than adult-onset type 2 diabetes; beta-cell dysfunction is rapid, complications begin early, treatment is less effective and insulin resistance becomes worse. Increase in prevalence of diabetic kidney disease (DKD) was from 1.16% to 3.44 % between 2002-2013, predominantly among adolescents with type 2 diabetes (T2D) who are at a

substantially higher risk of developing renal failure and requiring dialysis. Indeed, early mortality and an exacerbated cardiovascular disease pathway compromise the nosed status of DKD with premier importance [4].The increasing incidence of DKD in pediatric patients brings worry, especially considering the widening footprint of diabetes within this age group, thereby underscoring the importance of a good management strategy. Early identification of microalbuminuria (MA) during puberty would be an invaluable tool in assessing the risk of DKD in young diabetic patients who, through timely intervention, could either go into resolution or persist in their course[5]. In those children who are prone to T1DM, diabetic kidney disease is most probably starting as soon as possible after its diagnosis and proceeding through the adolescence period. Nonetheless, herein lies the irony: no matter what form diabetes has taken, the kidney failure MD renal diabetic nephropathy thy does not occur in children or adolescents. Thus renal function must be checked up regularly in diabetic patients and early evidence of renal impairment should be sought. Compromised kidney function is indeed quite rare, with only 1% to 1.5% of pediatric cases experiencing overt proteinuria, while the more usual deviation found in children and adolescents with diabetes is microalbuminuria (incipient DN) and a lesser degree of DN. Clinicians need to concentrate more on identifying risk factors for DN, implementing prevention methods, and appropriately accomplishing screening tests instead of dealing with far-advanced consequences because end-stage kidney disease is rare during this age group[5]. Results in favor of individually tailored pharmacological regimens are seen, showing ACEIs' and other renoprotective agents' high efficiency at mitigating the progression of renal damage toward kidney disease and retarding the advancement of DKD in juvenile patients. Given its multifaceted etiology, fuelled by genetic predisposition, hypertension and hyperglycemia, a personalized treatment plan is a must in order to improve outcomes for afflicted and unfortunate young individuals[6].

## EPIDEMIOLOGY OF DIABETIC NEPHROPATHY IN CHILDREN AND ADOLESCENTS:

### -Prevalence and incidence of type 1 & type 2 diabetic in children and adolescents

Recent years have seen a steep rise in juvenile obesity, mostly contributing to the escalation of Type-2 Diabetes Mellitus (T2DM) prevalence in such a way that now the dominance of T2DM has started to overshadow that of Type-1 Diabetes Mellitus. The highest rate of pediatric T2DM is found in China (at 520 cases per 100,000 people) and the United States almost coincidentally (at 212 cases per 100,000 people). In contrast, T1DM is the most common form of diabetes in children and adolescents. Currently, there is scarce epidemiological data on pediatric T2DM, with differing figures found in various countries.[7].In children, the annual prevalence of diabetes for was 1.86; by 2013, it had increased to 2.82 cases from 1,000. Type 1 diabetes, between 2002 and 2013, rose from being 1.48 cases per 1,000 to 2.32". The occurrence of type 2 diabetes in persons decreased from 2000 to 2006. Prevalence rose to 0.67 in 1,000. Declined by 2013 to 0.49. Whereas type 1 diabetes was more often seen in males with significance, females were more prone to willful type 2 diabetes[10]. Elsewhere, by 2019, there were 463 million people with diabetes mellitus (DM) across the globe; projections suggest that this number will choose to rise to 578 million by 2030. It is worth noting that, in recent decades, global incidence of Type 1 Diabetes Mellitus (T1DM) has increased significantly. About 20% of individuals with Type 2 Diabetes Mellitus (T2DM) are afflicted by diabetes kidney disease (DKD), whereas this figure is multiplied to 30% for Type 1 Diabetes Mellitus (T1DM). DKD is primarily the leading cause of end-

stage renal failure (ESRD) in people with diabetes, leading to increased morbidity and mortality. [8].Type 1 diabetes (T1D) is the commonest form of diabetes amongst young adults, representing about 50—60% of cases diagnosed before the age of 15. The annual increase rate of childhood-onset diabetes is approximately 3% around the world with an anticipated rise of 70% from 2005 to 2020. The projections have kept soaring for the number of cases in children under five, highlighting the growing problem of the new type 2 diabetes from children up to the age of 21. Its prevalence today in the US elderly is 8-45%. Hence, the incidence of childhood-onset type 2 diabetes rises in line with the problem of childhood obesity. [9].

