Research article

# Extracellular E-selectin levels and its association with insulin resistance: Putative role of E-selectin as a biomarker of oxidative stress linked vascular manifestations in diabetic nephropathy

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## ABSTRACT

**Introduction and aim:** E-selectin, a cell adhesion molecule depicting nexus with oxidative stress in hyperglycemia has been documented in several other clinical conditions. The present study centers around the putative role of E-selectin as a biomarker of diabetic nephropathy linked to oxidative stress.

**Materials and Methods:** 150 type 2 diabetics in the age group of 35 - 50 years were classified into three groups, comprising 50 each, based on albuminuria. Fifty healthy age and gender matched individuals constituted the control. Extracellular E-selectin and Insulin were quantitated appropriately. Measurement of HbA1c and microalbumin were also enabled. Routine biochemistry analyses were undertaken, based on established automated procedures. The study was initiated only following approval accorded by the Institutional Ethics Committee.

**Results:** E-selectin levels in serum were significantly associated with Urine Albumin-to-Creatinine Ratio (UACR) and Insulin resistance in the light of estimated Glomerular Filtration Rate.

**Conclusion:** E-selectin levels could thus act as a putative biomarker of diabetic nephropathy linked to oxidative stress, as observed in insulin resistant type 2 diabetes.

**Keywords:** E-selectin; type 2 diabetes mellitus (T2DM); glycemic control; insulin resistance (IR); HOMA-IR; nephropathy.

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disorder which has particularly been associated, in recent years, with a pronounced increase in developing countries (1). It must be said that aggressive intervention in patients with type 2 diabetes mellitus would eventually result in an attenuated risk of complications that include among others microangiopathy and cardiovascular diseases.

Evaluation of albuminuria and glomerular filtration rate (GFR) has become the mainstay, as recommended by the KDIGO: Kidney Disease Improving Global Outcomes CKD Work Group. The evaluation is with reference to end stage renal disease (ESRD) which is presently on the rise globally and hence it is imperative to monitor the progression of diabetic nephropathy (2). Careful monitoring of albuminuria is advocated in routine practice in diabetes, and it is underlined that GFR declines in both type 1 and type 2 diabetes (3). In such instances, however, it is not pragmatic to predict the natural course of diabetic nephropathy based on albuminuria and eGFR (4). It is with this perspective that the study was planned with a view to documenting the role of E-selectin as an objective biomarker, in combination with the conventional parameters, namely albuminuria and eGFR. This would fortify the prediction of vascular outcome as observed in diabetic nephropathy, thereby acquiring distinct relevance in clinical endocrinology and evidence-based medicine.

Acute hyperglycemia has a nexus with circulating proinflammatory cytokines, namely tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (5). E-selectin is considered as an indirect marker of oxidative stress that could be attributed to hyperglycemia (6). Evidence points to the fact that elevated E-selectin is associated with coronary artery disease (CAD) (7). Oxidative stress and insulin resistance mediate pathways related to the inhibition of insulin signal and dysregulation of adipocytokines. These points acquire cardinal relevance (8). It must be stated in all fairness that very few reports are available from South India pertaining to our present attempt, namely with reference to E-selectin as a biochemical marker of imminent nephropathy in type 2 diabetes. Hence, we decided to track the extracellular E-selectin levels and its association with microalbuminuria, insulin resistance and eGFR with a view towards the identification of an objective and reliable biomarker for impending diabetic nephropathy.

## SUBJECTS AND METHODS

One hundred and fifty Type 2 diabetics comprising both genders with a documentation of Diabetes mellitus spanning five years or more and aged between 35-50 years were enrolled for the study at a tertiary health care set up in South India. They were managed on rational oral hypoglycemic agents. The study was begun only following the due approval accorded by the Research Advisory Committee of the institute where the first author had enrolled himself as a doctoral candidate and following clearance obtained from the Institutional Ethics Committee (IEC). All procedures were performed in accordance with Helsinki declaration of 1975. The groups were divided as follows: 50 subjects with normoalbuminuria(i.e., <30 mg/g creatinine), and an equal number of subjects with microalbuminuria (i.e.,30–299 mg/g creatinine), and macroalbuminuria (i.e., ≥300 mg/g creatinine). Patients who were on insulin therapy, and such of those subjects who had consumed tobacco/ smokeless tobacco and alcohol were promptly excluded. Patients who were suffering from infections of the urinary tract and those who had possessed a history of miscellaneous renal complaints and inflammatory disorders were also excluded from the study. Patients afflicted with malignancy, impaired hepatic function, thyroid abnormalities, cardiovascular and peripheral vascular disease were also promptly excluded. 50 healthy age and gender matched subjects constituted the controls.

