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# Oxidative stress with glycemic and lipid investigation among adult patients of Diabetes Mellitus Type 2 in Riyadh, Saudi Arabia

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**ABSTRACT**

*Oxidative stress may play a crucial role in the pathogenesis of Type 2 Diabetes Mellitus (T2DM) and its complications, due to increased production of free radicals and impaired antioxidant defenses. Increased level of blood cholesterol may be attributed to the insulin resistance in T2DM. This is a case control study conducted in Riyadh region of Saudi Arabia among T2DM patients to investigate the biochemical parameters of oxidative stress, glycemic and lipid profile. This study was conducted among 107 T2DM patients having significant symptoms of hyperglycemia and were compared with 78 control subjects. Glycemic parameters of Fasting Plasma Glucose (FPG) and Glycohemoglobin (HbA1C) were found to be significantly higher ($p<0.05$) in patients. Significantly higher activity ($p<0.05$) of Catalase (CAT), Glutathione Peroxidase (GPx) and significantly higher level ($p<0.05$) of Malondialdehyde (MDA) representing higher lipid peroxidation were found in patients. Significantly decreased level of Reduced Glutathione (GSH) was found in patients ($p<0.05$). Significant positive correlation ($p<0.05$) of FPG with CAT, GPx and MDA; significant negative correlation ($p<0.05$) between FPG and GSH; significant positive correlation ($p<0.05$) of HbA1C with CAT, GPx and MDA; significant negative correlation ($p<0.05$) between HbA1C and GSH were found among patients. In conclusion, this study reports the alterations in activities of antioxidant enzymes leading to oxidative stress condition associated with hyperlipidemia and hyperglycemia among T2DM patients.*

***Keywords:*** *Oxidative stress, lipid investigation, Diabetes Mellitus Type 2 patients, Saudi Arabia*

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## INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a progressive metabolic disorder that begins with peripheral insulin resistance and ends with failure of pancreatic beta-cells resulting in high level of blood sugar. In most cases, peripheral insulin resistance, defined as the attenuated response to insulin infat tissue, liver, and skeletal muscle, appears long before the development of hyperglycemia [1]. Imbalance between oxidants and reductants within the body due to the excess production of peroxides and free radicals is defined as oxidative stress. This imbalance will cause decrease in total antioxidant capacity, damage to cellular components and tissues in the body [2]. Many earlier studies depicted that the oxidative stress plays a key mediatory role in the development and progression of T2DM and its complications, due to increased production of free radicals and impaired antioxidant defenses [3]. Oxidative stress plays a pivotal role in cellular injury from hyperglycemia. High glucose level can stimulate free radical production [4].

Free radicals which are formed during the glucose autoxidation process cause oxidative damage of lipids, proteins, and nucleic acids and other types of biological damage [5,6]. Lipid peroxidation of low density lipoprotein (LDL) by a superoxide-dependent pathway resulting in the generation of free radicals is found to be associated with Hyperglycaemia [7,8]. Beta-cell failure in the developing stage of type 2 diabetes are considered to be attributed with glucotoxicity and lipotoxicity [9].

Beta-cells express low levels of anti-oxidative enzyme including CAT and GPx, which make them particularly susceptible to oxidativestress [10].It has been reported that diabetic patients have significant

defects of antioxidant protections and generation of reactive oxygen species which may play an important role in the etiology of diabetic complications [11]. Decrease of Superoxide Dismutase (SOD), CAT, peroxidase, ceruloplasmin (Cp) and GPx activities as well as a decrease inthe Reduced Glutathione (GSH) level and an increase in the concentration of glutathione disulfide (GSSG) were observed in erythrocytes of diabetic patients and in tissues from diabetic animals [12].