**-Prevalence of diabetic nephropathy among diabetic children and adolescents.**

Diabetic kidney disease (DKD) is a microvascular complication that affects 25–40% of patients with Type 2 Diabetes Mellitus (T2DM), a condition increasingly common among young people with T2DM. Unlike nephropathy associated with Type 1 Diabetes Mellitus (T1DM), DKD typically develops earlier in life. The rapid progression of DKD in young individuals is driven by several accompanying risk factors, including obesity, hyperglycemia, dyslipidemia, insulin resistance, and hypertension. It is reported that approximately 50% of patients with persistent albuminuria progress to ESRD within 7–10 years after the diagnosis of diabetes, making it a significant risk factor[7]. It is estimated that 30% of T1DM and 20% of T2DM develop DKD, which is one of the most severe complications of diabetes. DKD is the leading cause of 50% of end-stage renal disease (ESRD) cases in developed countries. Although DKD has a complex origin and has been considered a glomerular disease, recent studies suggest that tubulointerstitial damage occurs early in the course of the disease. Early detection of DKD is important because of its significant impact on diabetes-related morbidity and mortality[8]. Adolescents with type 2 diabetes are much more likely to develop diabetic nephropathy than those with type 1 diabetes. A study of Japanese individuals with type 2 diabetes diagnosed before the age of 30 found that the incidence of nephropathy in children with type 2 diabetes was 255 per 1,000 person-years, while for children with type 1 diabetes, it was 487. Furthermore, type 2 diabetes had a much higher cumulative incidence of nephropathy after 30 years of postpubertal diabetes (444 per 1,000 person-years) compared to type 1 diabetes (202 per 1,000 person-years)[11]. Urinary albumin excretion is one of the hallmark indicators of diabetic nephropathy, a major complication of type 2 diabetes mellitus (T2DM), which progresses with time and often leads to end-stage renal disease (ESRD). Microalbuminuria occurs in about 10% of children and adolescents with type 2 diabetes and may lead to overt nephropathy. In one study, with increasing duration of diabetes from 5 to over 15 years, prevalence of microalbuminuria increased from 8.7% to 29.5%. Likewise, with longer duration of diabetes, prevalence of overt nephropathy also increased, from 9% to 34.4% [12]. In developed nations, diabetic nephropathy stands as the first cause of ESRD: it affects up to 40% of persons with diabetes more than 15–20 years after the development of the disease. In patients with the onset of childhood type 1 diabetes, the cumulative prevalence for microalbuminuria is at about 10–25% after 5-10 years with diabetes and can reach 50% after 19 years. However, in children diagnosed with T2D, the prevalence of MA is significantly higher and most commonly identified at diagnosis[9]. From 2002 to 2013, the prevalence of diabetic nephropathy in diabetic children increased from 1.16% to 3.44%, increasing on average by 25.7% annually from 2002 through 2005 and then dropping by 4.6% per year. Both of these trends were statistically significant at $P < 0.05$. The maximum prevalence occurred in the age group of 12 to 18 years

and varied between 1.62% and 4.30% in different phases of the study. Comparing type 1 and type 2 diabetes, no statistically significant difference was observed; however, the trend was slightly higher in females than in males [10]. According to reports, only 6.4% of children and adolescents with type 1 diabetes revealed diabetic nephropathy, and no cases of macroalbuminuria were recorded from the research population. Among the adults, aged between 18 to 36 years, microalbuminuria prevalence was reported to be as high as 21.6%, and about 7% showed macroalbuminuria. In a German and Austrian-based study, it was found that in adult patients with T1D who were diagnosed with it as children, microalbuminuria was reported to be as high as 25.4%. In summary, both age and the duration of diabetes play a significant role in the prevalence of DN [2].

