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Original Research Article

Oxidative stress and its correlation with glycated haemoglobin in patients of type 2 diabetes mellitus

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) has a heavy disease burden and is one of the leading causes of death worldwide. Oxidative stress leads to the generation of inflammatory mediators and reactive oxygen species, which results in an inflammatory state, which plays a key role in the pathogenesis of diabetes and its complications. We aimed to correlate the levels of Glycated Haemoglobin with Oxidative Stress.
Methods: This study included 200 subjects, 100 were type 2 diabetics and 100 healthy non-diabetic individuals. All the individuals were subjected to analysis of Fasting Plasma Glucose, Glycosylated Haemoglobin, Malondialdehyde, Superoxide Dismutase, Glutathione, Catalase, Uric Acid and Ascorbic Acid. The data thus generated was analyzed Statistically using the student 't' test. ANOVA for comparison of mean in more than two groups. Pearson's coefficient of correlation was used to calculate the correlation between different parameters. $p < 0.05$ was considered statistically significant.
Results: The results showed that as the Glycated Hb increased, the levels of FBS, MDA, Uric acid increased and Serum SOD, Glutathione, Catalase, and Ascorbic acid levels decreased this change was statistically significant ($p<0.05$). A positive significant correlation between HbA1c, and fasting blood Glucose, MDA, Uric Acid. SOD, Catalase, Ascorbic Acid and Glutathione showed a negative correlation with glycosylated Haemoglobin.
Conclusions: It is hereby concluded that when glycated Hb increases the natural antioxidants that are SOD, catalase, and glutathione decrease to combat the increased formation of ROS. Serum MDA, increased with increased glycated Hb and shows a positive correlation, indicating increasing lipid peroxidation

Keywords: Antioxidants, Glycated Haemoglobin, Type 2 diabetes mellitus, Oxidative stress

INTRODUCTION

Oxidative stress is an imbalance between the production of reactive oxygen and the ability of the biological system to detoxify the reactive intermediates or to repair the resulting damage. The destructive aspect of oxidative stress is the production of reactive oxygen species (ROS), which include free radicals and peroxides, that can damage nucleic acids, proteins, and cell membranes.[1] Oxidative stress occurs when ROS production exceeds their removal by the cellular defense mechanism. In humans, oxidative stress is involved in many diseases, such as diabetes mellitus (DM), atherosclerosis, myocardial infarction (MI), heart failure, Parkinson's disease, chronic fatigue syndrome, Alzheimer's disease, and fragile X syndrome.[2,3] Diabetes Mellitus is a continuous source of oxidative stress to the body and there is increased generation of ROS. These ROS have a very short half-life and cannot remain as such and react rapidly with DNA, protein, and lipids, thereby leading to oxidative damage. Oxidative stress occurs in diabetic patients due to an increase in the steady-state levels of ROS, which is a result of decreased antioxidant defence mechanisms and increased free radical generation. These

ROS are involved in the development of diabetic complications like blindness, renal failure, neuropathy, and myocardial infarction.[2,4] Hyperglycaemia is the initiating cause of oxidative stress in diabetics. It causes repeated acute changes in cellular glucose metabolism and long-term accumulation of glycosylated biomolecules and advanced glycation end products (AGEs). In the presence of uncontrolled hyperglycaemia, the increased formation of AGEs and lipid peroxidation products exacerbate intracellular oxidative stress, disruption in cellular signaling and homeostasis followed by inflammation and tissue injury such as endothelial dysfunction, arterial stiffening, and microvascular complications.[5] In diabetics, there are also other multiple pathways enhancing ROS production, which include; protein kinase C-dependent activation of NADPH oxidase, enhanced glucose auto-oxidation, uncoupled endothelial nitric oxide synthase activity, increased mitochondrial superoxide production and stimulation of eicosanoid metabolism.[4] Haemoglobin A1c (HbA1c) is an indication of chronic glycemia, and it can reflect an integrated index of glycemia over the past 120-day lifespan of the red blood cell. The HbA1c test can be used to diagnose diabetes in which a level of 6.5% is suggested as the cut point for the diagnosis.