In Diabetes Mellitus, the disorders of carbohydrates, lipids and proteins metabolism play predominant role in diabetic complications. Hypercholesterolemia and hypertriglyceridemia are mostly observed and related largely to the degree of diabetic control [13]. Serum HDL reported to be low in diabetic patients of both types of Diabetes Mellitus [14]. Hyperglycemia may alter lipoproteins to a form that promotes atherogenesis. Serum LDL levels are frequently altered in diabetic patients [15].

There are very few studies reported from Saudi Arabia to explore oxidative stress among T2DM patients. The aim of the present study is to investigate the activities of certain antioxidant enzymes and antioxidant to explore the oxidative stress condition among adult patients of T2DM in Riyadh, Saudi Arabia. This study also investigates the glycemic and lipid profile and its association with oxidative stress parameters.

## MATERIALS AND METHODS

### Study design and subjects:

This is a case control study conducted in Riyadh region of Saudi Arabia in year 2016 to 2018 among both males and females T2DM patients to investigate the biochemical parameters of oxidative stress, glycemic and lipid profile among them. This study was conducted among 107 T2DM patients who were compared with 78 control subjects who were medically fit, never suffered from T2DMand of same socio economic status. Study subjects voluntarily participated in this study and their informed written consent was obtained. The survey was conducted by asking the questions to volunteers directly face to face through a well-designed structured questionnaire. This study was approved by ethical committee, Institutional Review Board (IRB) of College of Medicine, Al Imam Mohammad Ibn Saud Islamic University.

### Questionnaire:

A well-designed structured questionnaire was used for getting information from both patients and control subjects related to general information of age, socio demographic characteristics, education, smoking habits, height, weight, BMI etc. and clinical symptoms of T2DM.

### Blood sample collection:

Approximately 5.0 ml venous blood was collected in the heparinised glass vials as coded samples from both the control and T2DM patients. 2.0 ml. of blood samples were used for the glycemic and lipid investigation in Medical Centre laboratory of Al Imam Mohammad Ibn Saud Islamic University. Remaining 3.0 ml. of blood samples for the assay of oxidative stress parameters were transported in ice-cold condition immediately after the collection to the laboratory of Human and Biomedical Research Centre, College of Medicine, Al Imam Mohammad Ibn Saud Islamic University. The assay of the biochemical parameters for oxidative stress were carried out within 24 hours of blood collection.

### Biochemical kits:

Biochemicals assay kits for CAT, GPx, GSH and lipid peroxidation were purchased from Biovision, USA.GSH, 5,5′-dithio-bis- (2-nitro benzoic acid) (DTNB), ThiobarbituricAcid (TBA), Tris [tris(hydroxy methyl) aminomethane], Hydrogen Peroxide ($H_2O_2$) (30%), Tris-HCl, Ethanol were purchased from Sigma Chemical Co., St. Louis, MO, USA.All these assay kits and chemicals used were of the highest purity received from commercial sources.

### Estimation of oxidative stress parameters:

Some of blood samples for oxidative parameters of CAT, GPx, GSH and lipid peroxidation were assayed by the protocols as mentioned in biochemical kits of Biovision, USA. Whereas some of the blood samples for oxidative parameters were estimated manually by the standard protocols as mentioned. Hemoglobin (Hb) content in the hemolysate was measured by the method of Drabkin and Austin, 1932 [16]. CAT activity in the hemolysate was determined by the method of Sinha, 1972 [17] using $H_2O_2$ as substrate and expressed as μmol $H_2O_2$ decomposed/min/g Hb. The activity of GPx in the hemolysate was assayed using $H_2O_2$ as substrate in the presence of GSH by the method of Rotruck et al., 1973 [18] and expressed as mol GSH oxidized/min/gHb. The extent of lipid peroxidation in whole blood was assayed by measuring the formation of Malondialdehyde (MDA) by the method of Stocks and Dormandy, 1971 [19] and expressed as nmol MDA formed per ml of blood. Reduced GSH was estimated in whole blood by Kuo et al., 1983 and expressed as μmol/ml blood [20].

