

Diabetic Nephropathy in Children with Type 1 Diabetes Mellitus with Vitamin D Deficiency and Dyslipidemia as Associated Risk Factors

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Abstract

Background: Diabetic nephropathy (DN) is one of the most common and significant chronic complications associated with diabetes mellitus (DM). Vitamin D (VD) deficiency is linked to poor control of diabetes and its complications including the microvascular one such as DN. Dyslipidemia is believed to play a role in DN progression. **Objective:** The aim of this article is to estimate the prevalence of DN in children and adolescents with type 1 DM and its association with VD deficiency and dyslipidemia as risk factors. **Materials and Methods:** We conducted a cross-sectional study over a period of 6 months on 45 patients (children and adolescents) who attended the Pediatric Endocrinology Clinic of the National Diabetic Center/Al-Mustansiriyah University in Baghdad city, Iraq. The age of study participants ranged from 10 to 17 years, with the duration of type 1 DM of 5 years or more. Data including age, gender, duration of diabetes, daily insulin dose per kilogram body weight, growth measurements, and blood pressure (BP) were reported. A venous blood sample was collected for glycated hemoglobin (HbA1c), lipid profile, VD level, whereas a urine sample was collected for albumin-to-creatinine ratio. Two of the three specimens were obtained within a 3–6-month period due to variability in urinary albumin excretion. **Results:** The majority of diabetic children (71.1%) had DN. There were no significant differences in age, gender, duration of diabetes, body mass index (BMI), and BP between patients with diabetes and nephropathy and those with only diabetes. Both insulin dose and the HbA1c levels were significantly greater in diabetic patients with nephropathy (P -value 0.018 and 0.04, respectively) compared with diabetic patients without nephropathy. Insufficient and deficient VD levels were significantly higher among diabetic patients with nephropathy, whereas the sufficient level was higher among diabetic patients without nephropathy ($P = 0.020$). Diabetic patients with nephropathy had significantly higher levels of triglyceride, low-density lipoprotein (LDL), very LDL but lower high-density lipoprotein levels than diabetic patients without nephropathy (P -values 0.004, 0.047, 0.024, and 0.030 respectively). **Conclusion:** DN was not significantly associated with age, gender, disease duration, BMI, and BP of patients. Patients with DN need higher doses of insulin therapy and had higher HbA1c levels. VD deficiency is linked to a higher risk of DN. Patients with nephropathy had more significant dyslipidemia than patients without nephropathy.

Keywords: Diabetic nephropathy, lipid, type 1 diabetes, vitamin D

INTRODUCTION

Diabetic nephropathy (DN) is a common and significant long-term complication of diabetes mellitus (DM). DN affects nearly a third of diabetic patients and is identified as a leading cause of end-stage kidney disease. Although overt DN is uncommon before puberty, the processes that lead to it begin early in the disease's course. Studies have revealed histological evidence for early stages of DN within 2–5 years following diagnosis of type 1 DM (T1DM).^[1] Hyperglycemia and hypertension are the two

main risk factors for DN; in contrast, DN develops in just approximately 40% of the patients, even when their blood pressure (BP) has been raised for a long time.^[2]

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In contrast, recent epidemiological studies discussed variant risk factors for DN, one of them has indicated that vitamin D (VD) deficiency is connected to poor control of diabetes and its complications including the microvascular one such as DN; however, the degree of this connection and its clinical significance are undetermined.^[3] Importantly, numerous researches have demonstrated that VD has a protective effect on the kidneys.^[4] Supplementation with VD is thought to slow the progress of DN, reduce proteinuria, and protect DN patients from renal damage.^[5] These findings make sense because of the significant role of VD in immunity, insulin sensitivity, and β -cell function. In addition, several studies revealed a link between VD deficiency and DN.^[6] On the other side, VD metabolism in DN patients had been investigated in just a few studies. Moreover, risk factors for the development of VD deficiency in patients with DN remain obscure.^[7]

