Is there a relationship between plasma levels of soluble endoglin and cardiovascular alterations in patients with hypertension and diabetes mellitus?

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Abstract: Diabetic complications are of two types, short term complications and long term complications. Long term complications are diabetic microvascular complications and include retinopathy, nephropathy and neuropathy. Cardiovascular disease causes most of the excess morbidity and mortality in diabetes mellitus; adults with diabetes are at a 2- to 4-fold increased risk of cardiovascular events relative to those without diabetes. Diabetes mellitus is an independent risk factor for coronary artery disease, and the risk is markedly increased when hypertension is present. Endothelial dysfunction is a hallmark for vascular diseases, and is often regarded as a key early event in the development of atherosclerosis. **Endoglin,** also known as CD105, is co-receptor for members of the Transforming Growth Factor (TGF) - superfamily. Endoglin has been shown to interact with TGF-β receptor-2 and TGF β receptor-1, is highly expressed on vascular endothelial cells and is essential for vascular integrity. Endoglin plays an important role in the vascular system and cardiac embryogenesis. ***Objective:*** To investigate a possible relationship between endoglin and cardiovascular system in hypertensive and diabetic patients. ***Subjects & Methods:*** This study included 20 patients with type 2 diabetes, 20 patients with hypertension, 20 patients with type 2 diabetes & hypertension and 20 healthy subjects as control. All study population were subjected to thorough history taking , complete clinical examination, routine laboratory investigations, fundus examination, ECG, pulse wave velocity and plasma level of endoglin. ***Results:*** There was no significant statistical difference as regards age and gender among the studied groups. Statistical analysis showed significant increase in left ventricular measurements and pulse wave velocity in all patient groups compared with control (*p*.value 0.001). The statistical analysis of laboratory findings showed significant increase in fasting blood glucose & HbA1c in groups I and II than in groups III and IV, and significant increase in proteinuria, serum cholesterol, triglycerides, and plasma level of endoglin in all patient groups compared with control (*p*.value 0.008). It was found that endoglin was higher in uncontrolled diabetic patients than in controlled patients (*p*.value 0.041). It was also higher in extreme dipper hypertension than in non dipper and in non dipper than in dipper (*p*.value 0.049). Also endoglin was higher in patients with proteinuria and renal impairment than in patients with proteinuria alone (0.041). ***Conclusion:*** Our data suggested that endoglin could be a useful marker in early detection of cardiovascular complications in diabetic and hypertensive patients and may have a role in its management.

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1. Introduction

The term diabetes mellitus describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion and/or insulin action [(1)]. Diabetic complications are of two types, short term complications and long term complications [(2)]. Long term complications are diabetic microvascular complications and include retinopathy, nephropathy and neuropathy.

Cardiovascular disease (CVD) causes most of the excess morbidity and mortality in diabetes mellitus [(3)]. The overlap between hypertension and diabetes substantially increases the risk of ischemic cerebrovascular disease, retinopathy, and sexual dysfunction. Hypertension is approximately twice as common in persons with diabetes relative to those without diabetes [(4)].

There are four major molecular signaling mechanisms activated by hyperglycemia in endotheial cells. These include: Activation of protein kinase C (PKC), increased hexosamine pathway flux, increased advanced glycation end product formation (AGE), and increased polyol pathway flux [(5)].

The clinical manifestations of CVD include coronary artery disease (CAD), cerebrovascular disease, and peripheral vascular disease [(6)]. The underlying disease mechanism is accelerated atherosclerosis [(7)]. In addition to atheroma formation, the combination of increased coagulability and impaired fibrinolysis likely

further increases the risk of vascular occlusion and cardiovascular events in type 2 diabetes [8]. Diabetes increases the risk that an individual will develop CVD which is the primary cause of death in people with either type 1 or type 2 diabetes [9].

The endothelium normally provides a non-thrombogenic surface because it contains heparin sulfate which acts as a cofactor for activating antithrombin III, a protease that cleaves several factors in the coagulation cascade [10].

Endothelial dysfunction, is a hallmark for vascular diseases, and is often regarded as a key early event in the development of atherosclerosis. Impaired endothelial function is often seen in patients with CAD, diabetes mellitus, hypertension, hypercholesterolemia, as well as in smokers [11].

