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Research Article

LIPID PER-OXIDATION IN TYPE-2 DIABETES MELLITUS PATIENTS

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A R T I C L E I N F O

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Key words:
ROS-Reactive oxygen species, IR-Insulin resistance, DM-Diabetes mellitus, NADPH-Nicotinamide adenine dinucleotide hydrogen, MAPK- Mitogen activated protein kinase pathway, EPK-extracellular-signal-regulated kinase pathway, HOMA-IR-Homeostatic model assessment of insulin resistance, GC-Glycaemic control, PDM- prediabetic and NG-normoglycaemic

A B S T R A C T

Lipid peroxidation is a process through which oxidants such as free radicals attack lipids specifically polyunsaturated fatty acids. From last four decades, an extensive literature regarding lipid peroxidation has shown its important role in cell biology and human health. The aldehyde degradation products of lipid peroxides are toxic to cells. Ferrous ion reacts with a lipid peroxide to generate the free radical that can propagate peroxidation reactions. The increase in free radical activity in type-2 diabetes mellitus with insulin resistance explain enhanced lipid peroxidation which may explain an important role in the complications of diabetes mellitus patients. The present study was conducted in CSSH, Meerut in the year 2008.100 controls & 100 T2DM patients of age 45-65 years were included for the study.

INTRODUCTION

Reactive oxygen species (ROS) are commonly identified as oxygen reactive molecules associated with a wide variety of physiologic events [1] as well as cancer, diabetes, obesity, neurodegeneration, and other age-related diseases [2, 3]. A reduction-oxidation (redox) reaction concerns the transfer of electrons (reducing power) from a more reduced (nucleo philic) to more oxidized (electrophilic) molecules. ROS can be classified in two groups: (1) free radical ROS containing one or more unpaired electron(s) in their outer molecular orbitals (i.e., superoxide radicals and hydroxyl radicals); (2) nonradical ROS which are chemically reactive and can be converted to radical ROS (i.e., hydrogen peroxide), although they do not have unpaired electron(s). In both cases, ROS can be produced by either enzymatic reactions (i.e. NADPH oxidase, metabolic enzymes such as the cytochrome P450 enzymes, lipoxygenase, and cyclooxygenase) or by nonenzymatic reactions, such as during the mitochondrial respiratory chain. These considerations highlight the concept that the source of ROS is extremely heterogeneous. Indeed, ROS can be found in the environment, as pollutants, tobacco smoke, and iron salts, or generated inside the cells through multiple mechanisms [4].

Free radical species are important physiological components in biological homeostasis [5-8], but when their production increases excessively and greater than the body's antioxidant capacity, then oxidative stress results [8]. Oxidative stress is a major upstream event for diabetes complications as well as insulin resistance development [9,10] inducing pathophysiologic molecular mechanisms and initiating a cascade of deleterious pathways leading to IR and DM [8,13]. Diabetes mellitus (DM) is characterized by disruption in glucose homeostasis and defects in insulin action on many target tissues including liver, muscle, pancreas, and adipose [14–16]. Diabetes is a common metabolic abnormality and is classified as two types: type I is pathologically based on the deficiency in insulin secretion by pancreatic β-islet cells and type II is characterized by insulin-resistance which renders target cells unable to adequately respond to insulin and thus unable to use blood glucose for energy [14–16]. To compensate, the pancreas makes increasingly more insulin, resulting in insulin resistance syndrome which includes obesity, high blood pressure, high cholesterol and eventually type 2 diabetes [15,16].

In this review, it will be discussed in reference to lipid peroxidation in type-2 diabetes mellitus patients.

MATERIAL AND METHODS

The present study was conducted in CSSH, Meerut.100 controls & 100, T2DM patients of age 45-65 years were included for the study.

