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Research Article

Cell Adhesion Molecules E-Selectin, ICAM-1, VCAM-1 In Prediabetes: An Early Indicator Of Cardiovascular Disease.

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ABSTRACT

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Background: Despite the association between increased soluble adhesion molecules (CAMs) such as E-Selectin, Vascular cell adhesion molecules (VCAM-1) and Intracellular cell Adhesion molecules (ICAM-1) and clinically overt diabetes mellitus, it is not clear whether increased concentrations of soluble adhesion molecules are present in patients with prediabetes. **Material and methods:** A cross sectional studied was carried out. Blood sample of each participant was collected and tested for blood glucose levels and depending on that results participants were divided into 3 groups i.e. controls, pre diabetic and diabetic type 2.

Results: The levels of E-Selectin in prediabetes was 57.59 ± 1.57 ng/ml and type 2 diabetes was 61.09 ± 0.93 ng/ml compared to controls 5.04 ± 0.34 ng/ml. p value was < 0.05 which shows significance. Plasma levels of ICAM-1 in prediabetes was

260.07 ± 2.37 ng/ml and type 2 diabetes was 267.30 ± 4.99 ng/ml compared to controls 253.37 ± 14.28 ng/ml. p value was < 0.05 which shows significance. Plasma levels of VCAM-1 in prediabetes was 479.91 ± 55.82 ng/ml and type 2 diabetes was 538.96 ± 42.47 ng/ml compared to controls 469.04 ± 16.04 ng/ml. p value was < 0.05 which shows significance.

Conclusion: The study concluded that the onset of endothelial dysfunction and increased oxidative stress manifest early in disease progression and are detectable as changes in biomarker levels are already at the prediabetic state. Well nourishment, education, diet counselling and supplementation knowledge for elevated threat group of diabetic persons is strongly recommended.

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INTRODUCTION:

Diabetes is a worldwide health problem affecting more than 6% of the world population and its prevalence is estimated to increase to about 552 million by 2030. However these numbers do not include the amount of people with prediabetes, of which 90% are unaware of their situation.^[1,2] Diabetes, which is defined as a fasting blood glucose level (FBGL) of greater than 6.9 mmol/L is associated with extensive organ dysfunction including diabetic retinopathy, kidney disease and cardiovascular disease (CVD), gastrointestinal disturbance, sexual dysfunction and diabetic neuropathy. The fatal macro vascular complications account for the majority of deaths among diabetic patients.^[3-6]

Adhesion of leucocytes to arterial endothelial cells and subsequent transendothelial infiltration is thought to be an important step in the development of atherosclerosis. This process depends on a group of receptors and binding proteins, i.e. adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM1), and E-selectin [7-9]. Recent studies have reported the presence of high serum concentrations of soluble adhesion molecules (ICAM-1, VCAM-1, and E-selectin) in patients with type 2 diabetes [10- 13]. Moreover, the levels of E-selectin correlate positively with the degree of hyperglycemia [14–16]. Despite the association between increased soluble adhesion molecules and clinically overt diabetes mellitus, it is not clear whether increased concentrations of soluble adhesion molecules are present in patients with prediabetes. The aim of present study is to evaluate CAMs level in prediabetes and type 2 diabetes patients and find the association between CAMs and other variables.

MATERIALS AND METHODS

This study was done in the Department of Biochemistry, People's College of Medical Science and Research Center (PCMS and RC), Centre for Scientific Research and Development (CSRD),

People's University, Bhopal. This is a cross-sectional descriptive study includes 250 type II diabetes patients, 265 prediabetes persons, and 290 controls during the period June 2017 to April 2019. The study was approved by Institutional Ethics committee with approval number IEC 2016/28 dated 15/09/2016 & written informed consent was taken from all participants after applying inclusion and exclusion criteria. Socio demographic data were collected by a self-designed questionnaire.