Endothelial dysfunction has also been shown to be predictive of future adverse cardiovascular events. One of the main mechanisms of endothelial dysfunction is the diminishing of nitric oxide (NO) & increase in reactive oxygen species, which can impair nitric oxide production and activity via several mechanisms [12].

Endothelial function cannot be measured directly in humans. Estimates of different types of endothelial dysfunction may be obtained indirectly by measuring endothelium-dependent vasodilatation, plasma levels of endothelium-derived regulatory proteins and, possibly, microalbuminuria [13].

Many studies have concluded that common risk factors explain at most a small part of the association between microalbuminuria and atherothrombosis [14, 15]. Other mechanisms must therefore be at work, which may include severe generalized endothelial dysfunction [16] and chronic low-grade inflammation [17].

Endothelial dysfunction indicated by impaired endothelium -dependent vasodilatation and increased plasma concentrations of markers of endothelial dysfunction is common in early and otherwise uncomplicated type 2 diabetes. Endothelial dysfunction, inflammation and urinary albumin excretion in Type 2 diabetes are progressive and closely interrelated [18].

Endoglin is type I integral membrane glycoprotein that may have roles in hematopoiesis, cardiovascular development, and angiogenesis. Endoglin has a disulfide-linked extracellular region, and a short, constitutively phosphorylated cytoplasmic tail [19]. It is encoded by ENG gene, located on chromosome 9: base pairs 130, 577, 290 to 130, 617 & 046 [20].

Endoglin and Activin Like Kinase-1 (ALK-1) proteins are specific endothelial receptors of the transforming growth factor - ß (TGF-ß) superfamily that are essential for vascular integrity. Genetic studies in mice and humans have revealed the pivotal role of TGF-ß signaling during angiogenesis [21]. Through binding to the TGF-ß type II receptor, TGF-ß can activate two distinct type I receptors (ALK1 and ALK5) in endothelial cells, each one leading to opposite effects on endothelial cell proliferation and migration[20]. Endoglin plays a pivotal role in the balance of ALK1 and ALK5 signaling to regulate endothelial cell proliferation in response to TGF- ß [22].

Endoglin is highly expressed on vascular endothelial cells, chondrocytes, and syncytiotrophoblasts of full term placenta. It is also found on monocytes, erythroid precursors, and a subpopulation of hematopoietic stem cells. Although its function remains elusive, levels of a circulating soluble form of Endoglin are elevated in patients with atherosclerosis and certain cancers including breast, colorectal, and myeloid malignancies [23-27].

Endoglin altered expression in association with cardiac defects further highlights its importance in normal cardiac embryogenesis and morphogenesis [28].

Mutations in the endoglin gene have been shown to be responsible for Hereditary Haemorrhagic Telangiectasia (HHT), or Rendu-Osler-Weber syndrome. This condition leads to frequent nose bleeds, telangiectases on skin and mucosa and may cause arteriovenous malformations in different organs including brain, lung, and liver [21].

Endoglin levels have been found to be elevated in pregnant women who subsequently develop preeclampsia [29].

Relevant to diabetic nephropathy, endoglin, expressed in vascular endothelial and smooth muscle cells, fibroblasts, and mesangial cells, negatively regulates extracellular matrix *(ECM)* [30].

Increased serum endoglin levels were found in patients suffering from systemic sclerosis (SSc) and elevated pulmonary arterial pressure [31]. Increased expression in fibroblasts and endothelial cells has been demonstrated in SSc patients, suggesting that deregulating Eng expression and/or function may be related to the vascular manifestation of SSc [32].

The over-expression of CD105 on proliferating endothelial cells of the tumour vasculature suggested that CD105 might also represent a good target for the immunoscintigraphy of tumors [33].

Selected anti-CD105 monoclonal antibodies (mAb) significantly inhibit the proliferation of cultured human microvascular and macrovascular endothelial cells, thus supporting the notion that

CD105 is a promising vascular target to implement innovative antibody-based therapeutic strategies in human cancer [34].

2. Subjects and Methods:

Design and study population: Subjects included in the study are classified into the following: *Group I:* Type 2-diabetic patients (20 patients), *Group II:* Type 2 Diabetic and hypertensive patients (20 patients), *Group III:* hypertensive patients (20 patients) & *Group IV:* Healthy control persons (20 patients).

