ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Association of glycosylated hemoglobin with urinary albuminuria for early detection and progression of renal damage in patients with type 2 diabetes mellitus

Moxda S Patel[1], Rugvi P Patel[2], Mananshi R Shah[3], Rajul R Shah[4]

[1]Assistant Professor, [2]Senior Resident, Department of Pathology, AMC MET Medical College, Ahmedabad, [3]First Year Resident, Department of Pathology, Sumandeep Vidhyapith, Vadodara, [4]Assistant Professor, Department of Pathology, Smt.N.H.L.Municipal Medical College, Ahmedabad, Gujarat, India

Submission: 08-04-2022 Revision: 22-05-2022 Publication: 01-07-2022

ABSTRACT

Background: Regular screening of levels of glycosylated hemoglobin and microalbuminuria (MA), diabetic nephropathy can be prevented.Recent studies found some of the sensitive and specific biomarker for early detection and progression of nephropathy in type 2 diabetes mellitus (T2DM) patients. **Aim and Objectives:** This study was carried out to correlation of glycosylated hemoglobin with urinary albuminuria for early detection and progression of nephropathy in patients with T2DM. **Materials and Methods:** This was a case–control study was conducted at tertiary care institute of India. A total 300 subjects included in the present study diagnosed with T2DM according to American diabetes association criteria and the cases are sub grouped based on albumin creatinine ration, the 100 patients T2DM with normoalbuminuria (NA) (ACR Ratio: <30 mg/dL) and 100 patients T2DM with MA (ACR Ratio: 30–299 mg/dL) along with that 100 healthy subjects were included in the study.FBS, PPBS, Urea, Creatinine, Uric acid, HbA1C, and Urinary Albumin was analyzed using laboratory standard methods. **Results:** The plasma fasting blood sugar, post-prandial blood sugar, serum urea, creatinine, uric acid, Glycosylated hemoglobin, and urinary albumin levels were increased in two groups of T2DM Patients when compared to healthy controls. Significantly elevated levels of plasma fasting blood sugar, post-prandial blood sugar, serum urea, creatinine, uric acid, Glycosylated hemoglobin, and urinary albumin are observed in all the parameters elevated in between patients T2DM with MA when compared to patients T2DM NA. **Conclusion:** Elevated levels of Glycated hemoglobin as well as urinary albumin were useful for detection and progression of different stages of nephropathy in patients with T2DM and also this study suggest that continuous monitoring of these investigations were useful for treatment of different stages of T2DM.

Key words: Diabetes mellitus; Glycosylated hemoglobin; Microalbuminuria; Urinary albumin

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v13i7.44353

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Diabetes mellitus is a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbance in carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action or both.[1] Long-term effects of diabetes are responsible for the macro and microvascular complications.[2] Diabetes requires continuous medical care with multifactorial strategies aimed at preventing and decreasing risks of chronic complications. Chronic hyperglycemia is tied to long lasting consequences that manifest in various organ dysfunctions, especially kidneys and blood vessels.[3] Diabetes is the most common cause of kidney failure in the world, and it is estimated that diabetes increases the risk of end-stage renal disease (ESRD) approximately 12-fold.[4-6]

Address for Correspondence:
Dr. Rajul R Shah, Assistant Professor, Department of Pathology, Smt. N.H.L. Municipal Medical College, Ahmedabad - 380 051, Gujarat, India. **Mobile:** +91-9925073337. **E-mail:** rajulshah007@gmail.com

Diabetic nephropathy is a major microvascular complications of diabetes.[2] Its earliest manifestation is the appearance of low amounts of albumin in the urine of patients (>30 mg/day but <300 mg/day) referred to as microalbuminuria (MA).[7] It is easily measured but frequently overlooked as a tool for assessment of impairment of kidney functions and is associated with progression of chronic kidney disease (CKD) to more advanced stages or to ESRD.[8]Moreover, the prevalence of diabetes related CKD has exceeded that of glomerulonephritis-related CKD to become the leading cause of CKD.[9] To date, the diagnosis of DKD is dependent on both albuminuria and estimated glomerular filtration rate according to the relevant guidelines. However, albuminuria does not directlyreflect the extent of renal injury, and few DM patients have had progressive renal decline before albuminuria and MA among some patients with DKD can be regressed back to normoalbuminuria (NA). Glycated hemoglobin (HbA1c) is commonly used as a marker of glycemic status.[10-12] HbA1c was called as unusual hemoglobin in patients with diabetes when it was first discovered. After that discovery, it was established that HbA1c could be used as an objective measure of glycemic control and a validated relationship between A1C and average glucose across a range of diabetes types.[13,14]This study was carried out to correlation of glycosylated hemoglobin with urinary albuminuria for early detection and progression of nephropathy in patients with type 2 diabetes mellitus (T2DM).