Inclusion Criteria for Prediabetes According to American Diabetes Association

- Age: between 18 years and 60 years
- Fasting blood sugar level: 100 mg to 125 mg
- HbA1c: 5.7% to 6.4%
- Postprandial blood sugar level (after 2 hours of 75 g oral glucose): 140 to 199 mg/dL

Exclusion Criteria for Prediabetes

- Age more than 60 years and age less than 18
- Diagnosed diabetic patients
- Pregnant women
- HIV-positive patients

Inclusion Criteria for Type II Diabetes According to American Diabetes Association

- Age: between 18 years and 60 years
- Known case of type II diabetes (1–5 years)

Exclusion Criteria for Type II Diabetes

- Age not more than 60 years and age less than 18
- Pregnant women, HIV-positive patients
- Prolonged diabetes (>5 years)
- Patients on statin therapy

The study protocol was approved by Institutional Ethics Committee. All the participants were screened for age, gender, fasting glucose level, postprandial glucose level, HbA1c, family history, and any medication history. Prediabetic cases were included and excluded with the help of physician, Department of Medicine, PCMS and RC. Biochemical parameters investigations are as follows (Table 1):

Table No.1 Methods of Biochemical parameters

Sr. No.	Biochemical parameters	Method
1	Blood Glucose	GOD-POD Method ^[15]
2	Cholesterol	CHOD-POD Method ^[16]
3	TG	Glycerol phosphate oxidase-Peroxidase (GPO-POD Method) ^[17]
4	HDL	directly enzymatic colorimetric Quantitative determination. ^[18]
5	LDL	Friedewald equation assuming that total cholesterol is composed primarily. ^[19]
6	VLDL	By calculation ^[20]
7	E-Selectin	ELISA Method ^[21]
8	ICAM-1	ELISA method ^[22]
9	VCAM-1	ELISA method ^[23]

Statistical Analysis

SPSS (Chicago, IL, USA) version 21 was used for statistical analysis of data. Descriptive statistics for quantitative variables were presented as mean \pm SD. Analysis of variance (ANOVA) was used to compare between the three groups, $P < 0.05$.

RESULTS:

Table No. 2: Distribution of Demographic characteristics, Lipid profile and Cell adhesion molecules in Controls and Patients