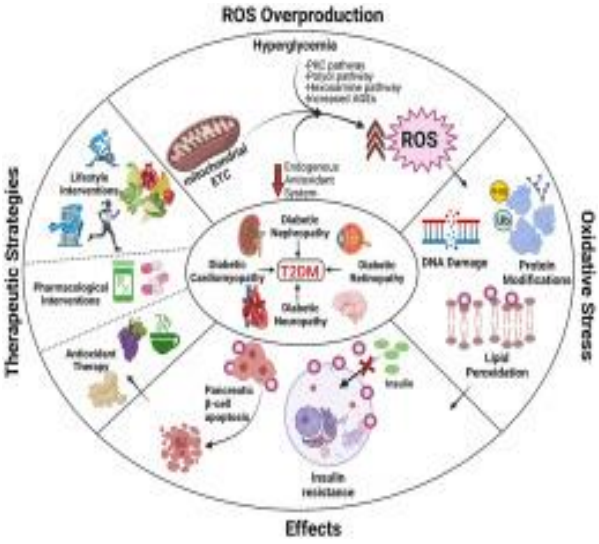

Figure 1: Oxidative stress in pathophysiology of Type 2 Diabetes Mellitus and its complications.

METHODS

This cross-sectional study was conducted from January 2022 to March 2023 in the Department of Biochemistry, Government Medical College and Guru Nanak Dev Hospital Amritsar, Punjab. The 200 subjects included 100 type 2 diabetic patients and 100 healthy non-diabetic individuals who were selected from the general population to serve as controls. The Institutional Ethics Committee provided their approval to the study. Written informed consent was taken from all the participants and they were subjected to a thorough medical history and examination, as well as biochemical and special tests.

Inclusion criteria

Diabetics: Patients with type II diabetes mellitus confirmed by fasting blood sugar, under medication (hypoglycaemic drugs and insulin) in the age group of 26-70 years. Controls: Normal healthy non-diabetic individuals in the age group of 26-70 years.

Exclusion criteria

The subjects with liver disease, renal disease, thyroid disease, tuberculosis, hypertension, pancreatitis, coronary artery disease (CAD, previous history) Stroke, individuals on drugs like glucocorticoids, Nicotinic acid, Thyroid hormones, β adrenergic antagonists and thiazide diuretics, drug addicts, patient with endocrinopathies such as acromegaly, patients with down syndrome were excluded from the present study.

Sample collection and biochemical analysis.

After an overnight fast of 8-10 hours, 7 mL of peripheral venous blood sample was drawn from the medial cubital vein. One mL of blood was transferred into a test tube containing sodium fluoride and potassium oxalate (1:3 ratio of 20mg/5mL) anticoagulant. 4 mL of the blood was transferred into additive-free tubes. The additive-free tubes were allowed to stand for 30 minutes for clot formation following which they were centrifuged at 3000 rpm for 5 minutes to obtain serum. 2ml of blood sample was transferred to the EDTA vial for estimation of HbA1c. The sodium fluoride and potassium oxalate additive tubes were immediately centrifuged at 3000 rpm for 5 minutes to obtain the plasma.Plasma samples were analyzed immediately for blood glucose and ascorbic acid. Serum samples were aliquoted into appropriately labelled vials and stored at -80°C until analysis of the biochemical parameters. which were used for the analysis of Uric acid, SOD, Glutathione peroxidase and MDA and Catalase. Investigations performed were fasting blood sugar (FBS) by GOD-POD method.[8] Glycated haemoglobin (HbA1c) by ion exchange resin method, Malondialdehyde (MDA) as described by Kei Satoh, Superoxide dismutase (SOD) as described by Marklund. Glutathione (GSH) by ELISA, Catalase (CAT) by ELISA, Uric acid by enzymatic method, Ascorbic acid by (2,6 dichlorophenolindophenol titration method), BMI was calculated after recording the weight and height of the patients as per standard protocol.[10-15]

Statistical analysis

The data thus generated was analyzed Statistically using the student ‘t’ test to compare the mean of two groups. ANOVA for comparison of mean in more than two groups. Pearson’s coefficient of correlation was used to

calculate the correlation between different parameters. P<0.05 was considered statistically significant.

RESULTS

All the individuals enrolled for the present study were studied under two headings Diabetics and Non-Diabetics. All the parameters studied were compared amongst the two groups. Observations thus made are listed in the tables.