Aims and objectives

This study was carried out to correlation of glycosylated hemoglobin with urinary albuminuria for early detection and progression of nephropathy in patients with T2DM.

MATERIALS AND METHODS

This was a case–control study was conducted at tertiary care institute of India. A total 300 subjects included in the present studydiagnosed with T2DM according to American diabetes association criteria[15] andpatients above 40 years of age with a minimum duration of 5 years of diabetes from the time of diagnosis, admitted in the Department of Medicine and Surgery were recruited in the study.The cases are sub grouped based on albumin creatinine ration, the 100 patients T2DM with NA (ACR Ratio: <30 mg/dL) and 100 patients T2DM with MA (ACR Ratio: 30–299 mg/dL) along with that 100 healthy subjects were included in the study. One hundred control subjects were selected from an age-matched population on the basis of the levels of glycosylated hemoglobin <6.5% who was on regular antiglycemic therapy.Ethical approval was taken from the institutional ethical committee and written informed consent was taken from all the participants.(IEC/2020-21/357).

Patients with T2DM and age more than 40 years were included in the present study.

Exclusion criteria

The following criteria were excluded from the study:

1. Diabetic patients with overt albuminuria,that is, urinary albumin excretion >300 mg/24 h.
2. Diabetic patients with anemia were excluded as the level of glycosylated hemoglobin is dependent on the life span of RBCs.

From the all subjects, after overnight fasting (12h), 5mL of venous blood was collected and 2mL transferred into anticoagulant tube contain fluoride and 3 mL transferred into plain tube. The second sample was collected for PPBS. Urine samples also collected from all the subjects. The collected samples were separated by centrifugation at 3000 rpm for 5 min and stored until biochemical analysis was done. The Plasma FBS, PPBS, HbA1C, Serum Urea, Creatinine, and Uric Acid were analyzed by laboratory standard methods; Urine Albumin Creatinine Ratio was measured by immunoturbidometric method.

Statistical analysis

The recorded data werecompiled and entered in a spreadsheet computer program (Microsoft Excel 2007) and then exported to data editor page of SPSS version 15 (SPSS Inc., Chicago, Illinois, USA). For all tests, confidence level and level of significance were set at 95% and 5%, respectively.

RESULTS

The plasma fasting blood sugar, post-prandial blood sugar, serum urea, creatinine, uric acid, glycosylated hemoglobin, and urinary albumin levels were increased in two groups of T2DM Patients when compared to healthy controls. Significantly elevated levels of plasma fasting blood sugar, post-prandial blood sugar, serum urea, creatinine, uric acid, glycosylated hemoglobin, and urinary albumin are observed in all the parameters elevated in between patients T2DM with MA when compared to patients T2DM NA (Table 1). The plasma fasting blood sugar, post-prandial blood sugar, serum urea, creatinine, uric acid with positively correlated with HbA1C, and urinary albumin levels were in two groups of T2DM patients (Table 2).

DISCUSSION

Hyperglycemia is a major risk factor for diabetes mellitus due to improper production and activation of insulin from the beta cells of pancreas results insulin resistance.[15] Diabetes associated hyperglycemia causes

Table 1: Distribution of data in between demographic and biochemical parameters in all the group subjects

Variable	Controls	T2DM Patients with Normoalbuminuria	T2DM Patients with Microalbuminuria	P value
Age (Years)	52.40±9.10	47.01±09.23	53.9±06.45	0.04*
Fasting Blood Sugar (mg/dL)	87.03±13.10	126.19±14.12	287.36±30.23	0.05*
Post-prandial Blood Sugar (mg/dL)	126.47±22.65	165.87±41.14	320.65±27.42	0.001*
Serum Urea (mg/dL)	33.21±5.47	41.48±7.74	102.47±9.22	0.03*
Serum Creatinine (mg/dL)	0.9±0.12	1.2±0.2	11.99±1.57	0.002*
Serum Uric Acid (mg/dL)	5.54±2.12	7.20±1.3	13.94±0.10	0.008*
HbA1C (%)	4.78±1.47	7.96±1.5	12.09±8.47	0.003*
Urinary Albuminuria (mg/dL)	14.57±0.99	26.88±1.6	196.90±46.78	0.01*