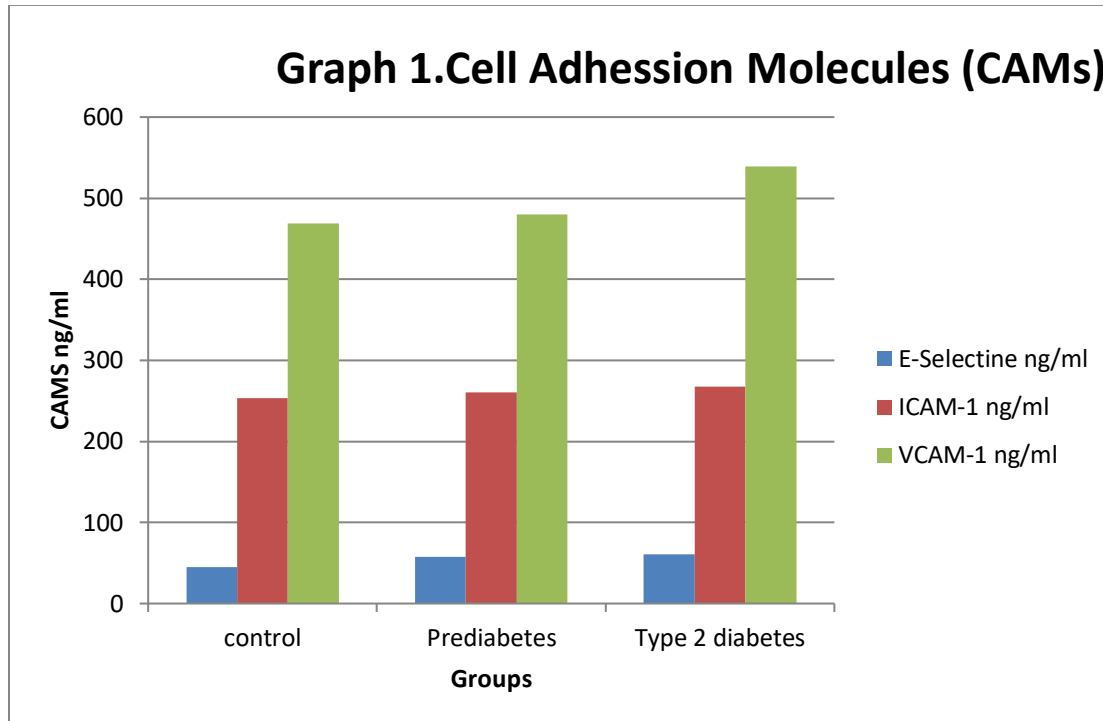
Demographic characteristics

Parameters	Control (n=290)	Prediabetes (n=270)	Type 2 Diabetes (n=255)	p-value
	Mean \pm SD	Mean \pm SD	Mean \pm SD	
Age	37.78 \pm 10.49	45.58 \pm 9.07	43.04 \pm 10.96	<0.001
Sex(M/F)	159/131	168/102	148/107	--
Cholesterol mg/dl	170.81 \pm 22.34	243.34 \pm 20.03	311.92 \pm 60.86	< 0.001
TG mg/dl	91.11 \pm 16.59	169.89 \pm 14.33	191.32 \pm 40.96	< 0.001
HDL mg/dl	42.19 \pm 5.82	31.10 \pm 4.33	27.97 \pm 4.96	< 0.001
LDL mg/dl	109.06 \pm 18.61	172.09 \pm 20.03	236.96 \pm 56.27	< 0.001
VLDL mg/dl	19.04 \pm 4.83	36.07 \pm 7.04	47.56 \pm 10.45	< 0.001
TG/HDL	2.19 \pm 0.49	5.58 \pm 1.00	7.23 \pm 2.22	< 0.05
LDL/HDL	2.61 \pm 0.56	5.74 \pm 1.08	8.94 \pm 3.43	< 0.001
E-Selectin (ng/ml)	45.04 \pm 0.34	57.59 \pm 1.57	61.09 \pm 0.93	< 0.05
ICAM-1 (ng/ml)	253.37 \pm 14.28	260.07 \pm 2.37	267.30 \pm 4.99	< 0.05
VCAM-1 (ng/ml)	469.04 \pm 16.04	479.91 \pm 55.82	538.96 \pm 42.47	< 0.001

P<0.05 - Statistically significance , P<0.01 - statistically highly significance

Table no 2 shows distribution of the demographic characteristics, lipid profile and Endothelial dysfunction markers in patients and controls. There

was significant difference observed in age, lipid profile and endothelial dysfunction markers between patients and controls.



The levels of E-Selectin in prediabetes was 57.59 ± 1.57 ng/ml and type 2 diabetes was 61.09 ± 0.93 ng/ml compared to controls 45.04 ± 0.34 ng/ml . p value was < 0.05 which shows significance. Plasma levels of ICAM-1 in prediabetes was 260.07 ± 2.37 ng/ml and type 2 diabetes was 267.30 ± 4.99 ng/ml compared to controls 253.37 ± 14.28 ng/ml. p value was < 0.05 which shows significance. Plasma levels of VCAM-1 in prediabetes was 479.91 ± 55.82 ng/ml and type 2 diabetes was 538.96 ± 42.47 ng/ml compared to controls 469.04 ± 16.04 ng/ml. p value was < 0.05 which shows significance. (Table. No.2 & graph no.1) Mean score of cholesterol in prediabetes was 243.34 ± 20.03 and type 2 diabetes was 311.92 ± 60.86 compared to controls 170.81 ± 22.34 . p value was <0.001 which was significant. Mean score of Triglyceride in prediabetes was 169.89 ± 14.33 and type 2 diabetes was 191.32 ± 40.96 compared to controls 91.11 ± 16.59 . p value was <0.001 which was significance. Mean score of HDL in prediabetes was 31.10 ± 4.33 and type 2 diabetes was 27.97 ± 4.96 compared to controls 42.19 ± 5.82 . p value was