Based on the levels of glycated haemoglobin levels the Diabetics were segregated in four groups. It was observed that the levels of glycated haemoglobin showed a statistically significant (p<0.001) variation when all the groups were compared amongst each other. Levels of various antioxidant enzymes decreased significantly (p<0.05) in patients with Type 2 diabetes mellitus as the levels of glycated haemoglobin increased.

Table 1: Demographic details of patients included in the present study.

Age group (years)	Diabetics		Non-Diabetics	
	Males	Females	Males	Females
≤40 years	9	8	23	20
41-60 years	20	37	20	21
> 60 years	13	13	9	7
Total	42	58	52	48

Table 2: Comparison of Biochemical parameters in Diabetic and Non-diabetic individuals.

Variables	Diabetics		Non-Diabetics		Significance	
	Mean	±SD	Mean	±SD	't' value	P value
FBS (mg/dl)	251.33	11.223	94.78	14.000	10.116	<0.001**
HbA1C (%)	8.77	2.564	4.80	0.366	15.319	<0.001**
Uric acid (mg/dl)	5.85	1.417	5.377	1.908	7.130	<0.05*
Ascorbic acid (mg/l)	7.18	0.632	7.839	1.717	7.160	<0.05*
MDA (nmol/ml)	13.67	11.26	4.73	8.62	13.670	<0.001**
SOD (ml)	0.668	0.244	1.09	0.417	- 6.902	<0.001**
Catalase (KU/L)	145.88	40.71	254.2	73.63	12.884	<0.001**
Glutathione(ng/ml)	25.21	10.80	15.79	8.25	-6.927	<0.001**

Student 't' test unpaired; *p<0.05; Significant; **p<0.001; Highly Significant

Table 3: Segregation of patients according to levels of glycated (Hb).

S.No	Group	Mean ± SD	P value
		HbA1C	
I	≤5.4%	4.29±1.23	0.00 HS (when all the groups were compared amongst each other)
II	>5.4% - 6.4%	6.06±0.23	
III	>6.4% - 8.0%	7.29±0.48	
IV	>8.0	10.62±1.84	

Table 4: Mean value of antioxidant status in diabetic patients according to HbA1C.

S.no	Group	MEAN±SD		
		SOD (u/ml)	Catalse	Glutathione(ng/ml)
I	≤5.4%	0.832±0.33	281.69±75.30	16.98±8.34
II	>5.4-6.4%	0.752±0.27	258.93±71.71	13.71±9.14
III	>6.4% - 8.0%	0.614±0.245	255.12±49.15	10.08 ±6.15
IV	>8.0	0.481±0.196	208.91±64.9.90	7.40±6.49

Table 5: Mean value of ascorbic acid and uric acid in diabetics patients according to HbA1C.

S.no	Group	MEAN±SD	
		Ascorbic acid (mg/l)	Uric acid (mg)
I	≤5.4%	8.87±2.71	5.16±2.00

Continued.

S.no	Group	MEAN±SD	
II	>5.4% - 6.4%	7.77±2.09	5.73±1.84
III	>6.4% - 8.0%	6.68±1.32	5.92±1.81
IV	>8.0	5.42±1.60	6.34±1.48

p<0.05 when all the groups were compared amongst each other.

Table 6: Mean value of lipid peroxidation in diabetic patients according to HbA1C.

S.no	Group	MEAN±SD	P value
		MDA (nmol/ml)	
I	≤5.4%	6.55±1.41	P<0.05 (statistically significant)
II	>5.4% - 6.4%	11.11±6.21	
III	>6.4% - 8.0%	15.39±13.64	
IV	>8.0	19.88±16.39	

The levels of ascorbic acid and uric acid were compared in these four groups, and it was observed that levels of ascorbic acid decreased significantly (p<0.05) as the levels of glycated haemoglobin increased, whereas levels of uric acid increased significantly (p<0.05) with increase in the levels of glycosylated haemoglobin.

Lipid peroxidation increased with increasing levels of glycosylated haemoglobin in patients of type 2 diabetes mellitus thus indicating increasing lipid peroxidation with increasing glycosylation. HbA1c showed a positive correlation with MDA, Uric Acid and BMI with glycated Hb in patients with type 2 diabetes mellitus, whereas a negative correlation was observed between HbA1c with glutathione, catalase, SOD, and ascorbic acid.

