A study on serum uric acid levels and insulin resistance in type-2 diabetic subjects

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Abstract

Insulin resistance (IR) is the principle etiological factor for development and progression of type-2 diabetes mellitus (T2DM) and decreased insulin function. Independently, increased serum uric acid (SUA) is known to play a critical role in the development of T2DM as well as in progression of its complications. To assess the correlation between SUA levels and IR in diabetic patients, data with lab investigations of HbA1c, fasting levels of serum glucose, UA, TAG, HDL-C of confirmed and known cases of T2DM were collected from the Hospital Biochemistry Laboratory, DMWIMS Hospital, Wayanad, Kerala. Fasting ratio of TAG to HDL-C was used as an index for IR. A significant increase in fasting serum glucose, SUA, HBA1C, TAG, TAG/HDL-C ratio (IR) and a significant decrease in HDL-C were observed in data of cases when compared with the data of normal healthy subjects. This study shows a positive correlation between SUA levels and IR in known cases of T2DM.

Keywords: type2 diabetes mellitus; serum uric acid; insulin resistance

Introduction

Insulin resistance (IR) is the principle etiological factor for development and progression of type-2 diabetes mellitus (T2DM) and decreased insulin function. Independently, increased serum uric acid (SUA) is known to play a critical role in the development of T2DM as well as in progression of its complications⁴. However, hyperuricemia is not always found in diabetic individuals. Conflicting data exist about UA levels in T2DM, as low levels were found in diabetic patients, while elevated SUA is a feature of hyperinsulinemia and impaired glucose tolerance⁵. The present study was undertaken to assess the correlation between SUA levels and IR in known cases of T2DM.
Materials and Methods

Study Setting & Data Source
A retrospective observational case control study was conducted in DM WIMS Hospital, Wayanad, Kerala, in collaboration with Department of Medical Biochemistry, School of Health Sciences, Palayad, Kannur University, Kerala, during the period from May 2019 to July 2019. Institutional Research Committee approval has been taken for conducting this study. A year data (from Jan 2018-Jan 2019) of confirmed and known cases of T2DM were collected along with the normal subjects’ data, from the Hospital Biochemistry Laboratory.

Study Subjects & Groups
The present study included data of total of 107 subjects out of whom 52 were of healthy normal individuals and 55 were of known cases of T2DM and were grouped as Group-1 and Group-2 respectively. The normal subjects had a mean age of 43.13 ± 5.98 years of which 23 were males and 29 were female and diabetic subjects had mean age of 61.06 ± 13.19 years of which 31 were males and 24 were females.

Inclusion criteria: Both male and female patients >35 years of age with known case of T2DM were included in this study.

Exclusion criteria: Patients with Type-1 DM, patients with acute complications of DM, those with a history of acute infections and other ailments like gross congestive heart failure, tuberculosis, gout, rheumatoid arthritis and skeletal muscle injury, those with serum creatinine levels of >1.5 mg/dl, renal failure, diabetic nephropathy, uric acid lowering drugs, were excluded from the study.

Study Parameters
Data of fasting serum levels of glucose (FBS), uric acid (UA), Triacylglycerol (TAG), High density lipoprotein- Cholesterol (HDL-C) and Glycated Hb (HbA1c), of both type-2 diabetic and normal subjects were assessed for the present study. Estimation principles of the studied parameters were as follows: Glucose by hexokinase method\(^{[3,4]}\), HbA1c by HPLC method\(^{[5]}\), TAG by enzymatic colorimetric test\(^{[6]}\), HDL-C by homogenous enzymatic colorimetric assay\(^{[7,8]}\), UA by enzymatic colorimetric test\(^{[9,10]}\). Data of serum TAG and serum HDL-C were used to calculate IR. There are many limitations to establish direct methods for measuring insulin resistance in vivo. So, an indirect method is used for calculating IR index. TAG to HDL-C ratio is the indirect method\(^{[11–13]}\), that has been reported to be closely related to IR in adults. All the parameters were estimated using Roche Cobas Integra 400 -Plus fully automated analyzer.

Statistical Evaluation
Data analysis was done using SPSS software version 24 (IBM, Armonk, NY, USA). The data were expressed as their Mean ± SD and the statistical significance was calculated using Mann Whitney U test. \(p < 0.05\) was considered as significant and \(p < 0.001\) was considered to be statistically highly significant. Pearson correlation ‘r’ was used to assess the correlation between serum uric acid levels and insulin resistance

Results
The results of the present study are depicted in Table 1 and Figure 1.

