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BIOCHEMICAL PREDICTORS OF NEPHROPATHY IN ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS

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ABSTRACT

Background: Diabetic nephropathy is the leading cause of end-stage renal disease. Inflammation and endothelial dysfunction are key factors in its onset and progression. **Aim:** To investigate the correlation between serum uric acid, insulin-like growth factor binding protein 1 (IGFBP1), and albuminuria as early predictors of nephropathy in adolescents with type 1 diabetes mellitus. **Methods:** A cross-sectional study was conducted at Children Welfare Teaching Hospital, Baghdad, from January to July 2023. It included 88 adolescents (aged 11-15 years) with type 1 diabetes: 44 newly diagnosed (Group 1) and 44 with poorly controlled diabetes for over three years (Group 2). Clinical examinations, urine albumin-to-creatinine ratio, serum uric acid, and fasting IGFBP1 were assessed. **Results:** Group 1 and Group 2 each constituted 50% of the participants, with mean ages of 12.5±0.7 and 13.2±0.7 years, respectively. In Group 2, 19 (43.18%) patients had albuminuria (15 with microalbuminuria and 4 with macroalbuminuria). Serum IGFBP1 and uric acid levels were significantly higher in Group 2 than Group 1 (p=0.006 and p=0.000, respectively). Within Group 2, uric acid was significantly elevated in those with nephropathy (p=0.000), but IGFBP1 showed no significant difference (p=0.434). IGFBP1 levels were significantly higher in Group 2 without albuminuria compared to Group 1 (p=0.001). **Conclusion:** Elevated serum uric acid and IGFBP1 are associated with nephropathy development in type 1 diabetes. IGFBP1 can serve as an early biomarker for predicting nephropathy before the onset of albuminuria.

KEYWORDS: Biochemical, Nephropathy, Adolescents, Type 1, Diabetes Mellitus.

INTRODUCTION

Diabetes mellitus (DM) is a complex syndrome of disturbed energy metabolism, involving carbohydrates, proteins, and fats, caused by an absolute or relative deficiency of insulin secretion. The primary symptom of hyperglycemia leads to classical signs such as polyuria, polydipsia, and weight loss. While metabolic disturbances in protein and fat metabolism are known, glucose remains the most commonly monitored metabolic parameter.[1] The history of diabetes dates back to approximately 1500 BC when Egyptian and Indian physicians first recognized the symptoms. The term "diabetes" originates from the Greek word "siphon," introduced by Aretaeus, referring to the excessive urination associated with the disease. The Latin term "mellitus," meaning "honeyed," was later added by Thomas Willis in the 17th century to describe the sweet-tasting urine of patients.[2] The discovery of insulin by Frederick Banting and Charles Best in 1921 revolutionized diabetes management, earning them the Nobel Prize in 1923. This marked a turning point in treatment, as insulin became a lifesaving therapy for type 1 diabetes.[3] Type 1 diabetes mellitus (T1DM) is a life-threatening autoimmune disorder characterized by T-cell-mediated destruction of pancreatic β-cells, resulting in insufficient insulin synthesis and secretion.[4] Globally, T1DM accounts for about 10% of all diabetes cases across all age groups. Studies have shown an annual incidence increase of 2–5%, with peaks of diagnosis during early childhood and puberty. This condition equally affects males and females, with no apparent link to socioeconomic status.[5] The etiology of T1DM involves genetic, environmental, and autoimmune components. Genetic susceptibility is closely linked to human leukocyte antigen (HLA) genes, such as DR3 and DR4, which significantly increase the risk of developing the condition. Environmental factors, including viral infections, dietary influences, and vitamin D deficiency,

also play crucial roles in disease onset.[6] T1DM symptoms, such as polyphagia, fatigue, and unexplained weight loss, arise from hyperglycemia and defective glucose transport. Without treatment, severe complications like diabetic ketoacidosis (DKA) can develop, which remains a leading cause of morbidity and mortality among newly diagnosed patients.[7] Early and accurate diagnosis is critical for effective management, often confirmed through laboratory assessments of glucose, hemoglobin A1c, and autoimmune markers.[5] Advances in treatment include insulin therapy, oral hypoglycemic agents, and lifestyle modifications such as carbohydrate counting and exercise, aimed at achieving optimal glucose control.[8] Nevertheless, the prevention of long-term complications such as diabetic nephropathy and cardiovascular disease remains a cornerstone of diabetes care.[9] Study objective to examine the relationship between serum uric acid, IGFBP1, and albuminuria as early indicators of nephropathy in type 1 diabetic adolescents.

