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# Syndecan-1 Levels In Type2 Diabetes Mellitus

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***Abstract:*** *Diabetes mellitus is the leading cause of end- stage renal disease (ESRD) worldwide. Diabetic nephropathy is characterised by early hemodynamic changes which finally leads to renal insufficiency. Syndecans are type1 transmembrane heparan sulphate proteoglycans (HSPGs) that have important roles during development, wound healing and tumour progression by controlling cell proliferation, differentiation and migration. Our aim was to compare and correlate the levels of serum Syndecan-1 in type2 diabetes mellitus with microalbuminuria and without microalbuminuria. Blood samples were collected from 200 patients out of which 100 patients were without microalbuminuria and 100 patients were with microalbuminuria. Serum Syndecan-1 levels were analysed by ELISA method. Syndecan-1 levels were significantly higher in patients with microalbuminuria (147.30±80.27) compared to patients without microalbuminuria (59.38 ± 27.79). There was a positive correlation between syndecan-1 and patients with microalbuminuria(r=0.570, p<0.001). The findings showed that increased serum levels of syndecan-1 in type2 diabetes mellitus suggest it may have a role in pathogenesis of diabetic nephropathy.*

***Key words*:***syndecan-1, diabetic nephropathy, extracellular matrix, microalbuminuria, ELISA.*

## I. Introduction

Diabetic nephropathy (DN) is a serious complication in diabetes. Major typical morphological changes are the result of changes in the extracellular matrix (ECM). Thus, basement membranes are thickened and the glomerular mesangial matrix and the tubulointerstitial space are expanded, due to increased amounts of ECM. One important ECM component, the proteoglycans (PGs), shows a complex pattern of changes in Diabetic nephropathy (DN)[1,2].Syndecans are type1 transmembrane heparan sulfate proteoglycans (HSPGs) that have important roles during development, wound healing and tumour progression [3].Studies show microalbuminuria is a strong predictor of diabetic nephropathy[4].During our literature survey, information on syndecan-1 in relation to type2 diabetes was less. There were limited studies on correlation between microalbuminuria and syndecan-1.Our aim was to study whether syndecan-1 can be an early indicator for diabetic nephropathy.

## II. Materials and Methods

The study group comprised of 200 subjects with type 2 diabetes aged 35-70 years.One group comprised 100 subjects diagnosed with type 2 diabetes mellitus with microalbuminuria and a second group of 100 subjects diagnosed with type 2 diabetes mellitus without microalbuminuria. The control group comprised 50 normal healthy individuals. Subjects with hypertension, chronic renal failure with non-diabetic cause, cardiovascular disease, liver disease and infectious disease were excluded from the study. . Ethical clearance was obtained from Central Ethical Committee of the University.

Fasting blood samples were collected from all subjects and following biochemical parameters were analysed Fasting plasma glucose (FPS), Urea, Creatinine, HbA1c, Cholesterol, Triglycerides, HDL cholesterol LDL cholesterol and VLDL cholesterol. Biochemical analysis was done on Hitachi 902 analyser using kits supplied by Roche, Germany. Syndecan-1 was measured using commercially available enzyme- linked immunoabsorbent (ELISA) kit (Diaclone, France). Urine samples were analysed for microalbuminuria using commercially available immunoturbidometric method assay kits from Transasia using semiautomatic analyser.

Statistical analysis

Data analysis was done using Statistical Package for Social Science(SPSS).Data were expressed as mean ±SD for normally distributed data and as median and range for skewed data.t-test was used to compare continuous variables. Mann-Whitney test was done for group wise comparison. A *p* value less than 0.05 was considered to be statistically significant.

## III. Results

Our study included a total number of 200 type2 diabetic subjects. 100 subjects were without microalbuminuria, out of which 58% were male and 42% were females. The 100 patients with microalbuminuria comprised 57 % males and 43% females. The mean age of the subjects with microalbuminuria was 55.28±8.10 years and the mean age in subjects without microalbuminuria was 49.47±10.21 years. The mean duration of

diabetes in subjects with microalbuminuria was 8.81±5.61 years whereas the duration of diabetes in subjects without microalbuminuria was 2.17±1.81 years which showed a significant long duration of diabetes in subjects with microalbuminuria compared to subjects without microalbuminuria

The mean fasting plasma glucose and HbA1c in subjects without microalbuminuria were 182.86 ± 58.07 mg/dl and 8.99 ± 1.33% and with microalbuminuria were 203.14 ± 57.13 mg/dl and 9.22 ± 1.53% respectively. The mean serum urea and creatinine level were 24.50 ± 5.53mg/dl and 0.78 ± 0.16 mg/dl in diabetic subjects without microalbuminuria and 28.15 ± 6.15mg/dl and 0.88 ± 0.24mg/dl in subjects with microalbuminuria. The above mentioned biochemical parameters were found to be more significantly altered in diabetic subjects with microalbuminuria compared to diabetic subjects without microalbuminuria and control.