### Estimation of glycemic and lipid profile:

Glycemic parameters in blood samples for Fasting Plasma Glucose (FPG) [mmol/L] and Glycohemoglobin (HbA1C) [%]; lipid parameters in blood samples for triglyceride [mmol/L], Low Density Lipid

(LDL)[mmol/L], High Density Lipid (HDL) [mmol/L], total cholesterol [mmol/L]were estimated through fully automated biochemical analyzer machine as per standard protocols.

**Statistical Analysis:**

Descriptive statistics have been generated to compare the parameters obtained T2DM patients and control subjects. Frequencies and percentages have been shown for all the categorical parameters. Students' t test was applied for comparison of the means and standard deviations of the continuous data outcomes (age, height, weight, BMI, oxidative stress parameters, glycemic and lipid profile). Chi-square test has been incorporated for the comparison of the categorical data outcomes (T2DM symptoms). The calculations of odds ratio (OR) with 95% confidence interval (CI) were done for T2DM symptoms. The criterion for significance was set at $p<0.05$. All the statistical analysis has been performed using an online MedCalc Software, 2018, Belgium.

## RESULTS

**1. Personal and demographic characteristics of study subjects:**

Table 1 represents the personal and demographic characteristics of T2DM patients and control subjects. Among 107 patients, 47.66% were males and 52.34% were females whereas all 78controls subjects were males(100%). Among patients, 81.31% were Saudi nationals and 18.69% were non Saudi, whereas 69.23% control subjects were Saudi nationals and 30.77% were non Saudi. 19.63% of patients were smokers and 80.37% were non-smokers, whereas 37.18% of control subjects were smokers and 62.82% were non-smokers. Only 4.67% patients developed type 1 diabetes mellitus and rest of the patients 95.33% were suffering from T2DM, whereas all control subjects were not having any type of diabetes (0%).

**2. Physical characteristics of study subjects:**

Table 2 exhibits the physical characteristics of T2DM patients and control subjects. Mean age of patients was significantly more than control subjects ($p<0.01$). Mean height of patients was significantly less than control subjects ($p<0.05$). Mean weight of patients was significantly more than control subjects ($p<0.01$). Mean BMI of patients was significantly more than control subjects ($p<0.01$).

**3. Self-reported symptoms of T2DM among study subjects:**

Table 3representsself-reported symptoms of T2DM among patients and control subjects. Control subjects have not reported for any symptom of T2DM (0%). Among patients with T2DM symptoms, 54.21% reported thirst (OR- 185.54), 68.22% reported dryness (OR- 334.47), 43.93% reported loss of appetite (OR-123.26), 12.15% reported nausea and vomiting (OR- 22.42), 15.89% reported abdominal pain (OR-30.35), 73.83% reported polyurea (OR- 437.94), 57.94% reported nocturia (OR-215.65), 17.76% reported morning headache (OR-34.59).

**4. Glycemic and lipid profile among study subjects:**

Table 4 exhibits the investigated values of glycemic and lipid profile in blood ofpatients of T2DM and control subjects. Glycemic parameters of FPG and HbA1C were found to be significantly higher ($p<0.05$) in patients as compared to control subjects. Lipid parameters of triglyceride, LDL, HDL and total blood cholesterol were found to be significantly higher ($p<0.05$) in patients as compared to control subjects.

**5. Oxidative stress parameters among study subjects:**

Table 5 shows the estimated values of oxidative stress parameters *viz.* CAT, GPx, GSH and MDA for extent of lipid peroxidation among patients of T2DM and control subjects.

***Activity of Catalase:*** Activity of blood CAT enzyme ($x10^4$μmol $H_2O_2$ decomposed/min/g Hb) was found to be significantly higher ($p<0.05$) in patients as compared to control subjects.

***Activity of Glutathione Peroxidase:*** Activity of blood GPx enzyme (μmol GSH oxidized/min/g Hb) was found to be significantly higher ($p<0.05$) in patients as compared to control subjects.