### Control and Test groups

Group-1 - Fifty healthy age, gender matched subjects were selected (controls).
Group-2 - Fifty patients with normoalbuminuria (<30 mg/g creatinine)
Group-3 - Fifty patients with microalbuminuria(30–299 mg/g creatinine)
Group-4 - Fifty patients with macroalbuminuria(≥300 mg/g creatinine)

### Biochemical analysis

Eight milliliters of venous blood samples were withdrawn from the subjects, following an overnight fast. Aseptic conditions were upheld. Blood glucose in the post absorptive/fasting state (FBS) was quantitated without any delay and an autoanalyzer was employed for the purpose. Blood samples (venous) were appropriately stored at −80 °C for quantitating the levels of insulin and E-selectin. First (morning) urine samples were collected in sterile containers and microalbumin as well as creatinine were duly quantitated.

Blood Glucose in the fasting state (FBS) was estimated by the Glucose Oxidase-Peroxidase method (enzymatic). Glycated Hemoglobin (HbA1C), a measure of glycemic control, was quantitated by immunoturbidimetry. Urinary Microalbumin was assessed based on a turbilatex method and urinary creatinine was quantitated by Jaffe's kinetic method. The routine biochemical analyses were performed on ERBA EM-200 fully automated analyzer, whereas (venous) insulin in the fasting state and E-selectin were estimated by employing ELISA kits provided by M/S Diametra, Spello, Italy and Boster Biotech Ltd, USA respectively. LISA SCAN(ERBA) ELISA reader was used.

### Insulin resistance

### Homeostatic model assessment for insulin resistance model (HOMA-IR)

HOMA-IR, a surrogate marker of insulin resistance (IR) was calculated taking into consideration fasting glucose and insulin values using the formula (9,10). HOMA – IR = Fasting insulin (μU/ml) X fasting glucose (mg/dL)/405.

HOMA –BETA was calculated using;
HOMA-beta=(360 × fasting insulin (μU/mL))/(fasting glucose (mg/dl)-63) (11,12).

Quantitative Insulin-Sensitivity Check Index(QUICKI) was estimated according to (13) using the formula :
QUICKI = 1/ [log (Fasting Insulin in μU/ml) + log (Fasting Glucose in mg/dl)].

### Estimated Glomerular Filtration rate (eGFR)

eGFR was calculated by CKD-EPI (Chronic Kidney Disease Epidemiology) formula (14,15).

**Table 1**: CKD-EPI (Chronic Kidney Disease Epidemiology) formula

| Gender | Serum Creatinine(Scr) | eGFR |
|---|---|---|
| Females | ≤0.7mg/dl | $144 \times (Scr/0.7)^{-329} \times (0.993)^{age}$ |
| | >0.7mg/dl | $144 \times (Scr/0.7)^{-1.209} \times (0.993)^{age}$ |
| Males | ≤0.9mg/dl | $141 \times (Scr/0.9)^{-0.411} \times (0.993)^{age}$ |
| | >0.9mg/dl | $141 \times (Scr/0.9)^{-1.209} \times (0.993)^{age}$ |

Statistical analysis of the obtained data was enabled through SPSS software, version-22.

## RESULTS

The results pertaining to the mean and standard deviation of the data belonging to the various study groups in terms of the biochemical parameters are depicted in Table 2. Whereas Table 3 depicts the comparison of all the groups for determining statistical significance of the various parameters when examined with control vs normoalbuminuric, control vs microalbuminuric, control vs macroalbuminuric,

Normoalbuminuric vs microalbuminuric,Normo- vs macroalbuminuric. albuminuric vs macroalbuminuric, microalbuminuric

