



Impact of glycaemia, dyslipidemia and anxiety level on oxidative stress in prediabetic and diabetic patients

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Article History:

Received on: 12.05.2019

Revised on: 20.08.2019

Accepted on: 25.08.2019

Keywords:Dyslipidemia,
Glycaemia,
Oxidative stress,
Prediabetes**ABSTRACT**

Diabetes is one of the growing health crises. The current study was conducted to analyze the impact of glycaemia, dyslipidemia and anxiety level on oxidative stress in prediabetic and diabetic subjects. This cross-sectional study comprised of 140 subjects. Based on ADA criteria, subjects were divided into diabetic patients (n= 54) and pre-diabetic patients (n=44). Forty-two healthy subjects with normal fasting blood glucose level were served as a control group. Anthropometric measurements and blood pressures were measured using standard procedures. The biochemical parameters for measuring oxidative stress, blood glucose levels and lipid profile were estimated. Anxiety level was measured using the STAI questionnaire. The serum malondialdehyde (MDA) levels (nmol /ml) were significantly higher in pre-diabetes (3.14 ± 0.42) and diabetes mellitus (3.43 ± 0.78) compared to normal controls (2.26 ± 1.08). The superoxide dismutase (SOD) activity (U/ml) were higher in diabetes (11.35 ± 3.51) and pre-diabetic subjects (8.55 ± 2.50) compared to healthy subjects (8.11 ± 4.11). MDA had a significant positive correlation with fasting blood sugar (FBS), Glycosylated hemoglobin (HbA1c), waist to hip ratio and waist circumference. SOD also had a significant correlation with FBS, HbA1c, waist circumference, waist to hip ratio and body mass index. The present study confirmed that diabetic and prediabetic patients are suffered from more oxidative stress than nondiabetic subjects and it is influenced by their glycemic status and abdominal obesity which is leading to the progression of the disease. Dyslipidemia and anxiety levels didn't mark influence on oxidative stress in prediabetic and diabetic patients.

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ISSN: 0975-7538

DOI: <https://doi.org/10.26452/ijrps.v10i4.1635>

Production and Hosted by

IJRPS | <https://ijrps.com>

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INTRODUCTION

Diabetes mellitus is one of the leading universal health crises of the 21st century. Among the worldwide population, 425 million people and 352.1 million people are estimated to have diabetes and impaired glucose tolerance, respectively. Prediabetes or impaired fasting glucose is midway between normal glucose level and diabetes diagnostic levels ([International Diabetes Federation, 2017](#)). Prediabetes is also associated with central obesity, dyslipidemia and hypertension ([American Diabetes Association, 2018](#)). According to ICMR-INDIAB study, the whole prevalence of diabetes mellitus in all 15 states of India was 7.3% and prediabetes was 10.3% ([Anjana et al., 2017](#)).

Oxidative stress is the equilibrium between generation and elimination of reactive oxygen species (ROS). In healthy conditions, cellular antioxidant enzymes are responsible for the regulation of reactive oxygen species productions (Tangvarasittichai, 2015). Because of the unique molecular structure, lipids are more vulnerable to oxidation. Malondialdehyde (MDA) is produced through peroxidation of polyunsaturated fatty acids and it is atherogenic (Ho *et al.*, 2013).

There are several mechanisms involved in the initiation of oxidative stress in increased blood glucose levels includes hyperactivity of hexosamine pathway, augmented transport of glucose via polyol pathway and increased production of advanced glycation end products (AGEs) within the cell (Brownlee, 2005). Several studies also reported higher oxidative stress and disturbance of antioxidant defense systems in subjects with varying glucose metabolism (Su *et al.*, 2008; Bandeira *et al.*, 2012).

Dyslipidemia is always associated with diabetes and it is the main cause of atherosclerosis. It is manifested as lipid triad which includes the presence of small dense, LDL (sdLDL), low levels of high-density lipoprotein (HDL) and increased triglycerides (Grundy, 1998; Taskinen, 2003; Ginsberg *et al.*, 2006). Studies in humans have also demonstrated increased MDA with progressive hyperlipidemia (Yang *et al.*, 2008). Studies also reported that induction of acute hyperlipidemia increases the oxidative stress marker (Lopes, 2003).

Recent studies have identified a robust association between anxiety and diabetes. It is reported that a high prevalence of anxiety symptoms in diabetic patients (Rajput *et al.*, 2016; Sun *et al.*, 2016; Atasoy *et al.*, 2013). Studies also suggest that individuals with anxiety are deficient in antioxidants, indicative of increased oxidative stress (Grases *et al.*, 2014). Studies in rodents reported that anxiety-like behaviour is influenced by oxidative stress (Salim *et al.*, 2010).