<0.001 which was significant. Mean score of LDL in prediabetes was 172.09 ± 20.03 and type 2 diabetes was 236.96 ± 56.27 compared to controls. 109.06 ± 18.61 . p value was <0.001 which was significant. Mean score of VLDL in prediabetes was 36.07 ± 7.04 and type 2 diabetes was 47.56 ± 10.45 compared to controls 19.04 ± 4.83 . p value was <0.001 which was significant. Mean score of TG/HDL in prediabetes was 5.58 ± 1.00 and type 2 diabetes was 7.23 ± 2.22 compared to controls 2.19 ± 0.49 . p value was < 0.05 which was significant. Mean score of LDL/HDL in prediabetes was 5.74 ± 1.08 and type 2 diabetes was 8.94 ± 3.43 compared to controls 2.61 ± 0.56 . p value was < 0.001 which was significant. (Table. No.2)

DISCUSSION:

Endothelial cells isolated from diabetic patients have been found to express higher amounts of E-Selectin, VCAM-1 than ICAM-1 when stimulated by cytokines in a high-glucose-mediated microenvironment [24] Elevated levels of ICAM-1 have been reported in the diabetic retina in the early stages of retinopathy, suggesting that ICAM-1

mediates the adhesion and transendothelial migration of circulating leukocytes through the retinal vessel walls, one of the earliest pathological changes observed in the course of the development of diabetic retinopathy.^[25] Meigs et al reported that endothelial dysfunction markers E-Selectin, ICAM-1, VCAM-1 predict non-insulin dependent diabetes among women.^[26] Cominacini L et al supported the role of endothelial dysfunction in the pathogenesis of non-insulin dependent diabetes.^[16] Elhadd T.A et al suggested the involvement of E-selectin in the diabetic angiopathic process. E-selectin may act as a precursor for smooth muscle proliferation. The underlying mechanisms for increased rate of cardiovascular morbidity and mortality among diabetic patients are not elicited, however elevated markers of systemic inflammation and endothelial dysfunction are associated with excess visceral adiposity.^[27] Furthermore Rubio-Guerra AF et al suggested that ICAM-1 and VCAM-1 are markers associated, and correlated with the degree of atherosclerosis in type-2 diabetic patients.^[28] Our study now extends this to the prediabetes stage and confirms the results of Gokulakrishnan K et al. This is consistent with our findings, in which elevated levels of soluble CAMs were observed in the early stages of diabetic complications. Excess CAMs may be localized on sites of inflammation, such as microvessels, and thus, in the late stages, their levels could be decreased or diminished in the circulation.^[29] Similarly Matsumoto K et al demonstrated raised concentrations of E-selectin in Japanese patients with IGT with rise insulin concentration. This may be associated with a premature atherogenesis.^[30] The results of present study, suggests that increased E-Selectin, ICAM-1, and VAM-1 contribute to development of endothelial dysfunction such as atherosclerosis due to pediatrics.

CONCLUSION:

The results showed that the onset of endothelial dysfunction and increased oxidative stress manifest early in disease progression and are detectable as changes in CAMs (E-Selectin, ICAM-1, VCAM-1) levels are already at the prediabetic state. These findings not only prove once more, that prediabetes is a clinical state that needs to be taken seriously since it is the precursor of diabetes, but much more

importantly offer reliable tools for early detection of diabetes development and the associated complications like CVD in prevention screenings. Well nourishment, education, diet counselling and supplementation knowledge for elevated threat group of diabetic persons is strongly recommended.

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