**Table 2:** Comparison of the biochemical parameters pertaining to glycemic control, insulin sensitivity, insulin resistance and E -selectin in the various groups

| S.No. | Parameters | Control (n=50) Group- 1 | | Normoalbuminuric T2 DM (n=50) Group-2 | | Microalbuminuric T2 DM (n=50) Group 3 | | Macroalbuminuric T2 DM (n=50) Group-4 | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean | S.D. | Mean | S.D. | Mean | S.D. | Mean | S.D. |
| 1. | UACR (in mg/gm of creatinine) | 19.1 | 1.94 | 23.27 | 3.4 | 132.51 | 38.57 | 430.08 | 55.4 |
| 2. | FBS mg/dl | 83.96 | 5.36 | 135.12 | 16.29 | 149.5 | 27.98 | 252.4 | 33 |
| 3. | HbA1c% | 5.76 | 0.55 | 7.75 | 0.84 | 8.45 | 0.99 | 9.53 | 0.49 |
| 4. | Insulin(µU/ml) | 6.66 | 0.58 | 10.67 | 2.65 | 15.3 | 3.18 | 18 | 2.27 |
| 5. | HOMA-IR | 1.38 | 0.14 | 3.59 | 1.07 | 5.69 | 1.68 | 11.25 | 2.13 |
| 6. | HOMA –β% | 122.62 | 35.26 | 55.69 | 18.8 | 46.35 | 17.88 | 35.39 | 8.17 |
| 7. | QUICKI | 0.36 | 0.01 | 0.32 | 0.01 | 0.3 | 0.02 | 0.27 | 0.01 |
| 8. | eGFR(CKD–EPI Formula) | 116.01 | 16.68 | 108.98 | 29.69 | 85.9 | 24.11 | 79.38 | 21.79 |
| 9.. | E-selectin (ng/ml) | 23.12 | 3.81 | 35.38 | 6.46 | 67.74 | 8.69 | 91.76 | 7.31 |

UACR-Urine Albumin-to-Creatinine Ratio; FBS-Fasting blood sugar(glucose); HbA1c- Glycated Hemoglobin; HOMA-IR-Homeostatic Model Assessment for Insulin Resistance; HOMA-β- Homeostatic model assessment – Beta; QUICKI-Quantitative Insulin-Sensitivity Check Index; eGFR- Estimated Glomerular Filtration Rate

**Table 3**: Comparison among the various groups using ANOVA for determining statistical Significance of the biochemical parameters

| S. No. | **Parameters** | **Comparison of Groups for 'values** | | | | | | **All Groups ANOVA** |
|---|---|---|---|---|---|---|---|---|
| | | **Group 1 vs 2** | **Group 1 vs 3** | **Group 1 vs 4** | **Group 2 vs 3** | **Group 2 vs 4** | Group3 vs 4 | |
| 1. | UACR (in mg/gm of creatinine) | 0.0074 | 0.0013 | 0.0087 | 0.0021 | 0.0010 | 0.0038 | 0.0025 |
| 2. | FBS mg/dl | 0.0026 | 0.0046 | 0.0053 | 0.0023 | 0.0032 | 0.0027 | 0.0018 |
| 3. | HbA1c% | 0.0080 | 0.0012 | 0.0078 | 0.0002 | 0.0043 | 0.0019 | 0.0033 |
| 4. | Insulin µIu/ml | 0.0014 | 0.0035 | 0.0051 | 0.0048 | 0.0013 | 0.0041 | 0.0073 |
| 5. | HOMA-IR | 0.0011 | 0.0020 | 0.0038 | 0.0075 | 0.0012 | 0.0013 | 0.0041 |
| 6. | HOMA -β% | 0.0021 | 0.0056 | 0.0047 | 0.0058 | 0.0041 | 0.0072 | 0.0022 |
| 7. | QUICKI | 0.0056 | 0.0063 | 0.0035 | 0.0039 | 0.0027 | 0.0043 | 0.0034 |
| 8. | eGFR (CKD–EPI) Formula) | 0.0056 | 0.0023 | 0.0014 | 0.0031 | 0.0029 | 0.0045 | 0.0024 |
| 9. | E-selectin ng/ml | 0.0057 | 0.0023 | 0.0014 | 0.0029 | 0.0016 | 0.0039 | 0.0011 |

1: Control; 2:Normoalbuminuric T2 DM; 3:Microalbuminuric T2DM; 4:Macroalbuminuric T2DM

P<0.05 – Significant and P<0.001 – highly significant

**Table 4:** Correlation between E-selectin and other biochemical parameters (UACR, HOMA-IR, HOMA-β, QUICKI, eGFR)

| **Parameter** | **Correlation Coefficient(r)** |
|---|---|
| UACR | 0.674** |
| HOMA-IR | 0.687** |
| HOMA-β | -0.664** |
| QUICKI | -0.732** |
| eGFR | -0.527** |

UACR-Urine Albumin-to-Creatinine Ratio; HOMA-IR- Homeostatic Model Assessment for Insulin Resistance; HOMA-β- Homeostatic model assessment – Beta; QUICKI-Quantitative Insulin-Sensitivity Check Index; eGFR-Estimated Glomerular Filtration Rate**Correlation is significant at the 0.01 level (2-tailed).