Figure 1: Showing Pearson’s correlation co-efficient for the correlation between SUA levels and TG/HDL -C ratio (IR) among Group-2 subjects

Fig 1. Pearson’s correlation co-efficent r=0.6 Insulin resistance (IR) was indirectly calculated as TAG/HDL-C ratio

Discussion
The association of hyperuricemia and development of T2DM have been observed by various researchers\(^{[1,14]}\). Many studies have also shown that elevated levels of SUA may lead to progression of chronic complications such as CVD and CKD in diabetic patients\(^{[15–17]}\). Hyperuricemia & hypertriglyceridemia are suggested to be associated with insulin resistance syndrome\(^{[18–20]}\).

The results of the present study show a positive correlation \((r = 0.605)\) between SUA & IR (calculated indirectly by measuring the ratio of TAG/HDL-C) [refer Table 1 & Figure 1]. This is consistent with the recent meta-analysis by Xu et al\(^{[21]}\). The mechanism for uric acid-induced insulin resistance appears to be mediated by the development of mitochondrial oxidative stress and impairment of insulin-dependent stimulation of nitric oxide in endothelial cells, mediated by the expression of CRP\(^{[22]}\). Pilot studies in
Lowering drugs are recommended. And to slow down the epidemic. Large clinical trials with SUA may prove to be a simple and inexpensive strategy to help.

The present study shows a positive correlation between SUA and independent variables, and fails to account for any due to small sample size, not analyzing sufficient dependent independent variables, and fails to account for any confounders effect.

**Limitations of the study**

This study may come short of generalizability and authenticity due to small sample size, not analyzing sufficient dependent independent variables, and fails to account for any confounders effect.

**Conclusion**

The present study shows a positive correlation between SUA and IR in type-2 diabetic patients suggesting that SUA may serves as a better risk indicator of IR status. Lowering SUA may prove to be a simple and inexpensive strategy to help prevent the development of diabetes and/or its complications and to slow down the epidemic. Large clinical trials with SUA lowering drugs are recommended.

**References**

1) Kodama S, Saito K, Yachi Y, Asumi M, Sugawara A, Totsuka K, et al. Association Between Serum Uric Acid and Development of Type 2 Diabetes. *Diabetes Care.* 2009;32(9):1737–1742. Available from: https://dx.doi.org/10.2337/dc09-0288.

2) Čaušević A, Semiz S, Macić-Džanković A, Cico B, Dujić T, Malešić M, et al. Relevance of uric acid in progression of type 2 diabetes mellitus. *Bosn J Basic Med Sci.* 2010;10(1):54–59. Available from: https://doi.org/10.17305/bjbsms.2010.2736.

3) Neelley WE. Simple Automated Determination of Serum or Plasma Glucose by a Hexokinase/Glucose-6-Phosphate Dehydrogenase Method. *Clinical Chemistry.* 1972;18(6):509–515. Available from: https://dx.doi.org/10.1093/clinchem/18.6.509.

4) Bondar RJ, Mead DC. Evaluation of glucose-6-phosphate dehydrogenase from Leuconostoc mesenteroides in the hexokinase method for determining glucose in serum. *Clin Chem.* 1974;20(5):586–590.

5) Mayer TK, Freedman ZR. Protein glycosylation in diabetes mellitus: a review of laboratory measurements and of their clinical utility. *Clin Chem Acta.* 1983;127(2):147–184. Available from: 10.1016/s0009-8981(83)80002-3.

6) Siedel J, Schmuck R, Staepels J, Town MH. Long term stable, liquid ready to use monoreagent for the enzymatic assay of serum or plasma triglycerides (GPO-PAP method). *AACC Meeting Abstract 34.* *Clin Chem.* 1993;39(1127).

7) Suguchi H, Uji Y, Okabe H. Direct measurement of high-density lipoprotein cholesterol in serum with polyethylene glycol-modified enzymes and sulfated alpha-cyclodextrin. *Clin Chem.* 1995;41(5):717–723.

8) Matsuhashi Y, Kawaguchi E, Morita Y, Mashihe F, Ohisa S, Nakahara K. Evaluation of two kinds of reagents for direct determination of HDL-cholesterol. *J Anal Bio-Sc.* 1996;19:419–446.

9) Kageyama N. A direct colorimetric determination of uric acid in serum and urine with uricase-catalase system. *Clinica Chimica Acta.* 1971;31(2):421–426. Available from: https://doi.org/10.1016/0009-8981(71)90413-x.

10) Digioia J, Henry RJ. Clinical chemistry: Principles and Techniques. Vol. 84. Harper and Row. 1972.

11) Li C, Ford ES, Meng YX, Mokdad AH, Reaven GM. Does the association of the triglyceride to high-density lipoprotein cholesterol ratio with fasting serum insulin differ by race/ethnicity? *Cardiovascular Diabetology.* 2008;7(1):4. Available from: https://dx.doi.org/10.1186/1475-2840-7-4.