Dyslipidemia is a well-known complication of DM and is believed to play a role in DN progression. Dyslipidemia can be the result of compromised lipoprotein lipase activity, leading to higher triglyceride (TG) levels in the blood and lower high-density lipoprotein cholesterol levels (HDL-C). Furthermore, modified low-density lipoprotein (LDL), for example, oxidized and glycated LDL, plays a key role in the development of vascular and renal cellular damage.^[8] Increased serum TGs, total cholesterol, and LDL in type 1 DM patients were connected with both micro- and macroalbuminuria.^[9] Furthermore, the progression of DN along with cardiovascular disease hastened by accelerating aberrant lipoprotein metabolism.^[8] The aims of this study are to estimate the prevalence of DN in children and adolescents with type 1 DM and its association with VD deficiency and dyslipidemia as risk factors.

MATERIALS AND METHODS

A cross-sectional study is conducted over a period of 6 months, from 1st of March to 1st of September 2021, on 45 patients of children and adolescents who attended the Pediatric Endocrinology Clinic of the National Diabetic Center/Al-Mustansiriyyah University in Baghdad city, Iraq for follow-up visit. Inclusion criteria are patients with T1DM for 5 years and more, with age ranging from 10 to 17 years; these criteria were chosen to meet the American Diabetes Association (ADA) guidelines screening criteria for DN.^[10] Exclusion criteria were patients with short course hyperglycemia (1 day before visit), exercise, urinary tract infection, cardiac disease, renal disease, diabetic ketoacidosis, acute febrile illness and patients receiving drugs during the previous week known to affect urinary albumin excretion such as corticosteroids. Informed consent was obtained from every participant.

Data considering age, gender, duration of diabetes, and daily insulin dose per kilogram body weight were reported.

Clinical assessment was carried out for each patient and included general examination and growth measurements (weight, height); these anthropomorphic measurements were utilized for the measurements of body mass index (BMI), BMI for age weight status categories, and the corresponding percentiles are as follow: underweight for those less than the 5th percentile, normal healthy weight for those between 5th percentile and less than the 85th percentile, overweight for 85th to less than the 95th percentile, and obese for those percentile equal to or greater than the 95th percentile.^[11] BP was recorded using a mercury sphygmomanometer (Riester, Germany) in the supine position with a cuff of appropriate size (three different sizes were used) twice at 10 min interval in two separate visits. BP standards based on age, gender, and height provide an accurate classification of BP readings. Hypertension in children and adolescents is defined as systolic BP and/or diastolic BP that is, on repeated measurements, ≥ 95 th percentile, whereas BP reading between the 90th and 95th percentiles had been labeled as prehypertensive.^[12]

From all patients, a venous blood sample was drawn between 08:00 and 11:00 am after a 12-h overnight fasting for laboratory analyses of glycated hemoglobin value (HbA1c), total cholesterol, TG, LDL, very LDL (VLDL), HDL, and 25 hydroxy-VD levels. Criteria for definition of abnormal lipid profiles were based on the Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (2011).^[13] 25 Hydroxy-VD levels were measured by Minividus using the ELFA (enzyme-linked fluorescent assay) technique; the Endocrine Society determined a minimal target value of 30 ng/mL for 25(OH) vitamin D3 concentration, with values of 20–29 and <20 ng/mL classified as insufficient and deficient, respectively.^[14]

Urine was collected for the albumin-to-creatinine ratio (ACR) analysis for diabetic patients by dividing urinary microalbumin (mg/L) by creatinine (g/L) using Combilyzer13 Human, Germany. Two of the three specimens of ACR were obtained within a 3–6 month period due to variability in urinary albumin excretion. Microalbuminuria is defined as ACR of 30–300 mcg/mg, whereas macroalbuminuria is defined as ACR above 300 mcg/mg.^[15]

The –Statistical Package for Social Sciences (SPSS v23) was utilized for data analysis of this study. The mean difference between the two continuous variables was determined using Pearson's independent sample *t*-test. The Mann–Whitney and χ^2 tests are used. A *P*-value of ≤ 0.05 was considered significant.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of

Helsinki. It was carried out with patients' verbal and analytical approval before the sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local Ethics Committee according to the document number 3/2022 (including the number and the date in 12/03/2022) to get this approval.