METHOD

This comparable cross-sectional study was conducted at the Endocrine Ward and Pediatric Endocrinology Clinic of the Children Welfare Teaching Hospital, Baghdad Medical City, from January 2, 2023, to July 1, 2023. The study aimed to assess the correlation of serum uric acid and IGFBP1 with nephropathy status in adolescents with type 1 diabetes mellitus (T1DM).

Study Participants: A total of 100 adolescents aged 11–15 years with T1DM were recruited. Participants were divided into two groups.

- **Group 1**: Newly diagnosed T1DM or within a few months of diagnosis (n=44).
- **Group 2**: Patients with poorly controlled T1DM for more than 3 years (HbA1c >10% over three readings annually or positive prayer sign). Group 2 was further divided into:
  - **Group 2A**: Without nephropathy (n=25).
  - **Group 2B**: With nephropathy (n=19; 15 with microalbuminuria and 4 with macroalbuminuria).

Nephropathy Status: Nephropathy was determined by albuminuria in 2 or 3 samples over 3–6 months. Microalbuminuria was defined as an albumin-to-creatinine ratio (ACR) of 30–300 mg/g for males or 42–300 mg/g for females, while macroalbuminuria was defined as ACR >300 mg/g.

Laboratory Measurements

- **Urine Sample**: First-morning void for ACR was processed within 30 minutes.
- **Serum Uric Acid**: Measured using a colorimetric assay (Cobas c311, Roche) with a normal range of 3.4–6 mg/dL.
- **IGFBP1**: Collected under fasting conditions, centrifuged, and stored at -60°C before processing using an ELISA kit. The kit's sensitivity was <0.065 ng/mL with a normal range of 0.75–60 ng/mL.

Exclusion Criteria: Participants with chronic kidney disease unrelated to diabetes, malignancy, chronic drug use (except insulin or captopril), urinary tract infections, marked hyperglycemia, febrile illnesses, menstruation, or abnormal BMI (<3rd or >85th percentile) were excluded.

Statistical Analysis: Data were analyzed using SPSS version 26. Independent sample t-tests, Mann-Whitney U tests, and correlation coefficients were used. Statistical significance was set at $p \leq 0.05$. Ethical approval was obtained, and informed parental consent was secured.

RESULTS

Duration of diabetes (in months) was recorded as 1.5±1.5 and 59.3±15.2 respectively. The mean of serum IGFBP1 level was 16±14.1 and 50.2±77.5 in group 1 and group 2 respectively and 44.1±44.7 and 58.2±107.6 in patients without nephropathy and with nephropathy respectively. While the mean of serum uric acid level was 4.1±0.7 and 5.1±1.2 in group 1 and group 2 respectively, and 4.3±0.8 and 6.1±0.8 in patients without nephropathy and with nephropathy respectively.

Table 1: Characteristics of all participants regarding socio-demographic, clinical and biochemical data.

Variable	Group 1 N=44 (50%)	Group 2 N=44 (50%)		
		Group 2A N=25 (56.8%)	Group 2B N=19 (43.2%)	Total N=44
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Gender[&]				
Male	21(47.73%)	13(52%)	9(47.37%)	22(50%)
Female	23(52.27%)	12(48%)	10(52.63%)	22(50%)
Age (years) *	12.5±0.7	13.3±0.8	13.1±0.7	13.2±0.7
Duration of disease(month)*	1.5±1.5	59.5±16.1	59.1±14.2	59.3±15.2
IGFBP1*	16±14.1	44.1±44.7	58.2±107.6	50.2±77.5
S. Uric acid*	4.1±0.7	4.3±0.8	6.1±0.8	5.1±1.2

There was no significant difference was found between male and female, p=0.704 and 0.420 respectively and table 2 illustrated this. As in table 2.

Table 2: Relationship of gender with biochemical characteristics of the patients.

Variable	Gender				P value
	Male		Female		
	Frequency N=43	Percent 48.86%	Frequency N=45	Percent 52.13%	
IGFBP1					
Mean ± SD	29.3±44.3		36.8±68.9		0.704[1]
S. Uric acid					
Mean ± SD	4.5±1.1		4.7±1.1		0.420[2]

[1]Mann-Whitney U test, [2]Independent sample t test

In the present study it was obvious that there was a highly significant difference in the duration of the disease between group 1 and group 2; p=0.000. Mean± standard deviation of serum IGFBP1 was 16±14.1 and 50.2±77.5 in group 1 and group 2 respectively, (p=0.006) which was statistically significant. Regarding serum uric acid level, also it was higher in group 2 and the difference was statistically significant (p=0.000). These correlations were shown in table 3.