**PATHOPHYSIOLOGY OF DIABETIC NEPHROPATHY:**

The onset of diabetic nephropathy (DN) is characterized by the development of microalbuminuria (MA), which is defined by albumin excretion rates (AER) between 20 and 200 mg/min. This condition is a significant predictor of the progression to overt DN. The pathogenesis is a mix of metabolic and hemodynamic variables, including hyperglycemia[15]. The main cause of diabetic nephropathy is chronic hyperglycemia, which leads to metabolic imbalances and the formation of advanced glycation end products (AGEs), thus worsening kidney damage and inflammation. Glomerular hyperfiltration is a characteristic feature of DN, which includes increased pressure and flow in the glomeruli, causing structural changes such as glomerulosclerosis. Early signs of DN include changes in kidney blood flow and glomerular filtration rate. (GFR) tends to appear before microalbuminuria as a critical marker of kidney dysfunction. Elevated levels of globulin (GLB) have been known to increase the risk for diabetic nephropathy due to enhanced expressions of inflammatory cytokines, such as TNF-α, IL-6, and IL-1β. The renal tissue damage and dysfunction also result from this inflammation. This increase in GLB also leads to an increase in kidney damage through a decrease in the expression of protective proteins such as BCL2 [13].Even before microalbuminuria is detectable, urinary markers such as neutrophil gelatinase-associated lipocalin (NGAL) have been associated with renal impairment and indicate tubular damage[14]. In diabetes, genetic predisposition and hypertension significantly increase the chances of developing diabetic nephropathy [6].

**CLINICAL PRESENTATION OF DIABETIC NEPHROPATHY:**

The clinical signs include decreased glomerular filtration rate and microalbuminuria, which is described as the best marker of the early stages of DKD. Patient's elevated level of neutrophil gelatinase-associated lipocalin is seen for tubular damage even before the diagnosis of microalbuminuria[8]. Hypertension, proteinuria, and aggravation in kidney function are common clinical manifestations reported very often that can increase the risk of cardiovascular diseases and mortality. About 50% of patients with chronic albuminuria progress to ESRD within 7–10 years, making it a major risk factor for both nephropathy and cardiovascular disease[7]. Diabetic kidney disease often goes undetected until ten to fifteen years after the onset of diabetes, so it is not possible to detect DKD early. Increases in urinary albumin excretion rate (AER) are usually the first sign of DKD, and microalbuminuria develops in a large number of children and adolescents after many years of living with diabetes. It has been reported that between 25% and 40% of young individuals with diabetes have hyperfiltration characterized by an increased

glomerular filtration rate, which is the strongest predictor for future GFR decline and DKD progression. Recurrent episodes of AKI, especially in the setting of DKA, can accelerate the onset of DKD [16].

## DIAGNOSIS OF DIABETIC NEPHROPATHY:

Diabetic nephropathy is normally diagnosed based on clinical criteria established by the WHO, ADA, and others[18]. The common method for diagnosing diabetic nephropathy is through measurement of the ACR in urine which indicates a high value greater than 30 mg/g as nephropathy. According to the above-mentioned threshold value ACR, the subjects are grouped into those without diabetic nephropathy and those with diabetic nephropathy[13]. The monitoring of UACR in diabetic patients is encouraged to facilitate early detection of microalbuminuria, which could help delay or reverse the progression of diabetic kidney disease[2]. Screening for albuminuria should begin annually five years after a diagnosis of diabetes, starting at puberty or age ten, whichever occurs first[16]. In some instances, a renal biopsy would be done to affirm diagnosis and assess severity of kidney damage[17]. Presuming all other causes of chronic kidney disease have been ruled out, diagnosis requires an abnormal estimated glomerular filtration rate (eGFR) for at least three months. Critical indicators include persisting hyperfiltration, urinary abnormalities like pathological albuminuria or proteinuria, and GFR less than 90 mL/min/1.73 $m^2$. Within 7–10 years from the time of its presentation, approximately 50% of patients with persistent albuminuria will develop ESRD, making it an important risk factor for both nephropathy and cardiovascular disease[7]. Blood pressure is also measured, and a systolic pressure of 140 mmHg or diastolic pressure of 90 mmHg is considered to be hypertensive. Early detection of diabetic nephropathy can be facilitated through this approach, as well as guiding early intervention[13].

## RISK FACTORS FOR DIABETIC NEPHROPATHY IN PEDIATRIC POPULATIONS:

Diabetic nephropathy (DN) is mainly related to blood pressure, average HbA1c levels, and age. The most basic risk factor for DN is a higher average HbA1c, since poor glycemic control elevates its incidence [2]. Risk factors of diabetic nephropathy are characterized by age, gender, race, and other biochemical markers which are GGT, BUN, glycosylated hemoglobin, ALP, TP, UA, GLB, TG and also smoking and hypertension [13]. Development of chronic kidney disease is characterized by increased blood pressure, including both systolic and diastolic, in children and adults. Male gender is a risk factor in some populations, while in others female gender is found as a risk factor[2]. The AER is elevated, which is an important risk factor for nephropathy in people with type 1 diabetes. High blood pressure, which is frequently seen in diabetic patients, is another important risk factor that worsens renal damage[6]. The degree of complications in IDDM is primarily due to poor long-term glycemic control. A family history of diabetes or hypertension, especially with affected parents or siblings, increases the risk of developing DN[15]. Persistent microalbuminuria is a critical marker for the development of diabetic nephropathy in children and adults and is considered to be a leading risk factor. Although it often does not develop into proteinuria, puberty has been identified as a critical onset period for microangiopathic complications[3]. A positive family history for cardiovascular risk factors is associated with an increased risk of microvascular problems in children. It is also associated with an increased risk of kidney disease and earlier onset of renal complications, including childhood obesity[9].