***Reduced Glutathione level:*** Blood GSH level (μmol/ml blood) was found to be significantly decreased ($p<0.05$) in patients as compared to control subjects.

***Malondialdehyde level:*** Blood MDA (nmol/ml blood) level as an end product of lipid peroxidation was found to be significantly more ($p<0.05$) in patients as compared to control subjects.

**6. Correlation of oxidative stress parameters with glycemic parameters among T2DM patients:**

Table 6 represents correlation between different oxidative stress parameters and glycemic parameters for both FPG and HbA1C among T2DM patients. There was significant positive correlation of FPG with CAT, GPx and MDA ($p<0.01$) and there was significant negative correlation between FPG and GSH ($p<0.01$). There was also significant positive correlation of HbA1C with CAT, GPx and MDA ($p<0.01$) and there was significant negative correlation between HbA1C and GSH ($p<0.01$).

**Table 1. Personal and demographic characteristics of study subjects:**

| Variables | | Control n(%) (N = 78) | Diabetic patients n (%) (N = 107) |
|---|---|---|---|
| Gender | Male | 78 (100) | 51 (47.66) |
| | Female | 0 (0) | 56 (52.34) |
| Nationality | | | |
| | Saudi | 54 (69.23) | 87 (81.31) |
| | Non Saudi | 24 (30.77) | 20 (18.69) |
| Smoking | | | |
| | Smokers | 29 (37.18) | 21 (19.63) |
| | Non smokers | 49 (62.82) | 86 (80.37) |
| Diabetic Mellitus | | | |
| | Type 1 | 0 (0) | 5 (4.67) |
| | Type 2 | 0 (0) | 102 (95.33) |

**Table 2. Physical characteristics of study subjects:**

| Variables | Control Mean ± SD (N = 78) | Diabetic patients Mean ± SD (N = 107) | p value |
|---|---|---|---|
| Age (years) | 49.23 ± 7.37 | 58.72 ± 8.93 | p<0.01 |
| Height (cm.) | 167.53 ± 3.72 | 159.33 ± 9.77 | p<0.01 |
| Weight (Kg.) | 62.31 ± 7.52 | 84.28 ± 12.38 | p<0.01 |
| BMI ($Kg/m^2$) | 23.76 ± 4.29 | 34.84 ± 5.42 | p<0.01 |

**Table 3. Self-reported symptoms of T2DM among study subjects:**

| Symptoms | Control n (%) (N = 78) | No. of patients n (%) (N = 107) | Odds Ratio (95% CI) | p value |
|---|---|---|---|---|
| Thirst | 0 (0) | 58 (54.21) | 185.54 (11.21 - 3070.56) | p<0.01 |
| Dryness | 0 (0) | 73 (68.22) | 334.47 (20.13 - 5555.31) | p<0.01 |
| Loss of appetite | 0 (0) | 47 (43.93) | 123.26 (7.44 - 2040.28) | p<0.01 |
| Nausea vomiting | 0 (0) | 13 (12.15) | 22.42 (1.31 - 383.32) | p<0.01 |
| Abdominal pain | 0 (0) | 17 (15.89) | 30.35 (1.79 - 513.10) | p<0.01 |
| Polyurea | 0 (0) | 79 (73.83) | 437.94 (26.27 to 7299.08) | p<0.01 |
| Nocturia | 0 (0) | 62 (57.94) | 215.65 (13.02 - 3570.58) | p<0.01 |
| Morning headache | 0 (0) | 19 (17.76) | 34.59 (2.05 - 582.44) | p<0.01 |