Variables: Data obtained included variables from the following domains: blood pressure, laboratory investigations including fasting blood glucose level, two hours postprandial blood glucose level, glycated hemoglobin (HBA1c), renal function tests, twenty four hours collection of urine for proteins, serum cholesterol and triglycerides, plasma levels of soluble endoglin, fundus examination of the retina, pulse wave velocity & determination of left ventricular hypertrophy by using an ECG. In addition, all of them were subjected to thorough history taking & complete clinical examination.

Determination of plasma Endoglin was done by quantitative sandwich enzyme immunoassay technique provided by ADIPO BIOSCIENCE (USA) Catalogue skoo697-01[35].

Statistical analyses:

Statistical presentation and analysis of this study was conducted, using the mean, standard deviation and chi-square test by SPSS V.16. Probability values of less than 0.05 were considered of statistical significance [36].

3. Results:

The demographic data of the twenty patients of group I showed that 11 (55%) were males and 9 (45%) females with a mean age of 60.1±7.15 years . The twenty patients of group II showed that 9 (45 %) were males and 11 (55%) females with a mean (± SD) age of 60.55 ± 6.1years. The twenty patients of group III showed that 10 (50 %) were males and 10 (50 %) were females with a mean (± SD) age of 59.35 ± 7.3 years. The twenty subjects of group IV showed that 10 (50 %) were males and 10 (50 %) were females with a mean (± SD) age of 60.4 ± 6.91 years. Comparison between all the studied groups as regard age and gender showed no statistically significant values in all analysis.

Statistical analysis showed significant increase left ventricular measurement and pulse wave velocity in all patient groups compared with control (*p*.value 0.001) (Tables 1 & 2).

The statistical analysis of laboratory findings showed significant increase in fasting blood glucose & HbA1c in groups I and II than in groups III and IV (Tables 3 & 4) and significant increase in proteinuria, serum cholesterol and triglycerides, and plasma level of endoglin in all patient groups compared with the control (p.value 0.008) (Tables 5- 8).

It was found that endoglin was higher in uncontrolled diabetic patients than in controlled patients (*p*.value 0.041) (Table 9).

Also endoglin was higher in patients with proteinuria and renal impairment than in patients with proteinuria alone (0.041) (Table 10).

Table (1): Comparison between the studied groups regarding pulse wave velocity.

Pulse Wave Velocity (m/sec)	Diabetic	Diabetic & HTN		HTN	Control
Mean	12.6	16		12.4	7.5
±SD	3.51	2.81		3.54	1.77
F. test	6.325				
p. value	0.001 *HS*				
Scheffe test					
Diabetic & diabetic HTN	Diabetic & HTN	Diabetic & Control	Diabetic HTN & HTN	Diabetic HTN & Control	HTN & Control
0.036S	0.963	0.002S	0.002S	0.001 *HS*	0.001 *HS*

m/sec: meter per second; p. value <0.05 (significant) (S), p. value <0.001 (highly significant) (HS).

Table (2): Comparison between the studied groups regarding left ventricular measurement.

LV measurement (mm)	Diabetic	Diabetic & HTN		HTN	Control
Mean	39.1	42.8		36	5.4
±SD	5.53	4.40		5.77	0.20
F. test	6.325				
p. value	0.001 *HS*				
Scheffe test					
Diabetic & Diabetic HTN	Diabetic & HTN	Diabetic & Control	Diabetic HTN & HTN	Diabetic HTN & Control	HTN & Control
0.041S	0.050S	0.001HS	0.022S	0.001 HS	0.001 HS

LV: Left ventricle

Table (3): Comparison between the studied groups regarding fasting blood glucose level.

Fasting Blood Glucose level (mg/dl)	Diabetic	Diabetic & HTN	HTN	Control
Mean	141.6	158.9	89.8	90.4
±SD	3.73	20.31	17.83	11.32
F.test	5.325			
p. value	0.008 *HS*			
Scheffe test				

Diabetic & Diabetic HTN	Diabetic & HTN	Diabetic & Control	Diabetic HTN & HTN	Diabetic HTN & Control	HTN & Control
0.041 *S*	0.001 *HS*	0.001 *HS*	0.001 *HS*	0.001 *HS*	0.996 *NS*

Table (4): Comparison between the studied groups regarding HbA1C

HBA1c (%)	Diabetic	Diabetic & HTN	HTN	Control
Mean	8.5	9.63	4.99	4.01
±SD	0.41	0.82	0.39	0.75
F.test	5.325			
p. value	0.041*S*			
Scheffe test				

Diabetic & Diabetic HTN	Diabetic & HTN	Diabetic & Control	Diabetic HTN & HTN	Diabetic HTN & Control	HTN & Control
0.996 *NS*	0.008 *S*	0.001*HS*	0.001 *HS*	0.001 *HS*	0.528

Table (5): Comparison between the studied groups regarding 24 hours protein in urine.