Most of the previous studies about oxidative stress in diabetes examined the above concepts separately. So in the current study, we evaluated the impact of glycemic status, dyslipidemia and anxiety levels on oxidative stress in nondiabetic, prediabetic and diabetic subjects.

MATERIALS AND METHODS

This cross-sectional study was carried among employees of Little Flower Hospital and Research Center, Angamaly. Institutional ethics committee clearance was obtained before the commencement

of the study. A screening camp was conducted to identify the subjects by using FPG according to ADA criteria (American Diabetes Association, 2018). All the participants provided written informed consent. Subjects with serious morbid diseases (infection, liver or kidney dysfunction, stroke, myocardial infarction, major surgery, malabsorption) pregnant or lactating mothers, chronic smokers and alcoholics, secondary diabetes, mental health problems or taking vitamin supplements were excluded from the study. A total of 140 subjects have participated in the present study.

Anthropometric indices included weight, height, hip and waist circumferences. Waist to hip ratio (WHR) and body mass index (BMI) were also calculated. Blood pressure (BP) was measured with a mercury sphygmomanometer using standard recommended procedure. Blood collection was carried out after twelve hours of fasting. The fasting plasma glucose and HbA1c levels were estimated by glucose oxidase-peroxidase and immunoturbidimetric method, respectively. The total cholesterol, triglycerides and HDL were estimated in fully automated clinical chemistry analyzer by the diagnostic kit method. Low-density lipoprotein and very-low-density lipoprotein were computed using friedwalds equation.

For measurement of superoxide dismutase (SOD) and MDA, samples were kept cooled and centrifuged for 10 minutes at 4°C and 4000 rpm. The collected serum was stored at -20°C and analyses were performed within one week. The concentration of SOD and MDA were determined by spectrophotometric method. The SOD activity was measured by using Marklund and Marklund protocol (Marklund and Marklund, 1974). The MDA levels were measured using Beuge and Aust method (Buege and Aust, 1978).

The level of anxiety was measured by the Malayalam adaptation of Spielberger State-Trait Anxiety Inventory (STAI) (Alice, 2003). The questionnaire consists of two forms: one is used to measure state anxiety and the other one is for measuring trait anxiety. Each scale includes of 18 statements and is rated on a 4-point scale (not at all, somewhat, moderately so, very much so). The minimum and maximum scores of the STAI on both subscales are 18 and 72 respectively.

Statistical analysis

Descriptive statistics were used to assess the baseline characteristics of the data. The quantitative variables were expressed as mean \pm SD. The comparisons of parameters between the groups were carried out using one-way ANOVA. Karl Pearson cor-

Table 1: Baseline parameters and anthropometric measurements of studied subjects

Variable	Non-diabetic (n= 42)	Prediabetic (n=44)	Diabetic (n=54)
Age (years)	47.50±9.59	49.82±9.57	55.39±6.34
BMI (Kg/m ²)	24.79±3.53	26.30±3.44	26.88±3.74
WC	88.52±5.94	95.14±9.27	95.54±7.49
WHR	0.94±.03	0.96±.02	0.97±0.03
SBP (mmHg)	126.43±15.07	131.86±15.24	136.70±15.60
DBP (mmHg)	80.29±7.16	81.68±6.37	82.22±8.18

Values are expressed as mean ± SD. BMI- body mass index, WC-waist circumference, WHR-waist to hip ratio, SBP- systolic blood pressure, DBP- diastolic blood pressure

Table 2: Comparison of biochemical parameters, oxidative and antioxidant parameters and anxiety levels among groups

Variable	Non-diabetic n= 42	Prediabetic n=44	Diabetic n=54	P value
FBS(mg/dl)	90.17±7.18	110.80±7.92	143.69±37.87	.000*
HbA1c %	5.22±.24	5.79±.32	7.32±1.02	.000*
TC(mg/dl)	199.02±40.83	211.07±55.91	186.94±36.26	.031*
HDL(mg/dl)	42.38±8.30	45.11±9.80	42.41±7.21	.211
LDL(mg/dl)	130.29±38.39	135.07±45.54	118.19±33.73	.090
VLDL(mg/dl)	27.79±12.35	28.61±16.88	26.17±11.69	.666
TC/HDL	4.81±1.02	4.77±1.07	4.46±.83	.153
State anxiety	46.26±3.04	44.55±3.11	45.52±3.71	.060
Trait anxiety	49.00±5.14	45.32±3.91	45.52±5.10	.000*

Values are expressed as Mean ± SD. One-way ANOVA. FBS - Fasting blood sugar, HbA1c - Glycated haemoglobin, TC - total cholesterol, HDL- high-density lipoprotein, LDL - low-density lipoprotein, VLDL - very-low-density lipoprotein, MDA - malondialdehyde, SOD - superoxide dismutase. *-statistically significant