RESULTS

Forty-five (13 males and 32 females) patients with 5 years and more of type 1 DM duration were involved in this study, the majority of them (71.1%) had DN.

Regarding demographic and clinical characteristics, no significant differences were detected for age and disease duration between diabetic patients with and without DN. On the contrary, insulin dose and the levels of HbA1c were significantly higher in those patients with DN (*P*-value 0.018 and 0.04, respectively) compared with patients with no nephropathy [Table 1].

Table 2 showed that no significant differences were detected regarding gender, BMI, or BP between diabetic patients with and without DN.

Among all patients, VD was deficient in 23 patients (51.1%), insufficient in 15 patients (33.3%), and sufficient in 7 patients (15.6%). The cross-tabulation between VD level and nephropathy status shows a significant relationship, in which the insufficient and deficient levels were significantly higher among diabetic patients with nephropathy, whereas the sufficient level was higher among diabetic patients without nephropathy (*P* = 0.020), as demonstrated in Table 3.

The results showed that patients with DN had significantly higher TG, LDL, VLDL levels, and lower HDL levels (*P*-values 0.004, 0.047, 0.024 and 0.030, respectively) compared with diabetic patients without nephropathy. Meanwhile, serum cholesterol levels were not significantly different between the two groups, as shown in Table 4.

DISCUSSION

Among the 45 patients who had diabetes for more than 5 years and included in the study, DN appeared in 32 patients (71.1%); this was close to Alzubaidi's study^[16] in Iraq (70%), but was higher than other studies such as

Table 1: Relationship of patients' age, duration of diabetes, insulin daily dose, and HbA1c with DN

Variable	Diabetic patients with DN (mean ± SD)	Diabetic patients without DN (mean ± SD)	<i>P</i> -value
Age (year)	13.9 ± 1.9	14.1 ± 1.6	0.877
Duration of disease (year)	7.8 ± 2.3	6.8 ± 1.9	0.164
Insulin dose (IU/kg/day)	1.2 ± 0.2	1.0 ± 0.3	0.018
HbA1c %	10.5 ± 1.3	9.6 ± 1.4	0.04

*The used test: *t*-test

Table 2: Relationship of patients' gender, BMI, and blood pressure with DN

Variable	Diabetic patients with DN No. (%)	Diabetic patients without DN No. (%)	<i>P</i> -value
Gender			
Male	10 (31.3)	3 (23.1)	0.725
Female	22 (68.8)	10 (76.9)	
BMI			
Underweight	2 (6.3)	0 (0)	0.381
Normal	21 (65.6)	11 (84.6)	
Overweight	8 (25.0)	1 (7.7)	
Obese	1 (3.1)	1 (7.7)	
Blood pressure			
Normal	23 (71.9)	6 (46.2)	0.19
Prehypertension	3 (9.4)	1 (7.7)	
Hypertension	6 (18.8)	6 (46.2)	

*The used test: χ^2

Table 3: Vitamin D level according to nephropathy status

Variable	Diabetic patients with DN No. (%)	Diabetic patients without DN No. (%)	<i>P</i> -value
25 OH-vitamin D level			
Sufficient	2 (6.3)	5 (38.5)	0.02
Insufficient	13 (40.6)	2 (15.4)	
Deficient	17 (53.1)	6 (46.2)	

*The used test: χ^2 test

Table 4: Lipid profile level of the participants according to nephropathy status

Variable	Diabetic patients with DN (mean $\pm$ SD)	Diabetic patients without DN (mean $\pm$ SD)	P-value
Serum cholesterol (mg/dL)	194.9 $\pm$ 35.7	179.4 $\pm$ 31.7	0.181
Serum triglycerides (mg/dL)	102.2 $\pm$ 37.7	67.3 $\pm$ 27.1	0.004
Serum LDL (mg/dL)	122.4 $\pm$ 33	101.4 $\pm$ 26.5	0.047
Serum HDL (mg/dL)	43.0 $\pm$ 14.0	54.1 $\pm$ 17.4	0.03
Serum VLDL (mg/dL)	17.8 $\pm$ 7.7	12.5 $\pm$ 4.1	0.024