DISCUSSION

Oxidative stress has focused interest on various clinical research in recent times. There is growing evidence connecting the action of oxidative stress to the pathogenesis and complications in diabetes mellitus and many other diseases. Oxidative stress plays a role in the pathogenesis of insulin resistance and β-cell dysfunction, caused by dysregulation of cell homeostasis and metabolism.[16] Hyperglycaemia is the principal metabolic alteration that is associated with diabetes mellitus, and increased glycaemic levels in body fluids have been implicated in increasing oxidants, causing cellular damage, vascular dysfunction, and pathogenesis of vascular disease.

Diabetic patients are susceptible to oxidative stress and higher blood glucose level has an association with free radical mediated lipid peroxidation and increase in antioxidant enzymes. These could be due to adaptive response to pro-oxidant diabetic state. Enhanced oxidative stress contributes to deterioration of pancreatic β cells progressively due to glucose toxicity, which leads to severe impairment of glucose stimulated insulin secretion, leading to degradation of β cells and their decreased number.[17,18] Many drugs may also cause toxicity in tissues and organs by inducing oxidative stress. These include anti-inflammatory drugs, which may also cause nephrotoxicity and hepatotoxicity. Use of drugs leads to increased oxidative stress and dysfunction of mitochondria.[19] Consumption leads to increased apoptosis and that in turn increases the expression of SOD/ catalase to protect the body organs against toxicity. Some drugs cause lipid peroxidation, mitochondrial dysfunction, and apoptosis, while some cause hepatotoxicity. The various drugs and other sources acting as source of oxidative stress are tabulated henceforth.

Table 1 represents the demographic details of the individuals included in the present study. It was observed that more females presented with diabetes as compared to males, though the variation was not significant 58 vs 42. All the parameters were compared among diabetics and non-diabetics and it was observed that the variations in glucose, glycated haemoglobin, MDA, SOD, catalase and glutathione were highly significant (p<0.001) when Diabetics and non-diabetics were compared amongst each other, whereas uric acid and ascorbic acid showed a significant variation (p<0.05) (Table 2).

Glycated haemoglobin (HbA1c) represents average blood glucose average level for the past 3 months. Therefore, it becomes a very important biochemical parameter that provides the long-term status of blood glucose levels and a tool for monitoring glycaemic control in patients of Type 2 diabetes mellitus.[20] In the present study patients of type 2 diabetes were divided into four groups (Table 3) depending on the levels of glycosylated haemoglobin. The variations in the levels of glycated haemoglobin were statistically significant when all the groups were compared amongst each other. All the parameters of oxidative stress were studied.

Superoxide dismutase

It dismutases superoxide to hydrogen peroxide and molecular oxygen, and in the presence of other enzymes it converts hydrogen peroxide into water.[21] As the levels

of glycosylated hemoglobin increased, levels of SOD decreased significantly (Table 4). Linear regression analysis showed a negative correlation between HbA1C and SOD (r=-0.025, p=0.05). SOD plays an important and protective role against cellular and histological damage that are produced by reactive oxygen species. Levels of SOD are related to expression of oxidative stress; decreased SOD in diabetics is related to the altered metabolic state. SOD has a major role to play in regulation of apoptosis and its mimetics are targeted to overcome oxidative stress and reduce ROS. Increased antioxidant enzyme has been shown to prevent Diabetes Mellitus.[22]

Table 7: Sources and examples.

Sources	Examples
Medications	Anti-inflammatory drugs Antiretroviral drugs Antineoplastic drugs Antipsychotic drugs
Decreased antioxidant defense	Decreased in glutathione level Decrease in antioxidant systems Decreased concentration of vitamins such as Vitamin E,C Alteration in concentration of other antioxidants (Ubiquinol, Carotene, Uric Acid etc.)
Alteration in enzymatic pathways	Increased polyol pathway activity Decreased glyoxalase pathway activity Alteration in mitochondrial oxidative metabolism Altered prostaglandin and leukotriene metabolism
Other sources	Ischemia reperfusion injury Pseudohypoxia Hyperglycemia Autooxidation of carbohydrates Autooxidation of fatty acids in triglycerides, cholesteryl esters and phospholipids Glycation and glycoxidation

