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Research Article

Nitric Oxide in Diabetic Patients and its Relation with HbA1c

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ABSTRACT

In diabetic patients, hyperglycemia leads to many complications like arteriosclerosis and coronary artery disease. Nitric Oxide plays a major role in micro and macro vascular complications. NO which is produced by endothelial cells has very short half life making it less available. The present study is undertaken to evaluate NO and its metabolites levels in diabetic patients.

Methodology: 55 diabetic patients attending diabetology consultant were compared with 25 controls attending OP, SRM Hospital. Serum NO and Urinary NO were estimated by griess method and FBS and HbA1c in AU400 autoanalyzer.

Results: Serum and urinary NO level were increased in diabetic patients compared to controls.

Key words: Diabetes mellitus, glucose, nitric oxide, superoxide ion.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia and insufficiency of secretion or action of endogenous insulin. Hyperglycemia in type II diabetes leads to a gradual progression to complications, including neuropathy, retinopathy, arteriosclerosis, and coronary artery disease. While exogenous insulin and other medications can control many aspects of diabetes, numerous complications affecting the vascular system, kidney, retina, lens, peripheral nerves, and skin are common and are extremely costly in terms of longevity and quality of life. Increased oxidative stress is a widely accepted participant in the development and progression of diabetes and its complications[1-4]. High glucose produces reactive oxygen species as a result of glucose auto-oxidation, metabolism and the development of advanced glycosylation end products[5].

NO has a short half-life (few seconds) and a short range of bioactivity. In general, NO is a relatively stable free radical that readily diffuses from the site of production, crossing cell membranes and interacting with targets without the need for special transporters or receptors[6,7]. Nitric oxide [NO] is not only important in host defence and homeostasis but it is also regarded as harmful and has been implicated in the pathogenesis of a wide variety of inflammatory and autoimmune diseases[8]. NO reacts with intracellular superoxide leads to the formation of peroxynitrite which is highly reactive and can damage many proteins. 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[9].

This study is undertaken in to study the levels of NO in diabetic patients, its correlation with HbA1c and its excretion in diabetic patients.

METHODOLOGY

The ethical clearance for the study was obtained from institutional ethical committee, SRM University. 55 subjects selected for the study were the patients attending Diabetology Department of **SRM** Medical College Hospital and Research Centre, Kattankulatur, Tamilnadu. 25 Controls were selected attending OP without any hypertensive, diabetic and any other known cause of increased oxidative stress conditions. Consent was obtained from diabetic patients as well as from controls.

Fasting blood sample was collected and serum was separated from it for analysis. Nitric oxide was estimated by griess method after deproteinising the sample with 96% ethanol. FBS was estimated by GOP-POD method and HbA1c by immunoturbidometry method. Random urine sample was collected and processed for NO levels immediately. All stastical analysis were performed using IBM SPSS 20.0 version.

RESULTS

NO is elevated in diabetic patients in both serum and urine when compared to controls and the increase is highly significant ($p<0.001$) (Table.1, chart.1). With increase in HbA1c serum NO and urinary nitric oxide are also increased showing strong correlation between HbA1c and serum NO (0.644*) and Urinary NO (0.503*) (chart.2).

DISCUSSION

Recently, a glucose-dependent increase in NO production, urinary excretion and action has become an attractive hypothesis for the pathogenesis of early diabetic nephropathy[10]. In our study, increase in serum NO metabolites and increased excretion of NO in diabetic patients is observed (chart.1). Seum NO and urinary NO show strong correlation with HbA1c indicating that high blood glucose levels cause an increase in NO levels

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Table.1: Mean±SD of patients and controls

Parameter	controls	patients
FBS(mg/dL)	124.96±17.02	197.89±76.16
HbA1c(%)	5.8±0.5	8.7±1.72
Serum NO(µM)	28.0±6.97	51.88±25.73**
Urinary NO(µM)	24.6±9.85	60.98±40.14**