*Indicates statistically significance at P≤0.05

Table 2: Pearson correlation in between the two groups of T2DM patients

Variable	Name of The Variables	R value	P value
Urinary Albuminuria (mg/dL)	Age (Years)	0.035	0.1
	Fasting Blood Sugar (mg/dL)	0.185	0.002*
	Post Prandial Blood Sugar (mg/dL)	0.229	0.003*
	Serum Urea (mg/dL)	0.16	0.05*
	Serum Creatinine (mg/dL)	0.903	0.001*
	Serum Uric Acid (mg/dL)	0.612	0.003*
	HbA1C (%)	0.590	0.002*

*Indicates statistically significance at P≤0.05

long-standing damage, dysfunction and collapse of many vital organs; mainly kidneys, eyes, nerves, heart, and blood vessels. Long-term complications of DM include nephropathy which leads to renal failure, retinopathy which potentially causes loss of vision, autonomic neuropathy which causes gastrointestinal and cardiovascular dysfunction and peripheral neuropathy which causes foot ulcers.[16,17]

The plasma fasting blood sugar, post parandial blood sugar, serum urea, creatinine, uric acid, Glycosylated hemoglobin and urinary albumin levels were increased in two groups of T2DM Patients when compared to healthy controls. In between the two groups of subjects, there are increased levels of FBS, PPBS, Urea, Creatinine, Uric Acid, HbA1C, and Urinary albumin elevated in patients T2DM with MA whencompared to patients T2DM with NA ($P<0.05$). The Pearson correlation analysis shows that HbA1C and urinary albumin were positively correlated with the plasma fasting blood sugar, post parandial blood sugar, serum urea, creatinine, uric acid in patients with two groups of T2DM. This correlation was highly significant and supported by the studies of Oellgaard et al.,[18] Neil et al.,[19] Wei et al.,[20] Tabaei et al.,[21] Bruno et al.,[22] Wu et al.,[23] Parvanova et al.,[24]and Naveen et al.[25] In the studies conducted by Pavithra et al.,[26] a rise in the levels of glycosylated hemoglobin was seen along with the increase in the duration of diabetes. The increase in these values is explained by the pathogenesis of formation of glycated hemoglobin. Longer duration of uncontrolled diabetes pathogenetically correlates with the higher values of glycated hemoglobin.

A highly significant correlation was also seen with the rise in the levels of MA along with the increase in fasting plasma sugar. This indicates increased renal damage with increase in fasting plasma sugar levels. This was supported by the studies of Bruno et al.[22], Adler et al.,[27] Rossing et al.,[28] Parvanova et al.,[24] Retnakaran et al.,[29] and Parving et al.,[30]

MA as an indicator of nephropathy and renal damage has been concomitantly correlated with fasting plasma sugar, glycosylated hemoglobin, and occasionally with serum creatinine by many workers. The study of Retnakaran et al.,[29] stated that these variables rise together if not intervened by antiglycemic drugs. However, multivariate model of the same study has found that the rise in glycosylated hemoglobin was an independent predictor of MA. Parving et al.,[30] in his study suggested that at the mean level of HbA1c of 7.5%, MA could be demonstrated in 39% of the patients and overt albuminuria in 9.8% of the patients while other remained normoalbuminuric. This study suggest continuous monitoring of these investigations were useful for detection as well as prognosis of nephropathy in patients with T2DM.

Limitations of the study

Limitation of the study is specific types of antihypertensive medication that may influence albuminuria or renal function, such as angiotensin converting enzyme 10 inhibitors or angiotensin II receptor blockers were not taken into account.

CONCLUSION

Elevated levels of glycated hemoglobin as well as urinary albumin were useful for detection and progression of different stages of nephropathy in patients with T2DM and also this study suggest that continuous monitoring of

these investigations were useful for treatment of different stages of T2DM.

ACKNOWLEDGMENT

We gratefully acknowledge the subjects who participated in our study, all colleagues and experts who contributed with sample processing and analysis.

