

RESEARCH ARTICLE

Role of serum uric acid and nitric oxide in the diagnosis of Type 2 diabetes mellitus - A case-control study

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ABSTRACT

Background: The studies have reported that high serum uric acid (UA) and low nitric oxide (NO) levels are strongly associated with prevalent health conditions such as obesity, insulin resistance, metabolic syndrome, diabetes, essential hypertension, and renal disease. None of the studies have examined the predictive value of serum UA and NO in the diagnosis of Type 2 diabetes, especially from India. **Aims and Objectives:** To find out the predictive value of serum UA and NO in the diagnosis of Type 2 diabetes. **Materials and Methods:** This was a case-control study. A total of 40 cases of Type 2 diabetes were included (20 male and 20 female). Age- and sex-matched apparently healthy subjects ($n = 40$) without any history or symptoms of diabetes and other metabolic disorders were chosen as the control (20 male and 20 female). **Results:** The serum UA was significantly ($P = 0.0001$) higher among the cases (16.23 ± 2.89) compared to controls (11.77 ± 5.92). However, NO was found to be significantly lower among the cases (47.33 ± 10.70) than controls (61.19 ± 10.48). The sensitivity and specificity of serum UA were 62.5% and 57.5%, respectively, with a cutoff value of 15.75. A moderate area under the curve (AUC) was found which was statistically significant. A reasonable sensitivity (70%) and specificity (77.5%) of NO were also observed, however, AUC was small. **Conclusion:** We found moderate sensitivity and specificity of serum UA and NO in the diagnosis of Type 2 diabetes.

KEY WORDS: Type 2 Diabetes; Serum Uric Acid; Serum Nitric Oxide; Sensitivity; Specificity

INTRODUCTION

Diabetes mellitus has been become the leading cause of death and disability worldwide.^[1,2] The global prevalence has been reported about 8% in 2011 and being predicted to rise to 10% by 2030.^[3]

India is at number two in the list of top 10 countries for the prevalence of diabetes.^[4] It has been projected that in 2020,

India will become the capital of diabetes in the world.^[5] Unfortunately, there is still inadequate awareness about the real dimension of the problem among the general public in India. There is also a lack of awareness about the existing interventions for preventing diabetes and the management of complications.^[6]

Uric acid (UA) is being formed by the breakdown of purines and by direct synthesis from 5-phosphoribosyl pyrophosphate and glutamine. Serum urate levels vary with age and sex. Levels begin to rise in males during puberty but remain low in females until menopause.^[7]

Nitric oxide (NO) is a key regulatory molecule with extensive metabolic, vascular, and cellular effects. The regulation of NO metabolism is particularly important in Type 2 diabetes, because activation of NO synthase (NOS) is under insulin control through the Akt pathway.^[8]

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Most of the studies have reported that high serum UA and low NO levels are strongly associated with the prevalent health conditions such as obesity, insulin resistance, metabolic syndrome, diabetes, essential hypertension, and renal disease.^[8,9] However, in our best knowledge, none of the studies have examined the predictive value of serum UA and NO in the diagnosis of Type 2 diabetes, especially from India.

Hence, the present case-control study was designed to find out the predictive value of serum UA and NO in the diagnosis of Type 2 diabetes.

MATERIALS AND METHODS

This case-control study was conducted in a tertiary care teaching hospital in north India. Subjects suffering from Type 2 diabetes for more than 1 year, aged between 30 and 50 years with hyperuricemia were included in the study. Patients with coronary artery disease due to other causes diagnosed for hypothyroidism, chronic alcoholics, taking antioxidant medication, using lipid lowering drugs, and with chronic diseases were excluded from the study. The study was approved by the Ethical Committee of the Institute.

A total of 40 cases of Type 2 diabetes were included (20 male and 20 female). Age- and sex-matched apparently healthy subjects ($n = 40$) without any history or symptoms of diabetes and other metabolic disorders were chosen as the control (20 male and 20 female).