12) Shenahalha C, Satyavani K, Sivasankari S, Vijay V, Ramachandran A. Serum triglycerides as a marker of insulin resistance in non-diabetic urban Indians. *Diabetes Res Clin Pract.* 2005;69(2):203–206. Available from: https://dx.doi.org/10.1016/j.diabres.2005.03.021.

13) Bovet P, Faeh D, Gabriel A, Tappy L. The Prediction of Insulin Resistance With Serum Triglyceride and High-Density Lipoprotein Cholesterol Levels in an East African Population. *Archives of Internal Medicine.* 2006;166(11):1236–1237. Available from: https://dx.doi.org/10.1001/archinte.166.11.1236-b.

14) Wu YT, He H, Wang X, Zhang M, An ZM, Huang HJ. Serum Uric Acid and Islet B-cell Function in Patients with Pre-diabetes and Type 2 Diabetes Mellitus. *Sichuan Da Xue Xue Bao Yi Xue Ban.* 2018;49(1):69–73. Available from: https://pubmed.ncbi.nlm.nih.gov/29737093/.

15) Zoppini G, Targarher G, Chonchol M, Oralted V, Abatutos C, Pichiri I, et al. Serum Uric Acid Levels and Incident Chronic Kidney Disease in Patients With Type 2 Diabetes and Preserved Kidney Function. *Diabetes Care.* 2012;35(1):99–104. Available from: https://dx.doi.org/10.2337/dc11-1346.

16) Culleton BF, Larson MG, Kannel WB, Levy D. Serum triglycerides as a marker of insulin resistance in non-diabetic urban Indians. *Diabetes Res Clin Pract.* 2005;69(2):203–206. Available from: https://dx.doi.org/10.1016/j.diabres.2005.03.021.

17) Mazzoli M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, et al. Elevated Uric Acid Increases Blood Pressure in the Rat by a Novel Crystal-Independent Mechanism. *Hypertension.* 2001;38(5):1101–1106. Available from: https://dx.doi.org/10.1161/hy1101.092839.

18) Yoo TW, Sung KC, Shin HS. Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. *Circ J.* 2005;69(8):928–933. Available from: 10.1253/circj69.928.

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**Table 1.** Showing fasting levels of serum glucose, SUA, HbA1c, serum TAG, serum HDL-C & IR as ratio of TAG/HDL-C, in both Group-1 & Group-2 subjects

| Parameters | FBS mg/dL | HbA1C % | SUA mg/dL | TAG mg/dL | HDL-C mg/dL | IR [TAG/HDL-C ratio] |
|------------|-----------|---------|-----------|-----------|-------------|---------------------|
| Group-1 (52) | 87.15±6.94 | 5.01±0.36 | 4.63±1.14 | 99.32±22.95 | 47.18±11.66 | 2.22±0.66 |
| Group-2 (55) | 198.34±65.79 | 9.50±2.04 | 8.30±1.30 | 213.05±47.19 | 40.07±9.79 | 5.47±1.47 |

P value < 0.001 < 0.001 < 0.001 < 0.001 < 0.002 < 0.001

p value of < 0.05 was considered significant. Insulin resistance was indirectly calculated as TAG/HDL-C ratio. Ratios of >3 in men and >2 in females are considered as abnormal/elevated IR.

Normal ranges of parameters: FBS- 70-100 mg/dL, TAG- M:50-200 mg/dL, F: 40-150, SUA – M:3.5-7 mg/dL, F: 2.5-5 mg/dL, HDL-C- 30-60 mg/dL, HbA1c- 5.7%

Number in parentheses shows the number of subjects.
19) Vuorinen-Markkola H, Yki-Järvinen H. Hyperuricemia and insulin resistance. *J Clin Endocrinol Metab*. 1994;78(1):25–29. Available from: 10.1210/jcem.78.1.8288709.

20) Cigolini M, Targher G, Tonoli M, Manara E, Muggeo M, Sandre D, et al. Hyperuricaemia: relationships to body fat distribution and other components of the insulin resistance syndrome in 38-year-old healthy men and women. *Int J Obes Relat Metab Disord*. 1995;19(2):92–96.

21) Yi-Li Xu, Kuan-Feng Xu, Jian-Ling Bai, Yun Liu, Rong-Bin Yu, Chun-Lan Liu, et al. Elevation of serum uric acid and incidence of type 2 diabetes: A systematic review and meta-analysis. *Chronic Dis Transl Med*. 2016;2(2):81–91. Available from: https://doi.org/10.1016/j.cdtm.2016.09.003.

22) Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. *J Am Soc Nephrol*. 2005;16(12):3553–3562. Available from: 10.1681/ASN.2005050572.

23) King C, Lanaspa MA, Jensen T, Tolan DR, Sánchez-Lozada LG, Johnson RJ. Uric Acid as a Cause of the Metabolic Syndrome. *Contrib Nephrol*. 2018;192:88–102. Available from: 10.1159/0004848283.