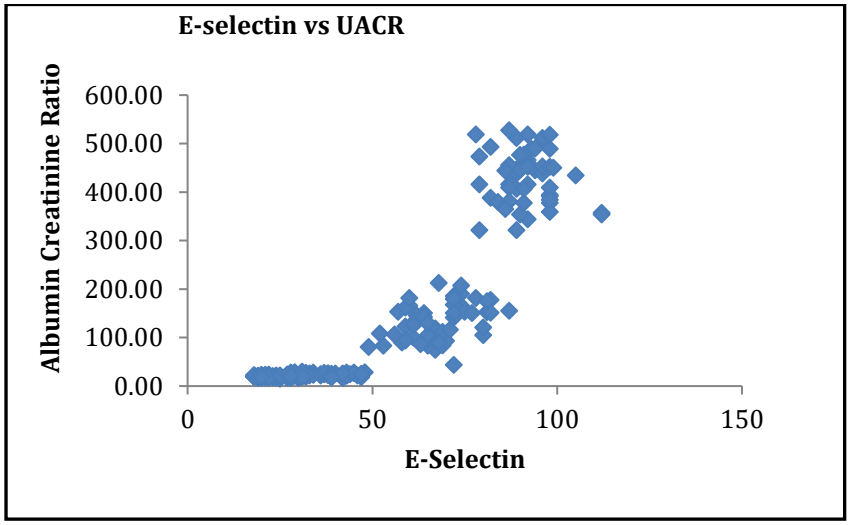


**Fig. 1:** Scatter plot of E-selectin vs albumin creatinine ratio

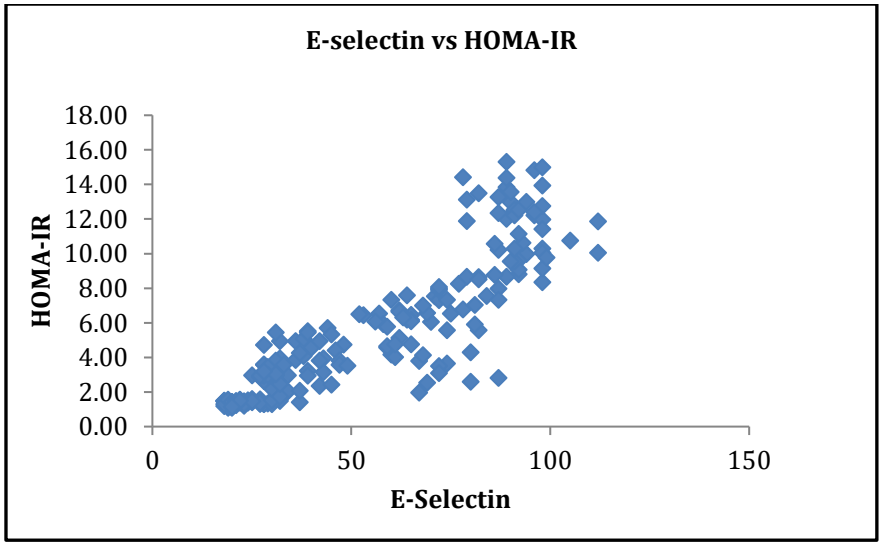


**Fig. 2:** Scatter plot of E-selectin vs HOMA-IR

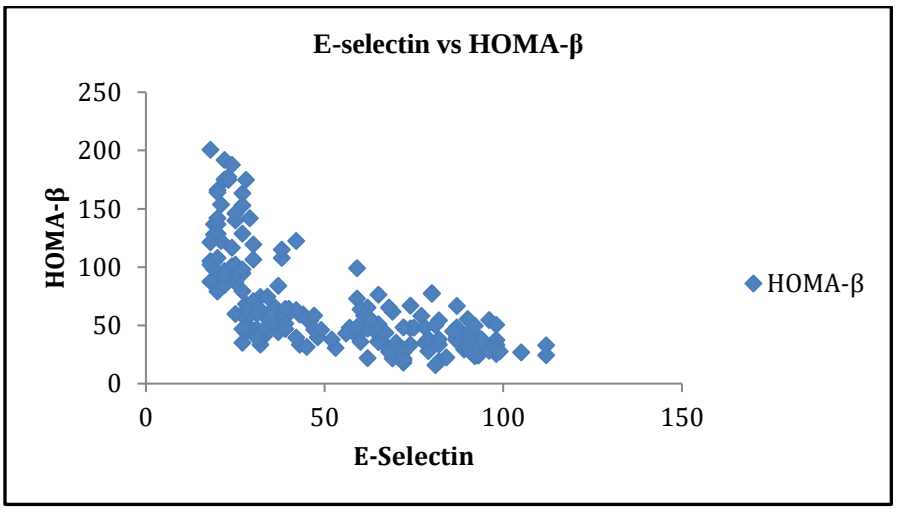


**Fig. 3:** Scatter plot of E-selectin vs HOMA-β

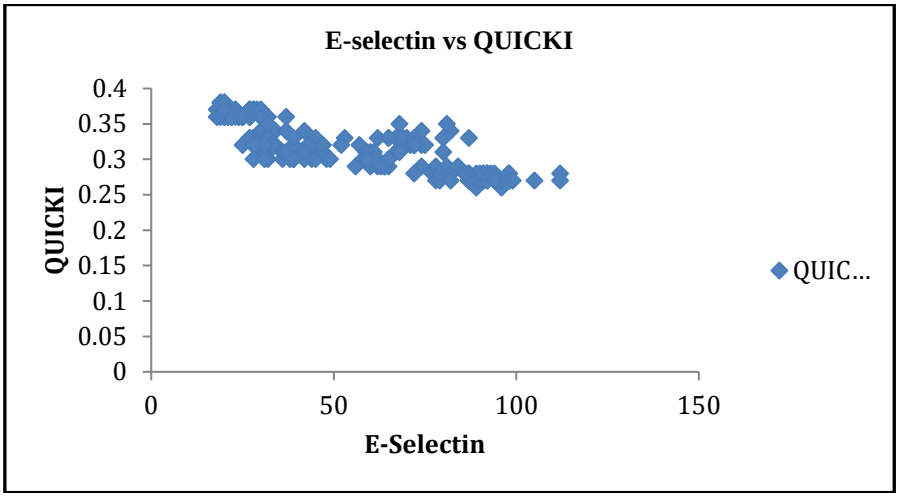


**Fig.4:** Scatter plot of E-selectin vs QUICKI

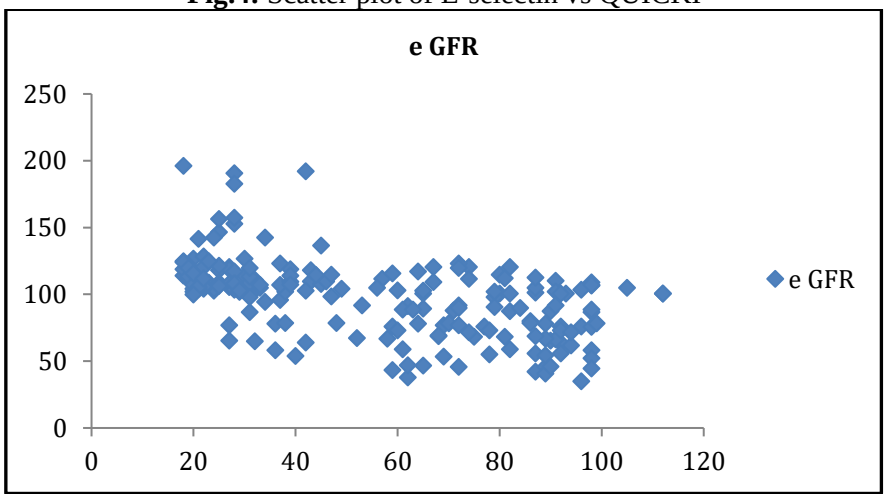


**Fig. 5:** Scatter plot of E-Selectin vs eGFR

Table 4 depicts the correlation among E-selectin with UACR, HOMA-IR, HOMA-BETA QUICKI and eGFR. From the results shown in Table 4, it is revealed that E-selectin correlates significantly with UACR, thereby upholding the diagnostic significance of E-selectin with reference to the nephropathy consequent to the progression of insulin resistance observed in T2DM. Marked correlation was noticed between E-selectin and insulin sensitivity, insulin resistance, as measured through the surrogate markers.