REFERENCES

1. Maitra A and Abbas A. The endocrine system. In: Kumar V, Abbas A and Fausto N, editors. Robins and Cotran Pathologic Basis of Disease. 8th ed. Philadelphia, PA: Elsevier; 2010.
2. World Health Organization. Report of a WHO Consultation, Part 1: Diagnosis and Classification of Diabetes Mellitus. World Health Organization, Department of Noncommunicable Disease Surveillance. Geneva: World Health Organization; 1999.
3. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, DeBoer IH and GoldsteinFuchs J. Diabetic kidney disease: A report from an ADA consensus conference. Am J Kidney Dis. 2014;64(4):510-533.
4. Guariguata L, Whiting D, Hambleton I, Beagley J, Linnenkamp U and Shaw J. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract. 2014;103(2):137-149.
https://doi.org/10.1016/j.diabres.2013.11.002
5. Fernandes JR, Ogurtsova K, Linnenkamp U, Guariguata L, Seuring T, Zhang P, et al. IDF Diabetes Atlas estimates of 2014 global healthexpenditures on diabete. Diabetes Res Clin Pract. 2016;117:48-54.
https://doi.org/10.1016/j.diabres.2016.04.016
6. NCD Risk Factor Collaboration: Worldwide trends in diabetes since 1980: A pooled analysis of 751 population-based studies with 4 4 million participants. Lancet. 2016;387(10027):1513-1530.
7. International Diabetes Federation. IDF Diabetes Atlas. 7th ed. Brussels, Belgium: International Diabetes Federation; 2015.
8. Sun K, Lin D, Li F, Huang C, Qi Y, Xue S, et al. Discordant associations of lipid parameters with albuminuria and chronic kidney disease: A population-based study. Lipids Health Dis. 2015;14:152.
https://doi.org/10.1186/s12944-015-0153-8
9. Adeosun OG, Anetor JI, Ogunlewe JO, Ikem RT, Kolawole BA, Arogundade FA, et al. Evaluation of alterations in the urine biochemical profiles of Type 2 diabetes mellitus patients in Southwest, Nigeria. Afr J Biotechnol. 2014;13(1):175-180.
https://doi.org/10.5897/ajb09.443
10. Nam GE, Han K, Kim DH, Park YG, Yoon YJ, Kim YE, et al. Relationship between dyslipidemia and albuminuria in prediabetic adults: The Korea national health and nutrition examination survey 2011-2012. Endocrine. 2015;48(2):557-565.
https://doi.org/10.1007/s12020-014-0411-y
11. Gluhovschi C, Gluhovschi G, Petrica L, Timar R, Velciov S, Ionita I, et al. Urinary biomarkers in the assessment of early diabetic nephropathy. J Diabetes Res. 2016;2016:4626125.
https://doi.org/10.1155/2016/4626125
12. Bello AK, Levin A, Tonelli M, Okpechi IG, Feehally J, Harris D, et al. Assessment of global kidney health care status. JAMA. 2017;317(18):1864-1881.
https://doi.org/10.1001/jama.2017.4046
13. Persson F, Rossing P. Diagnosis of diabetic kidney disease: State of the art and future perspective. Kidney Int Suppl. 2018;8(1):2-7.
https://doi.org/10.1016/j.kisu.2017.10.003
14. Weir MR. Microalbuminuria in Type 2 diabetics: An important, overlooked cardiovascular risk factor. J Clin Hypertens (Greenwich). 2016;6(3):134-141; quiz 142-143.
https://doi.org/10.1111/j.1524-6175.2004.02524.x
15. American Diabetes Association: Standards of medical care in diabetes-2017. Diabetes Care. 2017;40(Suppl 1):1-87.
https://doi.org/10.2337/dc17-er07d
16. Boer ID, Rue TC, Cleary PA, Lachin JM, Molitch ME, Steffes MW, et al. Long-term renal outcomes of patients with Type 1 diabetes mellitus and microalbuminuria: An analysis of the diabetes control and complications trial/epidemiology of diabetes interventions and complications cohort. Arch Intern Med. 2017;171(5):412-420.
https://doi.org/10.1001/archinternmed.2011.16
17. Satirapoj B and Adler SG. Comprehensive approach to diabetic nephropathy. Kidney Res Clin Pract. 2014;33(3):121-131.
https://doi.org/10.1016/j.krcp.2014.08.001
18. Oellgaard J, Gæde P, Rossing P, Persson F, Parving HH and Pedersen O. Intensified multifactorial intervention in Type 2 diabetics with microalbuminuria leads to long-term renal benefits. Kidney Int. 2017;91(4):982-988.
https://doi.org/10.1016/j.kint.2016.11.023
19. Neil A, Hawkins M, Potok M, Thorogood M, Cohen D and Mann J. A prospective population- based study of microalbuminuria as a predictor of mortality in NIDDM. Diabetes Care. 2016;16(7):996-1003.
https://doi.org/10.2337/diacare.16.7.996
20. Wei F, Chang B, Yang X, Wang Y, Chen L and Li WD. Serum uric acid levels were dynamically coupled with hemoglobin A1c in the development of Type 2 diabetes. Sci Rep. 2016;6:28549.
https://doi.org/10.1038/srep28549
21. Tabaei B, Al-Kassab A, Ilag L, Zawacki C and Herman W. Does microalbuminuria predict diabetic nephropathy? Diabetes Care. 2016;24(9):1560-1566.
https://doi.org/10.2337/diacare.24.9.1560
22. Bruno G, Merletti F, Biggeri A, Bargero G, Ferrero S, Pagano G, et al. Progression to overt nephropathy in Type 2 diabetes. Diabetes Care. 2017;26(7):2150-2155.
https://doi.org/10.2337/diacare.26.7.2150
23. Wu A, Kong N, de Leon F, Pan C, Tai T, Yeung V, et al. The MAPS Investigators. An alarmingly high prevalence of diabetic nephropathy in Asian Type 2 diabetic patients: The MicroAlbuminuria Prevalence (MAP) Study. Diabetologia. 2018;48(1):17-26.
https://doi.org/10.1007/s00125-004-1599-9
24. Parvanova A, Trevisan R, Iliev I, Dimitrov B, Vedovato M, Tiengo A, et al. Insulin resistance and microalbuminuria. A cross-sectional, case-control study of 158 patients with Type 2 diabetes and different degrees of urinary albumin excretion. Diabetes. 2016;22:1456-1462.
https://doi.org/10.2337/db05-1484
25. Naveen P, Kannan N, Vamseedhar A, Bhanu PG and Aravind K. Evaluation of glycated hemoglobin and microalbuminuria as early risk markers of nephropathy in Type 2 diabetes mellitus. Int J Biol Med Res. 2017;3(2):1724-1726.
https://doi.org/10.18535/jmscr/v5i8.37
26. Pavithra V, Revathy K and Swaminathan S. Association between uric acid and HbA1c in Type 2 diabetes mellitus in comparison with controls. Int J Curr Microbiol Appl Sci. 2016;5(4):585-589.