*The used test: *t*-test

Yang *et al.*^[17] in Taiwan (19.6%), Fares *et al.*^[18] in Lebanon (15.1%) and Svensson *et al.*^[19] in Sweden (18%); and this may be attributed to social, environmental, racial, and methodological factors and a poorly controlled disease in our patients.

Regarding demographic and clinical characteristics in the present study, in terms of age, gender, disease duration, BMI, and BP, there were no statistically significant differences in these parameters between patients with DN and those without. These findings are in agreement with a study in Lebanon by Fares *et al.*^[18] Similarly, Yang *et al.*^[17] showed no significant differences in age, disease duration, and BMI in study participants, but the proportion of females and BP were higher in patients with DN.

A study done in Egypt by Mohamed *et al.*^[20] also found no significant association regarding age, gender, and BMI with DN similar to the present study results, although BP was higher in patients with DN in the mentioned study. But this was incompatible to Alzubaidi's study^[16] who found a significant association regarding age of the patients and disease duration with DN, but similar to our study in that BMI and BP showed no significant association with DN.

The study revealed that patients with DN need higher doses of insulin therapy and had higher HbA1c levels (*P* values 0.018 and 0.04, respectively); and this was because of their poorly controlled disease, and this was compatible with Raile *et al.*^[21] in Germany (*P*-values 0.025 and 0.019, respectively) and also compatible with Yang *et al.*^[17] (*P*-values 0.031 and 0.001, respectively).

Both the studies of Fares *et al.*^[18] and Alzubaidi^[16] showed higher levels of HbA1c among patients with DN (*P*-values 0.003 and 0.04 respectively), similar to the present study's results, also nearly close to the results obtained by Metwalley *et al.*^[22] in Egypt who found that patients with DN had significantly higher HbA1c and insulin dose in comparison with those patients without DN.

The current study revealed that patients with DN had significantly lower VD levels than those who did not have nephropathy (*P*-value=0.020) as shown in Table 3, and this was compatible with Mohamed *et al.*^[20] in Egypt (*P*-value <0.001)^[20] and Diaz *et al.*^[23] in USA (*P*-value <0.01). In contrast, in a study from Slovakia, Vojtková *et al.*^[24] revealed no significant difference in VD between patients with and without DN.

In the present study, diabetic patients with nephropathy had considerably higher TG (*P* = 0.004), LDL (*P* = 0.047), VLDL (*P* = 0.024) levels and lower HDL levels (*P* = 0.030) than patients without nephropathy; conversely, the serum cholesterol level did not differ significantly between the two groups (*P*-value =0.181), as shown in Table 4. This was compatible with Raile *et al.*^[21] (*P*-values <0.0001 for all) and also compatible with Metwalley *et al.*^[22] in Egypt (*P*-values <0.001), Vojtková *et al.*^[24] and Yang *et al.*^[17] who also found a significantly higher level of total cholesterol (*P*-value 0.034) and TGs (*P*-value 0.003) in patients with DN. These results put dyslipidemia as a risk factor for DN.

CONCLUSION

DN was not directly linked to age, gender, disease duration, BMI, and BP. Patients with DN need higher doses of insulin therapy and had higher HbA1c level. In type 1 diabetic children, VD deficiency is linked to an increased risk of DN. Patients with nephropathy had significantly higher TG, LDL, VLDL levels and lower HDL levels than patients without nephropathy. Further studies are needed to comprehensively evaluate the impact of VD supplementation and regular assessment of lipid profile on renal function parameters in patients with DN.

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Conflicts of interest

None to declare.

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