**Table 4. Clinical investigation of glycemic and lipid profile among study subjects:**

| Parameters | Control Mean ± SD (N = 43) | Diabetic patients Mean ± SD (N = 87) | p value |
|---|---|---|---|
| Fasting Plasma Glucose (FPG) [mmol/L] | 5.94 ± 1.35 | 8.24 ± 5.77 | p<0.05 |
| Glycohemoglobin (HbA1C) [%] | 4.82± 1.21 | 7.57± 4.43 | p<0.01 |
| Triglycerides [mmol/L] | 1.28 ± 0.28 | 2.45± 1.47 | p<0.01 |
| Low Density Lipid (LDL)[mmol/L] | 1.31 ± 0.47 | 3.57± 1.85 | p<0.01 |
| High Density Lipid (HDL) [mmol/L] | 1.80± 0.77 | 1.02 ± 0.94 | p<0.01 |
| Total blood cholesterol [mmol/L] | 4.20± 1.95 | 5.54 ± 2.82 | p<0.05 |

**Table 5. Parameters for oxidative stress among study subjects:**

| Parameters | Control Mean ± SD (N = 43) | Diabetic patients Mean ± SD (N = 87) | p value |
|---|---|---|---|
| Reduced Glutathione (GSH) [μ mol/ml blood] | 22.73 ± 3.48 | 19.87 ± 1.27 | p<0.01 |
| Malondialdehyde(MDA) [nmol/ml blood] | 11.58 ± 2.73 | 15.47± 2.21 | p<0.01 |
| Catalase (CAT)[x$10^4$μmol $H_2O_2$ decomposed/min/g Hb] | 35.87 ± 4.52 | 41.77 ± 2.37 | p<0.01 |
| Glutathione peroxidase (GPx) [μmol GSH oxidized/min/g Hb] | 122.88 ± 2.43 | 142.82 ± 3.81 | p<0.01 |

**Table 6: Correlation of parameters for oxidative stress with glycemic parameters among T2DM patients**

| Parameters | Correlation coefficients | FPG | HbA1C |
|---|---|---|---|
| CAT | r value | 0.89 | 0.78 |
| | *p* value | p < 0.01 | p < 0.01 |
| GPx | r value | 0.92 | 0.75 |
| | *p* value | p < 0.01 | p < 0.01 |
| GSH | r value | -0.91 | -0.87 |
| | *p* value | p < 0.01 | p < 0.01 |
| MDA | r value | 0.88 | 0.82 |
| | *p* value | p < 0.01 | p < 0.01 |

**DISCUSSION**

Oxidative stress acts as mediator of insulin resistance and its progression to glucose intolerance and installation of diabetes mellitus [21]. Oxidative stress in diabetes mellitus causes several adverse effects on the cellular physiology. This is particularly relevant and dangerous for the Islet of Langerhans containing beta cells, which is among those tissues that have the lowest levels of intrinsic antioxidant defenses [22]. Multiple biochemical pathways and mechanisms of action have been implicated in the deleterious effects of chronic hyperglycemia and oxidative stress on the function of vascular, retinal and renal tissues [23].

It has been reported that insulin sensitivity in humans is directly related with the fatty acid composition of the phospholipids in the skeletal muscle cell membranes [24]. Insulin action through several potential mechanisms, including altering insulin receptor binding or affinity and influencing ion permeability and cell signaling could be influenced by specific fatty acid profile in cell membranes [25]. It is important to consider follow up studies on dietary fatty acids and insulin resistance due to the change of fatty acid profile in cell membranes requires at least several months [26].

In present study, we investigated the parameters of oxidative stress, glycemic and lipid profile among adult patients of Diabetes Mellitus Type 2 in Riyadh, Saudi Arabia. Most of the patients were females and non-smokers. Mean BMI was found to be significantly more as compared to control subjects which is considered as an important risk factor in the development of T2DM.

Regarding oxidative stress parameters, we found significantly higher activity of CAT, GPx, significantly increased level of MDA representing higher lipid peroxidation and significantly decreased level of GSH antioxidant molecule among patients. These results of investigation of these parameters show the imbalance in the oxidant and antioxidant environment, suggested the oxidative stress condition among patients. For glycemic parameters, we found FPG and HbA1C to be significantly higher among patients. Regarding lipid parameters, triglycerides, LDL, HDL and total blood cholesterol were found to be significantly higher among patients. The results of these investigation show the hyperlipidemia and hyperglycemia among patients.