The patients were defined as diabetes mellitus using the following criteria: Those with symptoms of diabetes with random blood glucose level ≥ 200 mg/dl or fasting plasma glucose ≥ 126 mg/dl or hemoglobin A1c $> 6.5\%$ or impaired oral glucose tolerance test with 2 h postprandial plasma glucose (PPG) level ≥ 200 mg/dl.

The study protocol was explained, and an informed consent was taken from each subject. After a minimum of 12 h of fasting venous, blood sample was collected in plain vial for serum UA and NO. Blood was collected from the antecubital vein, following precautions. The sample was then allowed to clot in the aliquot at room temperature for about 2 h and was then centrifuged at 3000 rpm for 10 min to separate the serum. For blood glucose, blood sample was taken in *P* vial and the blood glucose was estimated within 6 h of sample collection. Fasting blood glucose and PPG were estimated quantitatively by glucose oxidase/peroxidase technique. Serum NO was determined indirectly by the measurement of stable decomposition product (NO_2^-), employing the Griess reaction. Serum UA was assessed by uricase enzymatic method using Transasia UA kit.

Statistical Analysis

Data obtained were summarized as a mean $\pm$ standard deviation. The comparison of serum UA and NO levels between cases and control was done using unpaired Student's *t*-test. The sensitivity, specificity, positive predictive, and negative predictive value were calculated through receiving operating curve analysis. The $P < 0.05$ was considered statistically significant.

RESULTS

The serum UA was significantly ($P = 0.0001$) higher among the cases (16.23 ± 2.89) compared to controls (11.77 ± 5.92) (Figure 1). However, NO was found to be significantly lower among the cases (47.33 ± 10.70) than controls (61.19 ± 10.48) (Figure 2).

Table 1 and Figure 3 show the diagnostic value of serum UA and NO. The sensitivity and specificity of serum UA were 62.5% and 57.5%, respectively, with a cutoff value of 15.75. A moderate area under the curve (AUC) was found which

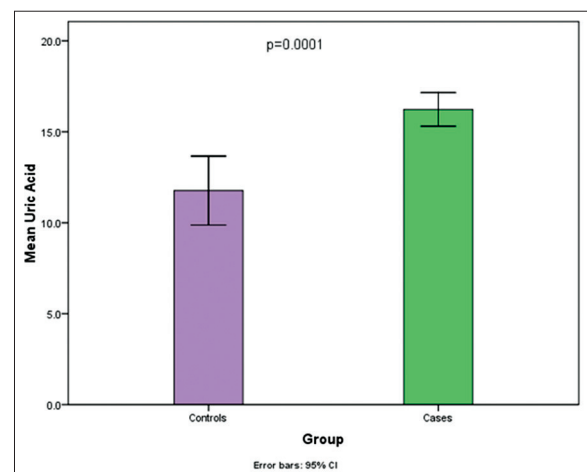


Figure 1: Level of serum uric acid in cases and controls

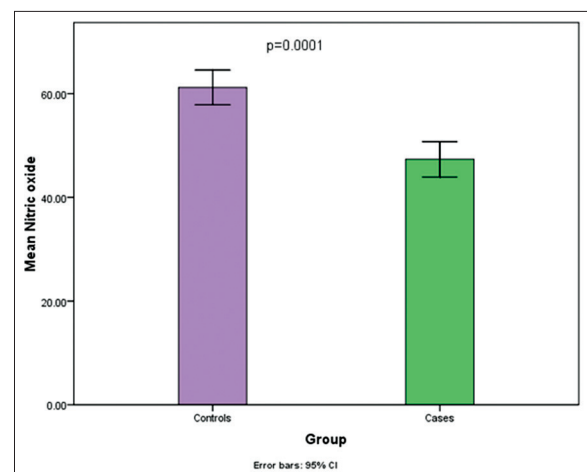
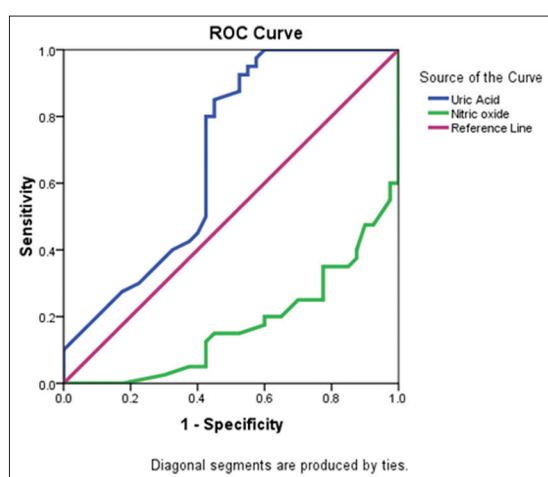


