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Evaluation of serum vascular endothelial growth factor (Vegf) and microalbuminuria in early diabetic nephropathy

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Abstract
Aim: To evaluate serum vascular endothelial growth factor (VEGF) and urinary microalbumin for early detection of diabetic nephropathy.
Method: The diabetic patients visiting the Medicine OPD were selected and evaluated for serum vascular endothelial growth factor and urinary microalbumin. The patients were divided into groups according to duration of diabetes. Group 1 with diabetes between 5-10 years, Group 2 with diabetes between 10-15 years, Group 3 with diabetes more than 15 years and Control Group.
Results: Serum VEGF level along with urinary microalbumin increased significantly in Group 2 (10-15 years duration) and further increases with increasing diabetic duration.
Conclusion: Serum vascular endothelial growth factor (VEGF) along with appearance of microalbumin in urine can predict diabetic nephropathy in early stages.

Keywords: diabetes, VEGF, microalbumin

Introduction
Diabetic nephropathy is a clinical disorder characterized by persistent albuminuria (>300 mg/24 hr), a constant GFR decline, raised arterial blood pressure and cardiovascular morbidity and mortality [1]. Diabetes has become the most common single cause of end stage renal disease in most countries and about 20-30% of patients with type 1 or type 2 diabetes develops nephropathy. Diabetic patients are 17 times more prone to develop kidney disease than normal population and the peak onset is between 10-15 years after the onset of diabetes [2]. The onset and course of diabetic nephropathy can be improved to a significant degree if detected early in the course of the development of this complication. High glucose concentration causes impairment of nitric oxide production and activity and induce vascular endothelial dysfunction finally leads to diabetic nephropathy [5] which is followed by formation of advance glycation end-products (AGEs), reactive oxygen species (ROS) and increase in the oxidative stress [6]. In both types of diabetes mellitus Vascular endothelial growth factor level is up-regulated and its inhibition with anti-VEGF has positive effects on diabetic nephropathy complications [7].
Microalbuminuria is defined as urinary albumin excretion of more than 30 mg/24 hr (20 µg/min), and 300 mg/24 hr (200 µg/min) or less, and its presence in urine is a powerful screening biomarker to detect diabetic patients at risk for diabetic nephropathy. About 20%–40% of type 2 diabetics with microalbuminuria progress to overt nephropathy; and about 20% will develop end stage renal disease after the development of overt nephropathy [3]. However, many patients experience GFR loss without deterioration in albuminuria and even normoalbuminuria [4] which support the discovery of other biomarkers to aid in prediction of impaired renal function. In this study we evaluate serum vascular endothelial growth factor (VEGF) level along with urinary microalbumin for early detection of diabetic nephropathy.

Material and Method
The present study was conducted in the Department of Biochemistry, in association with the Department of Medicine, S.M.S. Medical College and Hospital,Jaipur.The study comprised of total 160 subjects and were divided into groups as follows: Group 1: comprised of 40 patients with duration of DM (diabetes mellitus) more than five years and less than ten years.

Group 2: comprised of 40 patients with DM duration between 10 to 15 years Group 3: comprised of 40 patients with history of DM more than 15 years. Control group – 40 age and sex matched healthy individuals were taken as control.

Individual within age group 30-70 years with diabetic history of more than 5 years and HbA1C >8% were included in the study. Exclusion Criteria was taken to rule out other diseases which can alter the result of the study like thyroid disorders, past history of renal impairment, patients on glucocorticoid therapy. Venous blood sample was withdrawn for investigations taking all aseptic precautions. Serum was separated and investigated for vascular endothelial growth factor (VEGF) by ELISA method. Urine sample was collected in a sterile container and analysed for microalbumin by immunoturbidimetry method

Ethical approval and Informed consent

The Protocol was approved by institutional Ethics committee. Informed written consent was obtained from all study subjects.

Statistical Analysis

The data was analysed using SPSS version 20 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included computation of percentages, means and standard deviations were calculated. The statistical tests applied for the analysis were oneway ANOVA with Pearson Correlation Coefficient. For both the tests, confidence interval and p-value were set at 95% and ≤ 0.05 respectively.

Results

Table 1 demonstrates the level of VEGF and microalbumin in control and diabetic groups. Serum VEGF concentration was observed higher in diabetic patient groups as compare to control subjects and the level increases with increasing duration of disease (Figure 1). The urinary microalbumin level in control group was (10.03 ± 8.07) mg/l and in diabetic patient group 1, group 2, group 3 were (14.23 ± 3.99), (40.10 ± 12.31), (157.51 ± 61.49) mg/l respectively showing that microalbuminuria appears mostly after 10 years of diabetes and then increases with further increase in diabetic duration.