Triglycerides and VLDL cholesterol were also significantly higher in diabetic subjects with microalbuminuria compared to diabetic subjects without microalbuminuria and control . On the other hand HDL cholesterol was found to be significantly lower in subjects with microalbuminuria.

The serum Syndecan-1 levels were significantly higher in subjects with microalbuminuria (147.30±80.22) ng/ml compared to those without microalbuminuria (59.38 ± 27.79) ng/ml and control subjects (40.72±19.11) ng/ml.

**Table 1**Comparison of age, biochemical parameters and serum Syndecan-1 levels between control and type 2 diabetic subjects**.**

| PARAMETER | CONTROL | DIABETIC | |
|---|---|---|---|
| | | Without microalbuminuria | With microalbuminuria |
| n | 50 | 100 | 100 |
| Age(years) | 29.74±8.94 | 49.47±10.21$^{a**}$ | 55.28±8.10$^{(b, c)**}$ |
| FBS (mg/dl) | 77.08±4.46 | 182.86± 58.07$^{a**}$ | 203.14± 57.13$^{(b ,c)**}$ |
| Urea (mg/dl) | 22.58±3.16 | 24.50 ±5.53$^{a**}$ | 28.15 ± 6.15$^{(b ,c)**}$ |
| Creatinine (mg/dl) | 0.54±0.14 | 0.78 ±0.16$^{a**}$ | 0.88 ± 0.24$^{(b, c)**}$ |
| Total Cholesterol (mg/dl) | 195.52±35.71 | 191.94± 47.30 | 195.11±48.63 |
| Triglycerides (mg/dl) | 86.78±32.71 | 137.55± 47.54$^{a**}$ | 151.07± 55.43$^{b**}$ |
| HDL Cholesterol(mg/dl) | 48.62±9.86 | 43.72± 9.04$^{a**}$ | 39.93± 6.94$^{(b, c)**}$ |
| LDL Cholesterol (mg/dl) | 128.42±31.45 | 120.37±41.26 | 123.34± 41.91 |
| VLDL Cholesterol (mg/dl) | 17.56±6.44 | 27.10± 9.55$^{a**}$ | 30.17± 10.96$^{b**,c*}$ |
| HbA1c (%) | NA | 8.99±1.33 | 9.22± 1.53 $^{c*}$ |
| Syndecan-1 (ng/ml) | 40.72±19.11 | 59.38 ± 27.79$^{a**}$ | 147.30 ± 80.22$^{(b, c)**}$ |

Data are mean ± SD, **p<0.001,*p<0.05
a= comparison between normal and type2 diabetic subjects without microalbuminuria
b=comparison between normal and type2 diabetic subjects with microalbuminuria
c=comparison between type2 diabetic subjects with and without microalbuminuria