24 hours protein in urine (mg/24h)	Diabetic	Diabetic & HTN	HTN	Control
Mean	556.2	965.1	523.1	48.2
±SD	315.90	524.61	347.61	31.55
F.test	10.325			
p. value	0.001 *HS*			
Scheffe test				

Diabetic & Diabetic HTN	Diabetic & HTN	Diabetic & Control	Diabetic HTN & HTN	Diabetic HTN & Control	HTN & Control
0.001	0.252	0.001	0.001	0.001	0.001

Table (6): Comparison between the studied groups regarding serum cholesterol.

S.Ch. (mg/dl)	Diabetic	Diabetic & HTN	HTN	Control
Mean	267.5	283.7	278.5	136.5
±SD	85.28	82.88	101.30	21.11
F.test	4.203			
p. value	0.020 *S*			
Scheffe test				

Diabetic & Diabetic HTN	Diabetic & HTN	Diabetic & Control	Diabetic HTN & HTN	Diabetic HTN & Control	HTN & Control
0.014S	0.065	0.009 *S*	0.051	0.001 *HS*	0.001 *HS*

S.Ch: Serum cholesterol.

Table (7): Comparison between the studied groups regarding serum triglycerides.

S.TG. (mg/dl)	Diabetic	Diabetic & HTN	HTN	Control
Mean	154.6	162	144	100
±SD	56.31	49.3	54.31	26.20
F. test	6.325			
p. value	0.009S			
Scheffe test				

Diabetic & Diabetic HTN	Diabetic & HTN	Diabetic & Control	Diabetic HTN & HTN	Diabetic HTN & Control	HTN & Control
0.632	0.012 *S*	0.001 *HS*	0.035 *S*	0.001 *HS*	0.001 *HS*

S.TG: serum triglyceride.

Table (8): Comparison between the studied groups regarding plasma endoglin.

Plasma Endoglin (ng/dl)	Diabetic	Diabetic & HTN	HTN	Control
Mean	7.23	6.10	4.97	2.72
±SD	0.47	0.61	0.30	0.90
F.test	4.632			
p. value	0.001HS			
Scheffe test				

Diabetic & Diabetic HTN	Diabetic & HTN	Diabetic & Control	Diabetic HTN & HTN	Diabetic HTN & Control	HTN & Control
0.025 *S*	0.015 *S*	0.027 *S*	0.026 *S*	0.025 *S*	0.003 *S*

Table (9): Comparison between plasma endoglin in controlled and uncontrolled diabetes.

	Plasme Endoglin ng/dl	t. test	*p*. value
Controlled diabetes	4.97+0.36	2.325	0.041 *S*
Uncontrolled diabetes	7.60+1.21		

Table (10): Comparison between plasma endoglin in patients with proteinuria with and without renal impairment.

	Plasma Endoglin (ng/dl)	t. test	*p*. value
Endoglin and proteinuria with renal impairment	8.30 ± 0.99	2.625	0.041 *S*
Endoglin and proteinuria with no renal impairment	6.52 ± 0.53		
Endoglin and renal impairment without proteinuria	5.4 ± 0.4	1.546	0.2 *NS*

4. Discussion:

Diabetic complications are of two types, short term complications and long term complications [(2)]. Long term complications are diabetic microvascular complications and include retinopathy, nephropathy and neuropathy [(3)]. Cardiovascular disease causes most of the excess morbidity and mortality in diabetes mellitus [(3)].

Endothelial ysfunction, or the loss of proper endothelial function, is a hallmark for vascular diseases, and is often regarded as a key early event in the development of atherosclerosis. Impaired endothelial function is often seen in patients with coronary artery disease, diabetes mellitus, hypertension, hypercholesterolemia, as well as in smokers [(11)].

