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# Serum Endothelin-1 Elevation in Diabetes. A Reflection of Pathophysiological Process or a Biomarker beyond Expectation?

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Endothelin or endothelium-derived constricting factor was first discovered by O'Brien et al. in 1987 as a potent vasoconstrictor protein from culture medium of bovine aortic and pulmonary endothelium. The culture medium was shown to cause aortic ring constriction *in vitro* and vasoconstriction when perfused into rabbit coronary arteries [1]. Concomitantly, Yanagisawa et al. isolated and sequenced the 21 amino acid endothelin, which modulates voltage dependent channel and is a potent vasoconstrictor protein that is 10 times more potent than norepinephrine [2].

Endothelin has 3 isoforms (ET -1, -2, and -3) with the most abundant being ET-1 and recognized as a major vasoconstrictor and also a neuropeptide [2,3]. Endothelin levels were found to be elevated in patient with renal insufficiency [4] and diabetes [5]; however, elevation of immunoreactive-endothelin could not be accounted for by changes in blood pressure, duration of diabetes and presence of kidney disease, or presence of retinopathy [5]. ET-1 has abundant expression in glomerular endothelial cells and tubular cells, and especially high level of expression, 10x higher, in the medullary collecting tubules [6]. Endothelin, as an autocrine and paracrine hormone, has a pivotal role in kidney damage in diabetic nephropathy. In particular, it has auto (self) and paracrine (nearby cells) self-inflicting effects, such as initiation of inflammation, podocyte loss and effacement, mesengial hypertrophy, damage to basement membrane, glomerulosclerosis, and tubulo-interstitial fibrosis and atrophy [7]. It has detrimental role leading to proteinuria and progression to end stage renal disease. ET-1 has 3 receptors ($ET_A$, $ET_B$, and $ET_C$), where $ET_A$ receptor is promoting the vasoconstrictor and mitogenic signals of ET-1, while $ET_B$ receptor acts as an endogenous antagonist, promoting vasodilatation through nitrous oxide, preventing inflammation and proliferation [7] and clearing ET-1.

Podocytes are active and mobile cells residing on the exterior surface of basement membrane in bowman capsule and function as a barrier/filter for proteins, stabilize capillary tuft, and involve in the turnover of basement membrane protein. Podocyte injuries are evident in glomeruloscelrosis and affected early on in diabetic and hypertensive kidney disease [7]. It is important and relevant that hyperglycemia causes release of ET-1 from endothelial cells[8].

The autocrine and paracrine effect of endothelin finally causes not only nephron destruction but also involves in tubular and renal interstitium damage in diabetic subjects [8].

In this issue of Int. J of Diabetes and Clinical Research, Arifur Rahman et al. presented a unique view of serum ET-1 level among rural women living in Bangladesh. This population based study demonstrated that prevalence of diabetes is 9.1% and the serum levels of endothelin-1 is elevated among diabetic subjects and once adjusted for age, ET-1 is found to have positive correlation with waist circumference, fasting blood glucose and high density lipoprtein-cholesterol (HDL-C). It is well know and documented that type 2 diabetes develops in much lower BMI individuals in South Asia when compared to the western population [9], and more correlates with visceral fat as measured by waist to hip ratio in rural Bangladesh [10]. So it might not be surprising to find lack of correlation between BMI and ET-1, but rather correlated with waist circumference among diabetic and non diabetic subjects.

Taking into account ET-1's role in diabetic nephropathy, it seems conceivable to examine the value of serum ET-1 levels in predicting diabetic nephropathy during the early diagnosis of diabetes mellitus rather than relying on the level of microalbuminuria. Although helpful for the detection of early kidney disease, we are all well aware that once microalbuminuria is developed, despite use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 10 percent of subjects still progress and dies with chronic end stage renal disease [11] as well an increased risk of death from cardiovascular heart disease [12]. Considering the basic deleterious effect of hyperglycemia in initiating proteinuria and progression of diabetic kidney disease, and knowing the extreme cost of the rising epidemic of diabetes, any biomarker that would predict diabetic nephropathy before the development of microalbuminuria is of great value. However, elevated level of ET-1 in early diabetes may turn out to be more of scientific curiosity, rather a tool for real prevention of diabetic nephropathy before any detectable urine abnormality. No doubt that further research is warranted [13].

The multifaceted aspect of systemic vasoconstriction and hypertension involves many hormones, factors and receptors causing or opposing vasoconstriction with complex interplay to maintain homeostasis and hemodynamics. Thus, it is in my opinion that to expect only one factor to be responsible for vasoconstriction measured (ET-1) would not have an association with both systolic and diastolic hypertension, owing to multiple other factors playing and opposing each other, rather a balance of those hormones and known factors (e.g. nitrous oxide) would determine this association.

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