Table 3: The correlations of clinical and biochemical parameters with oxidative stress markers in the studied subjects

Variable	MDA		SOD	
	R value	P value	R value	P value
WC	.178	.031*	.269	.001*
BMI	.123	.146	.194	.021*
WHR	.242	.004*	.161	.049*
SBP	.111	.192	.043	.617
DBP	.032	.710	-.056	.511
FBS	.285	.001*	.279	.001*
HbA1c	.375	.000*	.299	.000*
TC	.071	.405	-.085	.318
HDL	.046	.587	-.014	.866
LDL	.036	.669	-.114	.182
VLDL	.071	.403	.054	.529
TC/HDL	.021	.806	-.104	.219
State anxiety	-.026	.758	.053	.537
Trait anxiety	-.092	.280	-.104	.222

WC-waist circumference, BMI- body mass index, WHR-waist to hip ratio, SBP-systolic blood pressure, DBP- diastolic blood pressure, FBS- fasting blood sugar, HbA1c- glycated hemoglobin, TC- total cholesterol, HDL-high density lipoprotein, LDL- low density lipoprotein, VLDL- very low density lipoprotein, MDA- malondialdehyde, SOD- superoxide dismutase. *-statistically significant

relation coefficient was used to analyze the correlation between parameters. A p-value of < 0.05 was considered statistically significant. Statistical package for social sciences (SPSS) version 20 was used to perform all statistical analyses.

RESULTS AND DISCUSSION

The subjects of this study consisted of 140 individuals aged 30-60 years with type 2 DM patients, prediabetic and healthy subjects. Of this, 62 were males, and 78 were females. The characterization of the study subjects was displayed in Table 1. This shows that the resting systolic and diastolic BP was higher in diabetic and prediabetic groups than the healthy controls. Diabetic and prediabetic subjects had significantly higher waist circumference, BMI and WHR as compared to healthy controls.

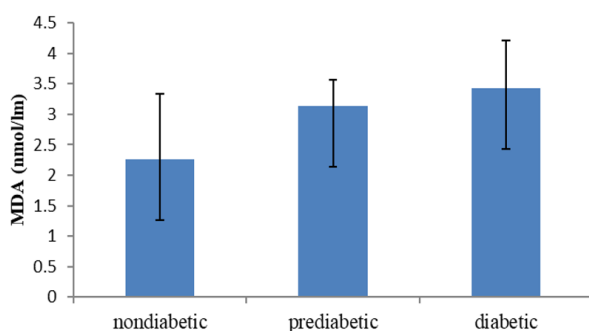


Figure 1: Serum levels of malondialdehyde (nmol/ml) in nondiabetic, prediabetic and diabetic patients. Results are expressed as mean \pm SD. MDA : malondialdehyde

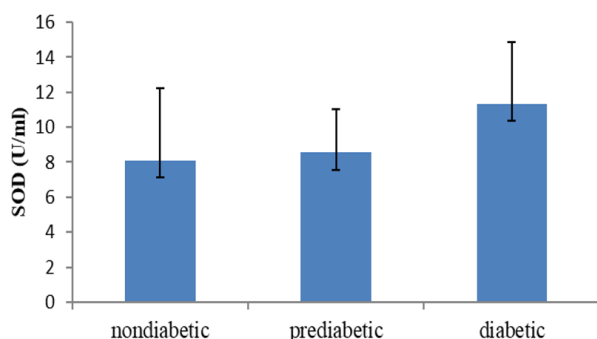


Figure 2: Serum levels of superoxide dismutase (U/ml) in nondiabetic, prediabetic and diabetic patients. Results are expressed as mean \pm SD. SOD : Superoxide dismutase

Comparison of biochemical parameters and anxiety levels among groups

The data in Table 2 show biochemical characteristics and anxiety levels of the groups. We observed that diabetic and prediabetic groups had significant

higher FBS and HbA1C as compared to healthy subjects. Concerning the lipid profile, only total cholesterol value provided a statistically significant difference among groups. We also observed that both state and trait anxiety levels were higher in non-diabetic and diabetic groups than prediabetic subjects.

Comparison of MDA and SOD levels among groups

Prediabetic and diabetic patients had significantly higher serum MDA levels compared to normal controls, as shown in Figure 1. The SOD activity was higher in diabetes and pre-diabetic subjects compared to normal subjects, as shown in Figure 2.

Correlation analysis

Table 3 shows the analysis of the Pearson correlation coefficient among MDA and SOD with other parameters in total study subjects. MDA had a significant positive correlation with WC, WHR, FBS, and HbA1c. SOD had a significant correlation with FBS, HbA1c, WC, WHR and BMI. A less negative correlation was seen in SOD with lipid profile which was not statistically significant ($P > .05$).