Endoglin, also known as CD105, is a 180 kDa homodimeric co-receptor for members of the TGF- β superfamily [(37)]. Endoglin has been shown to interact with TGF-β receptor 2 and TGF-β receptor 1, is highly expressed on vascular endothelial cells and is essential for vascular integrity [(21)].

Endoglin plays an important role in the vascular system and cardiac embryogenesis [(28)].

Gilbert et al. showed the relationship between placental ischemia, hypertension and alterations in angiogenic factors in the late gestation pregnant rat. They found that circulating sEng expression is increased in the serum and placenta of pregnant rats with ischemic placentas when compared to pregnant control rats with non-ischemic placentas [(29)].

The relevance of endoglin in the cardiovascular system is reflected by the fact that mutations in the endoglin gene cause a vascular disease called the Rendu-Osler-Weber syndrome or hereditary hemorrhagic telangiectasia [(38)].

Even if its functional role is not fully understood, several findings suggest for the involvement of CD105 in angiogenesis and vascular development, and in maintaining vessel wall integrity [(40)].

Our study showed that Sol-endoglin levels are higher in patients with diabetes who have increased levels of systolic blood pressure and as previously described, the impairment of endothelium dependent vasodilatation in patients with diabetes is due to the impaired NO bioavailability [(39)]. Endoglin expression and NO regulation are intimately related, as it had been demonstrated that endoglin plays a major role in regulating eNOS abundance and NO synthesis regulation based on two different mechanisms: First: endoglin regulates eNOS mRNA expression [(41)], second: the regulation of eNOS protein half-life and eNOS activity [(29)].

All the previous data showed endoglin is a component of the transforming growth factor beta (TGF-β) receptor complex present in endothelial cells that is involved in angiogenesis, cardiovascular development, and vascular homeostasis [(34)].

The role of endoglin in cardiovascular complication is emphasized by the study that showed serum levels of Eng in systemic sclerosis

patients with elevated pulmonary arterial pressure (SSc-sPAP) tended to be higher than in systemic sclerosis patients with normal pulmonary arterial pressure (SSc-normal sPAP) [31].

In our study, there is a positive correlation between endoglin levels and retionopathy. This was confirmed by ocular manifestations including conjunctival, retinal and choroidal telangiectasia in HHT [42].

Charytan D.M.*, HelfandA.M, Macdonald B.A *et al analyzed 216 individuals with various degrees of renal dysfunction and were unable to confirm an association between CKD and increases in the concentration of soluble endoglin [43]. They found, in fact, that patients with ESRD, the most severe form of renal dysfunction, had on average the lowest circulating concentration of soluble endoglin. The absence of an increase in soluble endoglin in patients with impaired renal function suggests that the increase in tissue concentrations of endoglin following renal injury is not accompanied by concomitant release of cellular endoglin into the circulation [43].

Our study showed that endoglin level was higher in patients with proteinuria and renal impairment than in patients with proteinuria alone.

In contrast to our study, ***Charytan D.M.*, HelfandA.M, Macdonald B.A *et al*** , another indicator of renal disease, was also not associated with circulating endoglin concentration in the subset of patients in whom albuminuria was measured [43].

Our study suggests that plasma soluble endoglin concentration could serve as an indicator of diabetes associated pathologies such as hypertension, endothelial dysfunction and cardiovascular risks. These results were in agreement with the study done by ***Blázquez-Medela A.M.***[44], the first study done in humans in 2010 which showed that plasma Sol-endoglin concentration could serve as an indicator of diabetes-associated pathologies such as hypertension, endothelial dysfunction and cardiovascular risks.

So our results showed that soluble endoglin plasma levels were significantly related to glycemia (fasting, post prandial blood glucose level and glycated hemoglobin), systolic blood pressure, also the circadian blood pressure pattern and the degree of left ventricular hypertrophy assessed by ECG.

Conclusion and Recommendations:

From the present study we conclude that endoglin could be a useful marker in early detection of cardiovascular complications in diabetic and hypertensive patients and may have a role in its management.

Other biomarkers for endothelial dysfunction should be included for comparison as a combination of biomarkers would give better sensitivity and specificity for early diagnosis of subclinical organ damage in patients with diabetes and hypertension and should be the matter of further study.

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