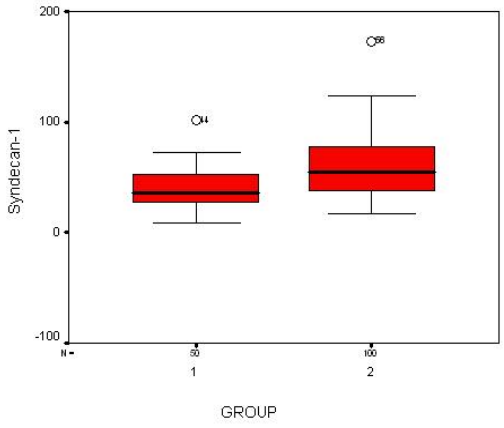


**Figure1**: Syndecan-1 concentration in control (group-1) and in diabetic subjects without microalbuminuria (group-2).

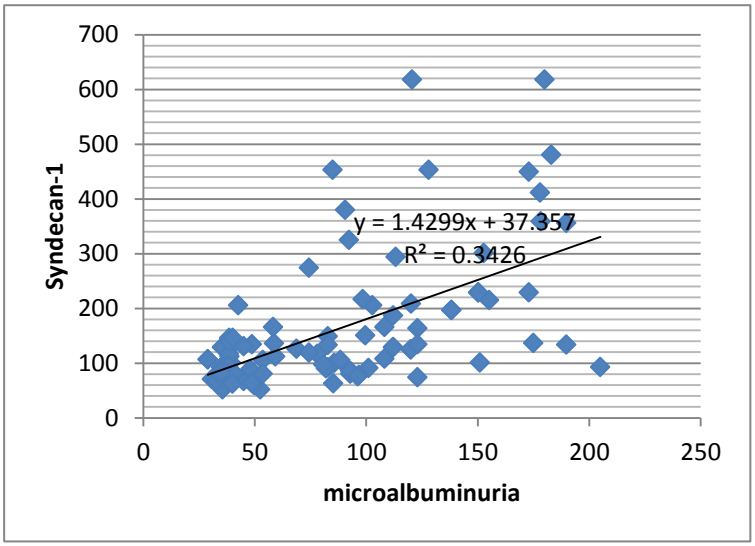


**Figure2**: Correlation between Syndecan-1 and levels of microalbuminuria in type 2 diabetic subjects with microalbuminuria.

r= 0.570, p< 0.001

## IV. Discussion

In the present study serum from subjects with type 2diabetes was analysed for Syndecan-1. The results showed that the concentration of Syndecan-1 in serum was elevated in the subjects with microalbuminuria.

Syndecans are type I transmembrane HSPGs, with an extracellular domain that contains several consensus sequences for GAG attachment, a single hydrophobic transmembrane domain, and a short C-terminal cytoplasmic domain [5].

There are 4 types of sydecan: syndecan-1 (syndecan), syndecan-2 (fibroglycan), syndecan-3 (N-syndecan), and syndecan-4 (ryudocan). The cytoplasmic and transmembrane domains provide anchorage to the protein, while the ectodomain has O-glycan structures terminating in heparan sulphate or chondroitin sulphate [6, 7].

In syndecan-1 the glycosaminoglycan attachment sites occur in two distinct clusters, one near the N-terminus and the other near the membrane-attachment site, separated by a proline-and-threonine-rich spacer[8].

Syndecan-1, -2, and -4 are expressed by vascular endothelial cells, predominantly at the basolateral surfaces.

Only syndecan-1 and -4 are expressed in the kidney. Syndecan-1 is present at the basolateral surface of renal epithelial cells, and syndecan-4 is predominantly present on endothelial cells [6,9and10].

The GBM plays a key role in glomerular filtration by providing mechanical support to the glomerular capillary wall and by regulating the access of plasma molecules to the tubular system of the nephron. The permeability through the glomerular capillary wall for a given molecule is highly dependent on its size, shape, and charge. The charge-selective permeability of the GBM is largely determined by the electrostatic properties of heparansulfate within the GBM [11, 12].

The extracellular matrix (ECM) in the basement membrane of the kidney glomeruli is very important for the filtration properties. Structural changes in mesangium and basement matrix are related to proteinuria and hypertension since it leads to progression of clinical diabetic nephropathy and kidney failure. Proteoglycans are found in ECM and on cell surfaces which help in kidney filtration. Recent studies have shown that serum concentrations of the proteoglycan syndecan-1 is higher in subjects with type 1 diabetes and microalbuminuria than in those without microalbuminuria [13] suggesting that it is a potential serum marker for kidney changes.

Previous studies have shown association of hyperglycaemia, diabetes, endothelial dysfunction and microalbuminuria. The endothelial cells are the first to be affected by hyperglycaemia [14]. The components of endothelial glycocalyx are shed in response to inflammation. Removing syndecan-1 from the cell coat may affect permeability of endothelium, leading to leakage of proteins [15, 16]. In diabetic patients, increased urinary heparansulphate (HS) has also been reported [17, 18].

Hence, loss of syndecan-1 may be one of the earlier events in the renal damage in diabetes mellitus. The results of our study support this assumption as increase serum syndecan-1 levels were observed even in absence of microalbuminuria.

## V. Conclusions

In the present study findings show that serum syndecan-1 levels increased in type 2 diabetes mellitus with microalbuminuria and also without microalbuminuria compared to normal subjects.Syndecan-1 plays an important role in kidney damage by affecting the permeability of endothelium in type 2 diabetes mellitus. Hence serum Syndecan-1 may be earlier marker compared to microalbuminuria.

Proteoglycans(PGs)such as Syndecan-1can be potential markers which can increase our understanding in the process, leading to kidney failure and possibly detect subjects with high risk of progression to kidney disease in diabetic patients and which may facilitate early treatment.

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