Figure 2: Level of serum nitric oxide in cases and controls

Table 1: Diagnostic value of serum uric acid and nitric oxide

Diagnostic parameters	Serum uric acid (mg/dl)	Serum nitric oxide ($\mu\text{mol/L}$)
Cut-off	>15.75	<49.65
Sensitivity (%)	62.5	70.0
Specificity (%)	57.5	77.5
PPV (%)	59.5	75.7
NPV (%)	60.5	72.1
Accuracy (%)	60.0	73.8
AUC (95% CI), P value	0.68 (0.56-0.80), 0.005*	0.17 (0.098-0.26), 0.0001*

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve, CI: Confidence interval, *Significant

**Figure 3:** Receiving operating curve curve showing sensitivity and specificity of serum uric and nitric oxide for the diagnosis of Type 2 diabetes

was statistically significant. A reasonable sensitivity (70%) and specificity (77.5%) of NO were also observed, however, AUC was small.

DISCUSSION

Diabetes mellitus being the major health problem throughout the developed and developing countries including India is a heterogeneous group of diseases, characterized by persistent hyperglycemia, resulting from a diversity of etiologies.

Serum UA is produced by xanthine oxidase from xanthine and hypoxanthine, which in turn are produced from purine. It is a strong reducing agent and in human over half of the antioxidant capacity of blood comes from serum UA.^[10] NO is a potent vasodilator and an endothelium-relaxing factor. This molecule is a short-lived free radical, with the physiological functions including smooth muscle relaxation, inhibition of platelet aggregation and nonadrenergic-noncholinergic neurotransmission.^[11] Uncoupling of endothelial NOS occurs in the blood vessels of diabetics leading to endothelial

dysfunction and excessive superoxide anion production causing decreased NO bioavailability.^[12]

Serum NO has emerged as a fundamental signal associated with the endothelial dysfunction in Type 2 diabetes.^[13] It is also stated that NO plays an important role in homeostatic vasodilatation and regulation of blood flow.^[12] A study has suggested that serum UA is a strong and independent risk factor for diabetes.^[14] A meta-analysis study summarized that quantitative relationship between serum UA level and risk of Type 2 diabetes indicated that each 1 mg increase in serum UA level resulted in 17% increase in the risk of Type 2 diabetes.^[15]

This study investigated the role of serum UA and NO in the diagnosis of Type 2 diabetes. The mean level of serum UA was found to be higher among the cases compared to control in this study. This finding is in accordance with other studies in which UA levels are higher among the subjects with pre-diabetes and early Type 2 diabetes than in healthy controls.^[15-17]

In this study, the level of NO was observed to be lower among the cases compared to controls which were in agreement with the study by Tessari et al.^[8] However, Di Nardo et al. reported reverse results.^[18] We found moderate sensitivity and specificity of serum UA and NO in the diagnosis of Type 2 diabetes. Since none of the studies have evaluated such findings, comparison could not be made.

The prognostic and diagnostic utilities of these biomarkers, especially UA and antioxidants with diabetes *per se* and its long-term complications need to be evaluated by further studies with a larger number of patients, to validate them as markers that can replace existing ones.

One of the limitations of this study was small sample size, the studies on larger sample size is required to have robust findings.

CONCLUSION

Authors found moderate sensitivity and specificity of serum UA and NO in the diagnosis of Type 2 diabetes.

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