https://doi.org/10.20546/ijcmas.2016.504.066

27. Adler A, Stevens R, Manley S, Bilous R, Cull C, Holman R, et al. Development and progression of nephropathy in Type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int. 2017;63(1):225-232.

    https://doi.org/10.1046/j.1523-1755.2003.00712.x

28. Rossing K, Christensen P, Hovind P, Tarnow L, Rossing P and Parving H. Progression of nephropathy in Type 2 diabetic patients. Kidney Int. 2019;66(4):1596-1605.

    https://doi.org/10.1111/j.1523-1755.2004.00925.x

29. Retnakaran R, Cull C, Thorne K, Adler A, Holman R and The UKPDS Study Group. Risk factors for renal dysfunction in Type 2 Diabetes U.K. prospective diabetes study 74. Diabetes. 2018;55(6):1832-1839.

    https://doi.org/10.2337/db05-1620

30. Parving H, Lewis J, Ravid M, Remuzzi G, Hunsicker L and The DEMAND Investigators. Prevalence and risk factors for microalbuminuria in a referred cohort of Type II diabetic patients: A global perspective. Kidney Int. 2020;69(11):2057-2063.

    https://doi.org/10.1038/sj.ki.5000377

Authors' Contributions:
MSP- Concept and design of the study, prepared first draft of manuscript; **RPP**- Interpreted the results; reviewed the literature and manuscript preparation; **MRS**- Concept, coordination, preparation of manuscript; RRS- statistical analysis and interpretation.

Work attributed to:
Department of Pathology, AMC MET Medical College, Ahmedabad, Gujarat, India.

Orcid ID:
Moxda S Patel - https://orcid.org/0000-0002-3724-0185
Rugvi P Patel - https://orcid.org/0000-0001-8288-8223
Mananshi R Shah - https://orcid.org/0000-0003-4746-274X
Rajul R Shah - https://orcid.org/0000-0002-5619-8189

Source of Funding: None, **Conflicts of Interest:** None.