Table 3: Comparison of group1 and group 2 regarding disease duration and biochemical characteristics.

Variable	Group 1		Group 2		P value
	Frequency N=44	Percent 50%	Frequency N=44	Percent 50%	
Duration of disease(months)					
Mean ± SD	1.5±1.5		59.3±15.2		0.000*[1]
IGFBP1					
Mean ± SD	16±14.1		50.2±77.5		0.006*1
S. Uric acid					
Mean ± SD	4.1±0.7		5.1±1.2		0.000*[2]

*Significant result [1] Mann-Whitney U test [2] Independent sample t test.

When comparing patients with and without nephropathy within the group 2, the duration of the disease was not statistically significant, (p=0.990). IGFBP1 level was higher in the patient with nephropathy, (its Mean ± SD was 58.2±107.6) than the patient without nephropathy (Mean ± SD was 44.1±44.7**)** but the result was not statistically significant (p= 0.434) Regarding serum uric acid, the value was higher in patients with nephropathy than in those without nephropathy and the result was highly significant (p=0.000). As shown in table 4.

Table 4: Comparison of patients in group 2 regarding disease duration and biochemical characteristics.

Variable	Diabetic without nephropathy		Diabetic with nephropathy		P value
	Frequency N=25	Percent 56.8%	Frequency N=19	Percent 43.2%	
Duration of disease					
Mean ± SD	59.5±16.1		59.1±14.2		0.990[1]
IGFBP1					
Mean ± SD	44.1±44.7		58.2±107.6		0.434[1]
S. Uric acid					
Mean ± SD	4.3±0.8		6.1±0.8		0.000*[2]

*Significant result, [1]Mann-Whitney U test, [2]Independent sample t test.

There was obvious significant difference in the duration of the disease between the newly diagnosed group 1 and the non nephropathic patients in group 2;(p=0.000). IGFBP1 level was significantly higher in patient without nephropathy (in the group 2) than the group 1 of newly diagnosed patients (p=0.001), but there is no significant difference in the level of serum uric acid between the two groups (p=0.257), despite of being higher in the non nephropathic group. (Table 5).

Table 5: Comparison of group 1 with non nephropathic patients of group 2 regarding disease duration and biochemical characteristics.

Variable	Group 1		Diabetic without nephropathy		P value
	Frequency N=44	Percent 50%	Frequency N=25	Percent 56.8%	
Duration of the disease					
Mean ± SD	1.5±1.5		59.5±16.1		0.000*[1]

IGFBP1			
Mean ± SD	16.0±14.1	44.1±44.7	0.001*[1]
s. uric acid			
Mean ± SD	4.1±0.7	4.3±0.8	0.257 [2]

*Significant result, [1]Mann-Whitney U test, [2]Independent sample t test.

Again there was a highly significant difference in the duration of the disease between the group 1 and the patients who were positive for nephropathy in the group 2, the p value was highly significant (0.000). Higher level of IGFBP1 was seen in nephropathic group, Mean±SD was 58.2±107.6 compared with 16±14.1 in the newly diagnosed group and p was significant 0.014, also highly significant difference regarding serum uric acid was seen between the two groups, (p=0.000). So both uric acid and IGFBP1 can be used as markers for diabetic nephropathy. This comparison was illustrated in table 6.

Table 6: Comparison of group 1 with the nephropathic patients of group 2 regarding disease duration and biochemical characteristics.

Variable	Group 1		Diabetic with nephropathy		P value
	Frequency N=44	Percent 50%	Frequency N=19	Percent 43.2%	
Duration of disease					
Mean ± SD	1.5±1.5		59.1±14.2		0.000*[1]
IGFBP1					
Mean ± SD	16±14.1		58.2±107.6		0.014*[1]
S. Uric acid					
Mean ± SD	4.1±0.7		6.1±0.8		0.000*[2]

*Significant result, [1]Mann-Whitney U test, [2]Independent sample t test.

The relationship between IGFBP1, serum uric acid and the duration of the diabetes is described by the correlation coefficient, there was positive relationship and they increased with the duration of the disease but the result is still statistically not significant due to inadequate sample, p:- 0.955 and 0.672 respectively, (table 7).

Table 7: Relationship between the duration of diabetes and the biochemical characteristics of group 2 participants.

Variable	Duration of disease	
	Correlation coefficient	P value
IGFBP1	0.009	0.955[2]
S. Uric acid	0.066	0.672[1]

[1]Pearson correlation, [2]Spearman correlation.