Catalase

It is an important antioxidative enzyme present in all living organisms. It acts as a main regulator of hydrogen peroxide metabolism.[23] In the present study this enzyme was found to decrease significantly as the levels of glycosylated hemoglobin increased (Table 4). Linear regression analysis showed a negative correlation between HbA1C and catalase (r=-0.096, p=0.05). Increased risk of Diabetes has been documented in patients with catalase deficiency, which in β cells may lead to increase in oxidative stress and ultimately failure of the cell. Low catalase activity in the present study is consistent with the hypothesis that long term oxidative stress may contribute to a late onset disorder such as Type 2 diabetes mellitus.[24]

Glutathione

It is a tripeptide present in all mammalian tissues and is the most abundant non- protein Thiol that defends against oxidative stress, it detoxifies free radicals and prevents tissue damage.[25] In the present study levels of glutathione decreased significantly (Table 4). Linear regression showed a negative correlation between HbA1C and glutathione (r=-0.164, p=0.013). Increased levels of glucose as indicated by glycosylated hemoglobin leads to depletion of glutathione. In long term complications of Diabetes, glutathione is involved in β cell dysfunction. Glutathione reductase plays an important role through the reduction of GSSG to GSH and oxidation of NADPH to NAD+. The glutathione reductase system can be overwhelmed if ROS are produced in excess. In uncontrolled Diabetes Mellitus severely deficient synthesis of glutathione has been reported.[26]

Uric acid

Serum uric acid is an endogenous antioxidant formed from purines and the increase in its levels indicates oxidative stress. Moreover, increased levels of uric acid are a risk factor for peripheral arterial disease, thus making the patients of diabetes mellitus more prone to associated micro and macrovascular complications leading to endothelial dysfunction and NO inhibition.[27] In the present study levels of uric acid increased with increasing glycosylated hemoglobin (Table 5). Linear regression showed a positive correlation between uric acid and HbA1C (r=0.318, p=0.05). Increased uric acid may be related to inhibition of uric acid reabsorption in the proximal tubule by high glucose levels in Diabetic individuals.[28,29] It has been reported that for every mg/dl increase in S. uric acid the risk of type 2 diabetes mellitus increases by 20%.[30]

Ascorbic acid

It is also an antioxidant which scavenges a wide range of reactive oxygen species thereby protecting essential biomolecules from oxidative damage.[31] Elevated levels of vitamin C may be depleting the vitamin C of individuals which is independent of their dietary intake. In the present study levels of ascorbic acid decreased significantly as glycosylated hemoglobin levels increased (Table 5). A negative correlation was observed between HbA1C and ascorbic acid (r=-0.242, p=0.05). Vitamin C is water soluble, thereby it is not stored in the body rather it is excreted readily by the kidneys, thereby maintaining saturating concentration of this vitamin in the plasma.[32]

MDA

It is another marker of oxidative stress as enhanced lipid peroxidation leads to an increase in free radical activity in type 2 diabetes mellitus.[33] Free radical production

includes autooxidation of glucose, glycation of protein, advanced glycated end product formation, activation of polyol pathway resulting in oxidative stress in a variety of tissues.[34] In the present study it was observed that levels of MDA increased significantly ($p<0.05$) with increased glycated hemoglobin (Table 6). Linear regression analysis showed a positive correlation between MDA and HbA1C ($r=0.340$, $p=0.000$). MDA measured as thiobarbituric acid reactive substance, which is an index of lipid peroxidation, in patients of type 2 diabetes mellitus is elevated, which leads to DNA and protein modification and lipid peroxidation, which becomes a basis for various micro and macrovascular complications of diabetes.[35,36]

The limitations of the present study were conducted on a small sample size; larger sample size may be required to clearly identify the changes in parameters of oxidative stress.

CONCLUSION

Thus, it can be concluded that changes in SOD, catalase, and glutathione activity. Increase in endogenous antioxidant uric acid, decrease in ascorbic acid and increased lipid peroxidation are affected by hyperglycaemic state leading to various micro and macro vascular complications of type 2 diabetes mellitus.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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