*** represents P<0.001*

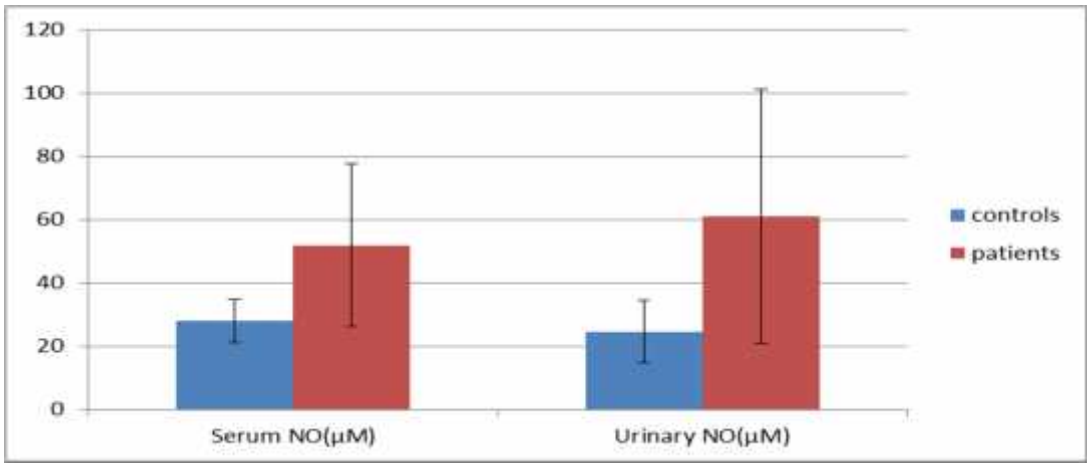

Chart.1: Urinary and serum NO_X levels in controls and pateints

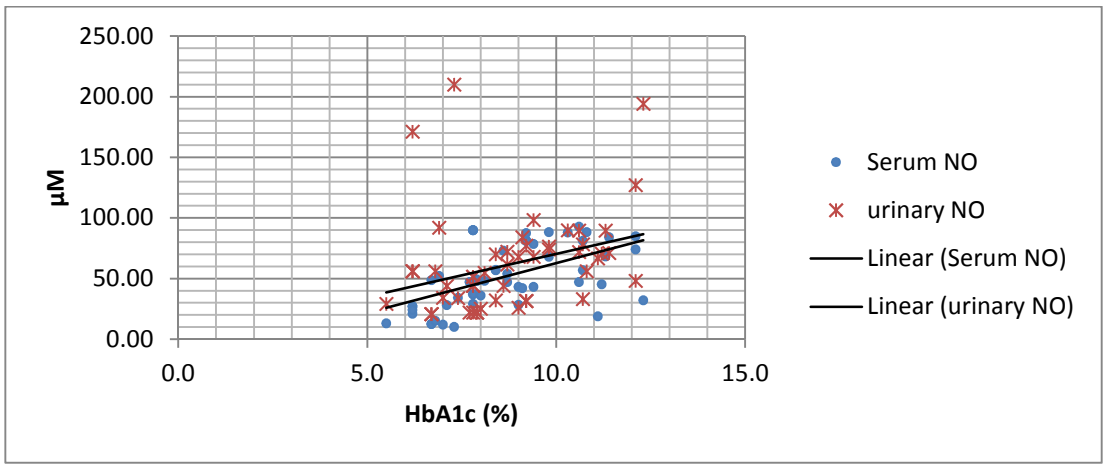

Chart.2: correlation between HbA1c, Serum NO and urinary NO

(chart.2). Similar results were observed in a study on type 1 diabetics showing strong correlation between NO_2, NO_3 and HbA1c[11]. Insulin, besides its stimulatory effect on NOx production, also increased NOx removal. Such an hypothesis is intriguing and not directly proven so far[12]. It has recently been demonstrated that the prolonged exposure of endothelial cells to high glucose increases both NO and superoxide anion production[13]. The increase in NO is due to increased expression of eNOS mRNA and NOS protein expression. Although NO metabolites may be increased in diabetes[14], bioactive NO is reduced[15] which might be explained by increase in superoxide production which overrules the increased NO and decreases its bioavailability by reacting with it.

In contrast to our study, reduced urinary excretion of nitric oxide–related products, in type 2 diabetic patients had been reported[16] which might be due to advanced glycosylation end products decreasing NOS expression[17].

CONCLUSION

Serum NO and their metabolites are not only produced in higher quantity but also excreted in higher levels in diabetic patients resulting in decreased bioavailability of NO. Further research is needed to study the mechanism of glucose activation of NO production and estimate NO availability in diabetic patients.

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ABBREVIATIONS

Superoxide dismutase (SOD), nitric oxide (NO), Fasting Blood Sugar (FBS), endothelial-Nitric Oxide Synthase (eNOS)

Conflict: None

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