Table 1: Serum Vascular Endothelial Growth Factor (VEGF) and Urine Microalbumin level in Control v/s Diabetic Groups

Character		Control	Group 1 (5-10 years)	Group 2 (10-15 years)	Group 3 (>15 years)
	Cases	40	40	40	40
VEGF (pg/ml)	Mean±SD	71.71±23.56	103.33±36.54	316.80±71.86	759.67±158.18
Microalbumin (mg/l)	Mean±SD	10.03±8.07	14.23±3.99	40.10±12.31	157.51±61.49

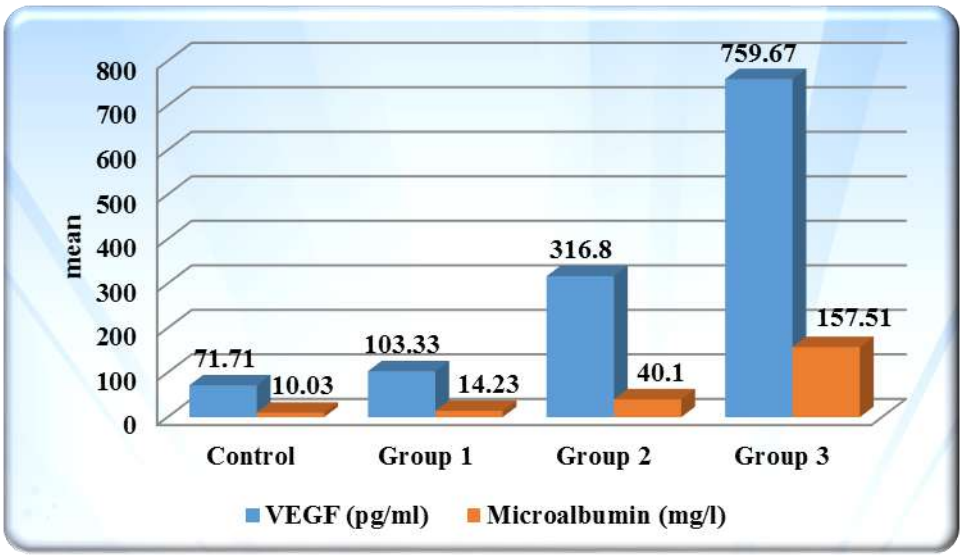

Fig 1: Serum VEGF and Urine Microalbumin in control v/s diabetic groups

Table 2: Correlation of Serum VEGF with Microalbumin in Control v/s Diabetic Groups

Variables		Control	Group 1 (5-10years)	Group 2 (10-15years)	Group 3 (>15years)
Microalbumin (mg/l)	r	0.12	0.28	0.66	0.76
	p	0.42	0.07	0.00	0.00

Table 2 shows correlation of serum VEGF with urinary microalbumin in control and diabetic groups. A strong positive correlation of VEGF with microalbumin was observed in group 2 (r=0.66, p=0.00) and group 3 (r=0.76, p=0.00).

Discussion

The findings of our study shows increased serum VEGF level in diabetic groups compared to control subjects and the level further increases with increasing duration of disease. Our result was consistent with Tavafi M. [8] who observed increasing rate of VEGF in diabetic nephropathy. VEGF is found to be involved in the pathogenesis of diabetic complications [9]. Metabolic abnormalities have been found in the pathogenesis of diabetic nephropathy which causes the activation of intracellular signaling molecules resulting in the dysregulation of cytokines and vascular growth factors, like VEGF and angiopoietins which are involved in

the functional and structural regulation of the glomerular filtration barrier [10]. Vascular endothelial growth factor (VEGF) can affect the filtration of large molecular weight proteins through glomerular filtration barrier by promoting endothelial cell proliferation and increasing vascular permeability. Our finding shows that microalbuminuria appears in diabetic patients with history of more than 10 years and then the level rises with increasing diabetic duration. These observations are well supported by SA Sheikh *et al.* [12] who observed a highly significant correlation of microalbuminuria with advancing age and duration of diabetes. In type 2 diabetic patients with nephropathy loss of ultrafiltration capacity (Kf) and impairment of glomerular barrier size-selectivity occurs due to reduction in the number of restrictive pores leading to progressive albuminuria and the extent of impairment of ultrafiltration capacity is related to the magnitude of the defect in the barrier size-selectivity [13]. The intensive treatment of glycemia aiming at HbA1c < 7% should be pursued as early as possible to prevent the development of microalbuminuria.

Our study results also shows a strong positive correlation of serum VEGF with urinary microalbumin in group 2(r=0.66, p=0.00) and group 3 patients (r=0.76, p=0.00), however in group 1 patients (r=0.28 p=0.07) no significant correlation was observed. So serum VEGF can be used as a marker to detect nephropathy in diabetic patients with history of more than 10 years along with urinary microalbumin. Similar result was observed by Wasada T *et al.* [14] showing that VEGF concentration tended to increase with increasing urinary albumin excretion in type 2 diabetic patients. In contrast to our study Cha DR *et al.* [11] observed significantly higher VEGF concentration in type 2 diabetic patients with overt proteinuria than in patients with normal or microalbuminuria.

Conclusion

Diabetic nephropathy is one of the leading causes of end-stage renal disease and early detection is necessary to treat patients for their better survival. The study pointed that serum vascular endothelial growth factor (VEGF) can be used as a potential marker to predict diabetic nephropathy in early stages along with appearance of microalbumin in urine.

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