DISCUSSION

Diabetic nephropathy (DN) remains a leading cause of end-stage renal disease (ESRD) despite advancements in diabetes management. The progression from normoalbuminuria to ESRD highlights the critical role of inflammation and endothelial dysfunction in DN's onset and progression.[10,11] Microalbuminuria, defined as elevated but clinically undetectable urinary albumin excretion, is an early marker of nephropathy. Current guidelines by the American Diabetes Association (ADA) recommend annual microalbuminuria screening for diabetic patients.[10] In this study, 19 out of 88 participants (10 females, 9 males) had nephropathic albuminuria, with age and diabetes duration comparable to findings from Yoshihito et al., where normoalbuminuric and albuminuric patients had similar age and diabetes duration.[12] This study demonstrated a significantly higher serum IGFBP1 level in albuminuric patients in Group 2 compared to Group 1 (p=0.006), consistent with findings by Anna Wedrychowicz et al.[13] IGFBP1 levels were also significantly elevated in non-albuminuric patients in Group 2 compared to Group 1 (p=0.001), indicating its potential as a biomarker for DN before albuminuria. Similar results were reported in type 2 diabetes by Al Majed H. et al.[14] However, no significant difference in IGFBP1 levels was observed between nephropathic and non-nephropathic patients in Group 2 (p=0.434), suggesting its elevation is linked to long-standing diabetes rather than albuminuria. This finding contrasts with studies by Gu T. et al.[15] and Hjortebjerg R. et al.[16], which reported higher IGFBP1 levels in albuminuric patients. Additionally, a weak positive correlation was found between IGFBP1 and diabetes duration (p=0.955), possibly due to sample size limitations. This result disagreed with GU T. Et Al., who demonstrated a significant association.[15] Gender did not significantly influence IGFBP1 levels (p=0.704), aligning with findings by Gu T. et al..[15] The study revealed significantly higher uric acid levels in Group 2 compared to Group 1 (p=0.000) and between

nephropathic and non-nephropathic patients in Group 2, consistent with studies by Jalal et al.[17] and Hovind P. et al.[18] However, no significant difference was observed between newly diagnosed diabetics and patients with long-standing normoalbuminuric diabetes (p=0.257), contrasting findings by Hovind P. et al., who reported significant uric acid differences even before albuminuria development.[18] Other studies, such as Ahola A. et al.[19], and Gul A. and Zager P.[20], also did not identify a causal link between uric acid and DN. A weak positive correlation between uric acid levels and diabetes duration (p=0.672) was observed, likely due to sample limitations, differing from findings by Latif H. et al., who reported a significant association.[11] Gender was not significantly associated with uric acid levels (p=0.420), consistent with findings by Behradmanesh S. et al..[21] However, studies from Brazil and China, such as those by Moulin Mares SR. et al.[22] and Yanga Y. et al.[23], reported higher uric acid levels in boys, particularly during puberty.

CONCLUSION

Elevated blood uric acid and IGFBP1 are linked to type 1 diabetes nephropathy, therefore they can be utilised as markers together with albuminuria. Serum IGFBP1 levels were considerably higher in long-term diabetics without albumin in their urine, predicting nephropathy before albuminuria and serving as a biochemical test for early identification. Serum uric acid was raised only in albumiuric individuals, not in diabetics without albuminuria, hence it cannot identify nephropathy before urine ACR.

REFERENCES

1 Mark A. Sperling, Joseph I. Wolfsdorf, Ram K. Menon, William V. Tamborlane, David Maahs, Tadej Battelino, Moshe Phillі: Diabetes Mellitus; in Mark A. Sperling: Pediatrics Endocrinology, 5th edition, China: Elsevier, 2020; Ch 21, p 814, 816,856,857.

2 Precechtelova J, Borsanyiova M, Sarmirova S, and Bopegamag S. Type I Diabetes Mellitus: Genetic Factors and Presumptive Enteroviral Etiology or Protection. Journal of Pathogens, 2014; p 21.

3 Aled Rees, Miles Levy and Andrew Lansdown; Diabetes Mellitus: in Clinical endocrinology and diabetes at a glance: 1st ed. England: Wiley, 2017; ch 10, P 103.

4 Akil AA, Yassin E, Al-Maraghi A, Aliyev E, Al-Malki K and Fakhro KA. Diagnosis and treatment of type 1 diabetes at the dawn of the personalized medicine era. Journal of Translational Medicine, 2021; (19): 137.