## PREVENTION AND MANAGEMENT STRATEGIES:

In youth-onset Type 2 Diabetes Mellitus (T2DM), prevention and treatment of Diabetic Kidney Disease (DKD) emphasize early detection and management of risk factors, such as hypertension, dyslipidemia, and hyperglycemia. Tight control of glycated hemoglobin (HbA1c) levels is critical to slow the progression of DKD and minimize the risk of cardiovascular events[7]. Lifestyle changes are essential to achieve a healthy weight and improve glycemic control through the right combination of diet and physical exercise. All efforts should be made to lower cardiovascular risks in the most prudent manner as possible with early introduction of drugs like statins and antihypertensives. Nonadherence to medical advice leads to increased morbidity and mortality[11]. Long-term results may be improved if the onset of loss of kidney function is delayed with the use of renoprotective treatments as early as possible. Some strategies include effective glucose control and monitoring of glucose, which may reduce the complications of diabetes[1]. Some examples of medications that have been shown to be effective in reducing microalbuminuria and improving kidney outcomes include SGLT2 inhibitors and GLP-1 agonists[7].

## CHALLENGES IN DIAGNOSING AND MANAGING DIABETIC NEPHROPATHY IN CHILDREN:

Diagnosing diabetic nephropathy (DKD) in children is challenging since its symptoms often overlap with those of other diseases, and proteinuria is usually not present. Rapid progression of DKD in youth-onset Type 2 Diabetes Mellitus (T2DM) complicates the issue of early intervention since most patients do not follow an expected disease progression. Besides that, the comorbid conditions like obesity and hypertension can complicate the diagnosis and treatment of DKD. Effective treatment is complex and needs a multidimensional approach including lifestyle modification, control of hypertension, and glucose control[7]. It is tough because the earliest damage in tubulointerstitial can't be identified using the traditional markers like microalbuminuria. Current guidelines are primarily focused on microalbuminuria. Less sensitive early signs, such as neutrophil gelatinase-associated lipocalin, which may correspond to an earlier sign of tubular damage, therefore go unnoticed. In addition, other biomarkers, like NFAT5 and HIF-1a, are also undetectable in human urine. The small sample sizes in studies limit the generalizability of the results further, and thus, need further research to establish reliable diagnostic criteria[8].

## COMPLICATIONS OF DIABETIC NEPHROPATHY:

Diabetic nephropathy (DKD) is associated with numerous complications, such as high cardiovascular (CV) risks that are significantly higher in DKD patients than in non-kidney damaged patients. Microalbuminuria is an essential marker of systemic vascular injury, which suggests an increased risk of cardiovascular disease and possible acute coronary syndromes [7]. A significant portion of all diabetic patients develops diabetic nephropathy (DKD), the most common long-term microvascular complication of diabetes, which predisposes them to a higher chance of ending with end-stage renal disease (ESRD) and eventual mortality[8]. The hallmark characteristics of DKD include a decline in GFR with progressive damage to the kidney, starting with microalbuminuria that can progress to macroalbuminuria.

**FUTURE RESEARCH:**

Since monoclonal antibodies' potential remains largely unexplored in real-world applications, it is high time to research their safety and efficiency regarding the treatment of diabetic kidney disease (DKD). Another group of important research is the use of stem cell therapy, although this area requires more considerable studies in order to evaluate their safety, feasibility, and long-term effects. Recent studies have shown promising results in the ongoing search for new therapeutic targets and the development of innovative treatments for DKD. Gaining a deeper understanding of the genetic and epigenetic mechanisms behind DKD could lead to more effective treatment strategies, particularly for high-risk younger populations[7]. Investigating the mechanisms linking the NAeGFR-phenotype to autoimmune disorders and male sex could aid in the development of more targeted treatments. Furthermore, studies should investigate long-term implications and risks presented by chronic kidney disease among pediatric patients with the NAeGFR-phenotype[18].

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