We also explored the association of oxidative stress parameters with glycemic and lipid profile, significant positive correlation of FPG with CAT, GPx and MDA; significant negative correlation between FPG and GSH; significant positive correlation of HbA1C with CAT, GPx and MDA; significant negative correlation

between HbA1C and GSH were found among patients which suggested a significant association of oxidative stress with hyperlipidemia and hyperglycemia.

CAT enzymatically processes hydrogen peroxide into oxygen and water and thus neutralizes it. Catalase protects pancreatic beta-cells from damage by hydrogen peroxide [27]. GPx metabolizes hydrogen peroxide to water by using GSH as a hydrogen donor [28]. Low levels of anti-oxidative enzyme including catalase and GPx is expressed in beta-cells, which make them particularly susceptible to oxidative stress [29].

GSH is an efficient antioxidant present in almost all living cells and is also considered as a biomarker of redox imbalance at cellular level [30].GSH participates in the cellular defense system against oxidative stress by scavenging free radicals and reactive oxygen intermediates. Thus, thedecrease in GSH level might reflect a direct reaction between GSH and free radicals generated by hyperglycemia in T2DM. [31].MDA has been documented as a primary biomarker of free radical mediated lipid damage and oxidative stress [32]. Significant changes in lipid metabolism and structure have been reported in diabetes, particularly in patients with vascular complications [33]. Increased level of MDA in diabetics suggests that peroxidative injury may be involved in the development of diabetic complications[34].

Some similar kind of earlier epidemiological studies reported the oxidative stress and hyperlipidemia among diabetic patients which show agreement with the findings of our study. A study conducted by Korkmaz et al. (2013) to investigate the status of markers of oxidative stressreported a significant reduced level of antioxidant power among diabetic patients, on the basis of result obtainedfrom their study they concluded that the increase in glucoseconcentrations can lead to tissue damage by increasing oxidative stress [35]. There are several reports that claim reduced level of GSH in diabetes [36,37]. Decreased GSH level may be oneof the factors in the oxidative DNA damage in type 2 diabetics [38]. In our study we found decreased level of GSH was found which might had resulted the increased activity of CAT and GPx and increased lipid peroxidation. Increased lipid peroxidation presents a close relationship with the high glycemic levels and oxidative stress in diabetes mellitus [39,40]. A clinical study was done for characterizing blood oxidative stress in diabetic patients reported a significant higher lipid peroxidation which showed a close relationship with high glucose levels as observed by the fasting glucose and HbA1c levels [41].

We found increased level of triglycerides, LDL, HDL and total blood cholesterol among patients associated with hyperglycemia. Similar kind of few epidemiologic studies have examined biomarkers of fatty acids as predictors of T2DM. In a 10 year follow-up study [42], men who developed T2DM had a higher proportion of saturated fatty acids and a lower proportion of linoleic acid in their serum cholesterol esters than did men who did not develop diabetes at baseline.

## CONCLUSION

In conclusion, this study reports the oxidative stress condition, hyperlipidemia and hyperglycemia among T2DM patients. Activities of antioxidant enzymes CAT and GPx were found to be increased, lipid peroxidation was found to be increased and level of antioxidant molecule GSH was found to be decreased among patients. Increased level of triglycerides, LDL, HDL and total blood cholesterol were found among patients. Most of the patients were found to be hyperglycemic since increased level of FPG and HbA1C were found in the blood of patients. We also found a significant correlation between oxidative stress parameters and glycemic parameters suggested the role of hyperglycemia in oxidative stress as a disease complication or might be the role of oxidative stress in insulin resistance for the pathogenesis of T2DMresulting in hyperglycemia. Less sample size of T2DM patients is the limitation of this study, so there is more such kind of case control and cohort studies are required in a large population of Saudi Arabia to establish more precise association of oxidative stress and insulin resistance in T2DM.

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## CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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