5 Britta M. Svoren and Nicholas Jospe. Diabetes mellitus in children: in Robert M. Kliegman: Nelson Textbook of Pediatrics, 21st ed., Philadelphia: Elsevier, 2020; Ch 607, p 3021, 3022, 3025.

6 Dimeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. The Lancet, 2018; 391(10138): 2449-2462.

7 Kahanovitz L, Sluss PM, Russell SJ. Type 1Diabetes – A Clinical Perspective. Point of Care, 2017; 16(1): 37–40.

8 Aslander-van Vliet E, Smart C, Waldron S. Nutritional management in childhood and adolescent diabetes. Pediatr Diabetes, 2007; 8(5): 323-39.

9 Ali H, Farha M, Alshawaf E, Devarajan S, Bahbahani Y, Al Khairi I, et al. Association of significantly elevated plasma levels of NGAL and IGFBP4 in patients with diabetic nephropathy. BMC Nephrology, 2022; 23: 64.

10 Warjukar P, Jain P, Kute P, Anjankar A, Ghangale SS. Study of Microalbuminuria and Uric Acid in Type 2 Diabetes Mellitus. International Journal of Current Research and Review, 2020; 12.

11 Latif H, Iqbal A, Rathore R, Butt NF. Correlation between Serum Uric Acid Level and Microalbuminuria in Type-2 Diabetic Nephropathy. Pakistan journal of medical sciences, 2017; 33(6): 1371-1375.

12 Barkai L, Tombacz A. Alteration in insulin like growth factor binding protein 1 and sex globulin levels in type 1 diabetic adolescents with microalbuminuria. Diabetes care, 2001; 24(3): 605.

13 Wedrychowicz A, Dziatkowiak H, Nazim J, Sztefko K. Insulin- like growth factor-1 and its binding proteins, IGFBP-1 and IGFBP-3, in adolescents with type-1 diabetes mellitus and microalbuminuria. Hormone Research, 2005; 63(5): 245-51.

14 Al Majed HT, Abu-Farha M, Alshawaf E, Devarajan S, Alsairafi Z, Elhelaly A, et al. Increased Levels of Circulating IGFBP4 and ANGPTL8 with a Prospective Role in Diabetic Nephropathy. Int. Journal of Molecular Science, 2023; (24): 14244.

15 Gu T, Falhammar H, Gu HF, Brismar K. Epigenetic analyses of the insulin-like growth factor binding protein 1 gene in type 1 diabetes and diabetic nephropathy. Clinical Epigenetics, 2014; 6: 10.

16 Hjortebjerg R, Tarnow L, Jorsal A, Parving HH, Rossing P,Bjerre M, et al. IGFBP-4 Fragments as Markers of Cardiovascular Mortality in Type 1 Diabetes Patients With and Without Nephropathy. Journal of clinical endocrinology and Metabolism, 2015; (8): 3032–3040.

17 Jalal DI, Rivarrd CJ, Johnson RJ, Maahs DM, Mcfann K, Rewers M, et al. Serum uric acid levels predict the development of albuminuria over 6 years in patients with type 1 diabetes: findings from the Coronary Artery Calcification in Type 1 Diabetes study. Nephrology Dialysis Transplantation, 2010;(25): 1865–1869.

18 Hovind P, Rossing P, Tarnow L, Johonson RJ, Parving HH. Serum uric acid as a predictor for development of diabetic nephropathy in type 1 diabetes: An inception cohort study. Diabetes, 2009; 58: 1668-1671.

19 Ahola AJ, Sandholm N, Forsblom C, Harjutsalo V, Dahlström E, Groop PH, et al. The serum uric acid concentration is not causally linked to diabetic

nephropathy in type 1 diabetes. Kidney International, 2017; 91(5): 1178-1185.
20 Gul A, Zager P. Does Altered Uric Acid Metabolism Contribute to Diabetic Kidney Disease Pathophysiology? Current Diabetes Reports, 2018; 18(4): 18.
21 Behradmanesh S, Horestani1 MK, Baradaran A, Nasri H. Association of serum uric acid with proteinuria in type 2 diabetic patients. Journal of Research in Medical Sciences, 2013; 18(1): 44.
22 Moulin-Mares SR, Zaniqueli D, Oliosa PR , Alvim RO, Bottoni JP , Mill JG. Uric acid reference values: report on 1750 healthy Brazilian children and adolescents. Pediatric Research, 2021; 89(7): 1855-1860.
23 Yanga Y, Zhoub W, Wanga Y, Zhou R. Gender-specific association between uric acid level and chronic kidney disease in the elderly health checkup population in China. RENAL FAILURE, 2019; 41(1): 97–203.