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INCREASED SERUM LEVELS OF VASCULAR ENDOTHELIAL GROWTH FACTOR–A ARE REVERSELY CORRELATED WITH TIMP-1 IN ATHEROSCLEROSIS IN EARLY STAGES OF TYPE 2 DIABETIC NEPHROPATHY

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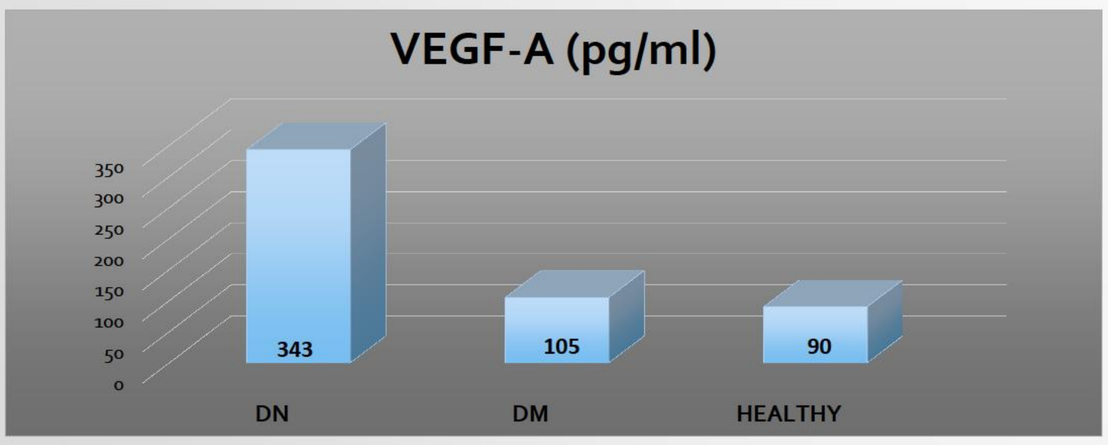
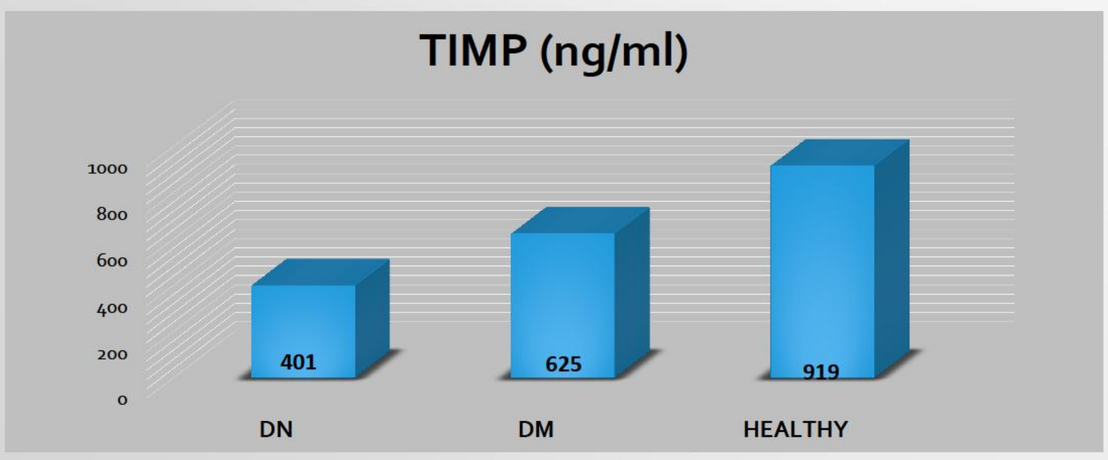
Background/ Aim: Recent evidence suggests that renal vascular changes contribute to progressive renal disease and that alteration of vascular endothelial growth factor-A (VEGF-A) might play an important role in modulating microvascular loss of macrovascular remodeling in the kidney, as well as in the vessels [1,2]. It remains controversial the mechanism by which VEGF works in the kidney, as well as in the vessels at least in the early stages of diabetic nephropathy (DN) and chronic kidney disease (CKD) [1-3] . Whether VEGF-A is detrimental in early stages of DN or other renal conditions has not yet been clearly answered [3,4]. Tissue inhibitor of metalloproteinase -1 (TIMP-1) has been identified in humans and its expression is regulated during development and tissue remodeling. TIMP-1 overexpression in a mouse model of atherosclerosis showed a lesion reduction [5]. The aim of the present study was to determine the serum levels of VEGF-A and TIMP-1 and to investigate their potential correlation with the atherosclerotic markers and albuminuria in early stages of type 2 DN.





Methods: CKD patients of stages 1 and 2 with type II DN (n=50) were included. As controls, there were two groups, patients with diabetes type II without CKD (n=40) and healthy individuals (n=40). Clearance of creatinine (Clcr) and albumin excretion were examined in the 24h urine. VEGF-A and TIMP-1 levels were measured by an ELISA method. Intima media thickness (IMT) of carotid and femoral arteries and atheromatic plaque were evaluated by a high resolution ultrasonography. Statistical analysis was performed with the use of a SPSS system.

Results: There was a statistically significant difference between VEGF-A (200±30, $p<0.0001$), TIMP-1 (400±20, $p<0.0001$) and IMT (0.3±0.09, $p<0.0001$) in the patient group. There was a statistically significant negative strong correlation between levels of VEGF-A and TIMP-1 ($r= -0.7$, $p<0.0001$), such as between TIMP-1 and IMT ($r= -0.65$, $p<0.0001$). There was a statistically positive correlation between VEGF-A and IMT ($r= 0.6$, $p<0.0001$). Further, VEGF-A and TIMP-1 levels were independently correlated with IMT and atheromatic plaque ($p<0.0001$).

Discussion: Previously, VEGF-A has been shown to play a role in both plaque vulnerability and in expansive arterial remodeling. Serum VEGF-A levels were higher in patients with acute coronary syndrome, suggesting that VEGF-A could be a marker of plaque instability in CVD. Further, circulating VEGF-A levels were strongly correlated with IMT in CKD patients and could be one factor that links CKD and CVD [1-5]. Therefore, there is a growing body of evidence implicating VEGF-A in CKD and CVD [6,7]. However, to date, there is no knowledge about the correlation between serum levels of VEGF-A and TIMP-1, proteinuria and atherosclerosis in patients with early stages of CKD and DN. Further Transforming Growth Factor-β1 (TGF-β1) may stimulate VEGF-A via an activated protein kinase – dependent pathway. In chronic non-inflammatory nephritis serum levels of TIMP-1 and VEGF-A remain still controversial [4-7]. Our patients were in the early stages of renal disease (CKD stages I and II) and were distinctly divided, between subjects with DN, which is considered an non- inflammatory leading cause of end-stage kidney disease with proteinuria, and those without kidney disease.

Conclusion: Our study suggests that serum levels of VEGF-A and TIMP-1 might present independent risk factors of atherosclerosis and albuminuria, at least in the early stages of type II diabetic nephropathy to the progression of CKD.

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