The scatter plots (Fig. 1-5) which indicate the association between the two variables and scatter plot matrix show all the pairwise scatter plots for the several variables. In the scatter plot, if the variables tend to increase and decrease together, the association is expressed as positive. If one variable tends to decrease as the other variable increases, the association is expressed as negative.

## DISCUSSION

Oxidative stress is emphatically perceived in type 2 diabetes, and this appears to signal the imminent cardiovascular disease as well as other complications emanating from insulin resistance. The major point of concern is attributable to the imbalance between the prooxidants and antioxidants that culminates in unfavorable outcomes including cellular damage. Free radicals are considered as highly reactive chemical species that are characterized by a lone electron in the outer orbital. This leads to the assault on the polyunsaturated fatty acids, synonymous with lipid peroxidation. Lipid peroxidation is a biochemical process that may be appropriately defined as an autocatalytic process mediated by free radicals whereby poly-unsaturated fatty acids localized in the cell membranes undergo breakdown to yield lower carbon containing compounds. The products of lipid peroxidation including malondialdehyde (MDA) are increased in T2DM patients (16). In the present study, we observed that E-selectin levels were significantly increased in T2DM subjects that could be attributed to oxidative stress. Significant difference was observed in macro and microalbuminuric diabetic patients in comparison to normoalbuminuric diabetic patients. Moreover, in the present study, we have made a sincere attempt to document E-selectin as a single objective marker of oxidative stress. In view of this, we have eschewed other conventional markers of oxidative stress.

It is well documented that the biochemical events, namely hyperglycemia and oxidative stress lead to inflammation and insulin resistance is regarded as central to this phenomenon (17). Furthermore, an

enhancement in the expression of adipokines and macrophage inflammatory proteins are being increasingly implicated in macrophage infiltration, as occurring mainly in the adipose tissue. This culminates in the intense production of reactive oxygen species (ROS) as well as cytokines that mediate the process of inflammation (18). The cascading effect involving adipose tissue dysfunction is linked to adipocyte-specific deletion of nuclear factor E2-related factor 2 (Nrf2), a redox-sensitive transcription factor binding to the promoter region of genes that code for antioxidant enzymes (19).

A pronounced association between E-selectin and other parameters, namely UACR, HbA1C,HOMA-IR, HOMA BETA, QUICKI and eGFR was observed in our study. The results pertaining to ROC analysis also reveal the usefulness of E-selectin as a reliable predictor of impending nephropathy, a common complication observed in insulin resistant type 2 diabetics. However, the results of the ROC analysis are not depicted here and hence would not form a component of further discussion.

Oxidative stress continues to be the focus of interest that is mainly related to cardinal biochemical pathways involved in the onset and progression of diabetic micro and macro vascular complications (20). Several important cellular events are mediated through ROS. These include the typical inflammatory response, extracellular matrix accumulation, endothelial aberrations, and abnormal angiogenesis (21). Several key factors including transcription factors are also implicated in this regard. Furthermore, studies undertaken in the recent past have also demonstrated that E-selectin is increasingly manifest in tissues inflicted by atherosclerosis (23). It is hence believed that oxidative stress is not only implicated in diabetes-induced cardiovascular dysfunction, but also could contribute significantly to the progression of diabetic nephropathy (24). This warrants neutralization of oxidative damage that could open newer vistas in the prevention and management of diabetic complications. Thus, E-selectin levels could prove to be a putative and novel biomarker of nephropathy in type 2 diabetic patients, especially at a juncture when very few simple, economically viable, specific, and sensitive predictors of insulin resistance induced diabetic nephropathy are available in the existing armamentarium.

### Limitation of the study

The study did not include other conventional markers of oxidative stress in type 2 Diabetes mellitus.

## CONCLUSION

It is concluded that the biochemical assessment of E-selectin could predict the progression of nephropathy, a major complication in type 2 Diabetes mellitus. Serum E-selectin could be used as a single putative biomarker of impending nephropathy in insulin resistant type 2 Diabetes mellitus, in the light of albuminuria and e-GFR thereby signaling the arrival of newer perspectives in the management of renal complications related to insulin resistance. We hereby advocate that larger and comprehensive multi centric prospective studies are required to reaffirm our claim.

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## CONFLICT OF INTEREST

The authors declare that the present study is not bound by any conflict of interest whatsoever.

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