Discussion

Diabetes mellitus is strongly connected to obesity. Type 2 Diabetes showed solid correlation with waist circumference is reported in urban Asian Indians (Anjana *et al.*, 2004). In the present study, we found that waist circumference, body mass index and waist to hip ratio are significantly higher in diabetic and prediabetic patients than healthy controls. It is also reported that obesity is associated with the disturbance of oxidant-antioxidant status and increased DNA damage (Latif and Rafique, 2018; Albuoli, 2014). In the present work, WHR and WC had positive correlations with serum MDA and SOD levels. The evidence that antioxidant enzymes may be stimulated during the developmental stages of obesity was given by (Dobrian *et al.*, 2000) who reported increased SOD activity, 10 weeks after diet-induced obesity in rats.

Oxidative stress has a vital position in cellular damage from hyperglycemia. In the current study, pre-diabetic and diabetic patients had significantly higher MDA levels compared to normal controls. A consistent result is obtained from the study conducted by (Likidilid *et al.*, 2010) who observed increased MDA levels in diabetic patients. Studies also demonstrated that patients with prediabetes also had higher plasma MDA concentration (Su *et al.*, 2008; Priyatharshini *et al.*, 2017). The study conducted in newly detected type 2 diabetic patients also observed increased MDA than normal glucose

tolerance patients (Siddiqui *et al.*, 2019). The markers of oxidative stress are higher in impaired fasting glucose patients (Thiyagarajan *et al.*, 2012). In the present study, we found that increased malondialdehyde levels with increased HbA1c and FBS. The increase in MDA levels is thought to be due to increased generation of lipid peroxide and their release in circulation, which would be consistent with the above studies.

SOD, the antioxidant enzyme has a defending role against cellular and histological injury (Tiwari *et al.*, 2013). We observed that the SOD activity was higher in diabetes and pre-diabetic subjects compared to normal subjects. The increased SOD activity in diabetes is reported by different authors (Bandeira *et al.*, 2012; Jiménez-Osorio *et al.*, 2014; Moussa, 2008). A different result is obtained by other authors they reported patients with diabetes and prediabetes had a lower plasma SOD activity than the normal glucose tolerance group (Su *et al.*, 2008; Likidilid *et al.*, 2010). It is observed that greater SOD activity in newly detected type 2 diabetic patients than normal glucose tolerance patients (Siddiqui *et al.*, 2019). It is also reported that decreased erythrocytic superoxide dismutase activity in elderly prediabetic patients (Dzięgielewska-Gęsiak *et al.*, 2014). The increase in the total SOD activity suggests an adaptive reaction, maybe due to the increased generation of superoxide anion radical, which would lead to an increase in the formation of H₂O₂ (Bandeira *et al.*, 2012). We observed that SOD activity had a positive correlation with high blood glucose levels. Kimura *et al.* (2003) found raised levels of a variant of extracellular SOD (EC-SOD) in diabetic patients. Vandana *et al.* (2014) observed an opposite relationship between HbA1C and SOD in diabetic patients that are not consistent with our finding.

We observed that the total cholesterol level, LDL and VLDL are increased in prediabetic patients than healthy controls, and it is decreased in diabetic patients than in the other two groups. The HDL is increased in prediabetic and diabetic groups than healthy controls. It has been reported that antidiabetic treatment, regardless of its type, has a beneficial role in lipid metabolism. Lipid values are found to be improved along with the improvement in glycemic control (Solano, 2006; Kassem and Raz, 2009). We also investigated the relationship between lipid profile and oxidative stress. The current work showed that no significant relationship exists between SOD and MDA with the lipid profile. It has been reported that higher oxidative stress and dyslipidemia are independent risk factors of

atherosclerosis (Rao and Kiran, 2011). Yang *et al.* (2008) observed a positive correlation between the atherogenic index and lipid peroxidation that is not consistent with our results.

It has been reported that mortality risk in individuals with diabetes mellitus is higher in the presence of depression or anxiety, or both (Naicker *et al.*, 2017). The current study demonstrated the higher levels of state and trait anxiety in nondiabetic patients and diabetic subjects than prediabetic subjects. It is observed a significant correlation between trait anxiety and ROS production in hypertensive cases (Yasunari *et al.*, 2006). In the present study, we could not find a significant correlation between anxiety levels and oxidative stress in the study subjects.

CONCLUSION

The findings strongly confirmed that oxidative stress in prediabetic and diabetic patients is influenced by glycemic status and visceral obesity. Hence therapies targeting oxidative stress and abdominal obesity can supplement other therapeutic management to reduce the complications of type 2 diabetes mellitus.

ACKNOWLEDGEMENT

Authors are grateful to the Management, Little Flower Hospital and Research Centre for providing the needed facilities for the research work. We are indebted to Dr Ramadasan Kuttan, Research Director, Amala Medical College, for his help during the study.

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