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Quantitative analysis of blood glucose- Hexokinase method
Principle

The enzyme hexokinase (HK) catalyzes the reaction between glucose and adenosine triphosphate (ATP) to form glucose-6-phosphate (G-6-P) and adenosine diphosphate (ADP). In the presence of nicotinamide adenine dinucleotide (NAD), G-6-P is oxidized by the enzyme glucose-6-phosphate dehydrogenase (G-6-PD) to 6-phosphogluconate and reduced nicotinamide adenine dinucleotide (NADH). The increase in NADH concentration is directly proportional to the glucose concentration and can be measured spectrophotometrically at 340 nm.

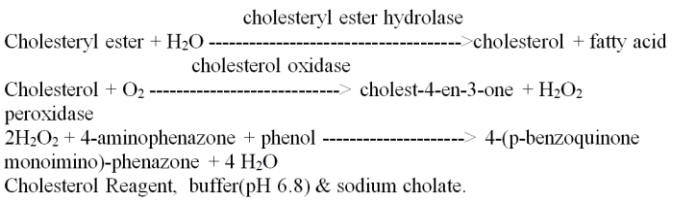
Quantitative Analysis of Malondialdehyde- Thiobarbituric Acid Method

Principle- MDA in the catabolite of lipid peroxide can react with thiobarbituric acid and produce red compound, which has a maximum peak at 532 nm.

Materials-double distilled water, normaline saline (0.9% NaCl), glacial acetic acid & absolute ethanol.

Quantitative Analysis of Cholesterol

Principle-Cholesterol is measured enzymatically in serum or plasma in a series of coupled reactions that hydrolyze cholesteryl esters and oxidize the 3-OH group of cholesterol. One of the reaction byproducts, H_2O_2 is measured quantitatively in a peroxidase catalyzed reaction that produces a colour. Absorbance is measured at 500 nm. The colour intensity is proportional to cholesterol concentration. The reaction sequence is as follows:



Cholesterol Reagent, buffer (pH 6.8) & sodium cholate.

RESULTS

Table I Demographic data

Mean age		Cases	Control
55 ± 9	Males	53	51
50 ± 7	Females	47	49
Hypertensive	Yes	80 %	20 %
	No	20 %	80%
Smokers	Yes	80 %	20 %
	No	20 %	80 %
Alcoholics	Yes	80 %	20 %
	No	20 %	80 %

Table II

Subject	No.of patients	Glucose (mg/dL)	Malondialdehyde (nM/dL)	Cholesterol (mg/dL)	P value
Control	100	90.1± 10.2	57.8 ± 6.5	188.7± 25.3	p<0.001
T2DM	100	179.8± 24.4	118.6 ± 16.1	190.1 ± 23.8	p<0.001

In the present study, control group and study group values of biochemical parameters significantly increases glucose as mean of 90.1± 10.2(mg/dL) in control group and 179.8± 24.4(mg/dL) in T2DM group (p<0.001). Both groups include total number of 200 patients. Mean values of malondialdehyde were significantly increased 118.6 ± 16.1(nM/dL) as compared to control group 57.8 ± 6.5(nM/dL) (p<0.001).The level of cholesterol increases significantly with mean value of 188.7 ± 25.3(mg/dL) in control group and 190.1±23.8(mg/dL) in T2DM group(p<0.001).

DISCUSSION

As in previous study finding, diabetes mellitus has been known to be a state of hyperglycemia with the generation of free radicals. Excessive production of free radicals observed both in type 1 and type 2 diabetes and its insufficient removal results in damage to cellular proteins, membrane lipids and nucleic acids. Griesmacher *et al* have shown increased lipid peroxidation owing to elevated free radicals in both type 1 and type 2 diabetes. Turk *et al* shown an increase in superoxide dismutase activity and decrease in catalase activity. It suggested that these alterations may be owing to the compensatory mechanisms of the antioxidant systemin type 2 diabetics.

In type 2 diabetes, which is associated with insulin resistance, there is an increase in free radical production and prevention of the development of the typical secondary complications would require strategies to normalize free radical production[17].

As discussed earlier, free radicals are said to be necessary evil, as they play role in origin and evolution of life. These are important for activating different signaling pathways inside the cell, such as the Mitogen activated protein kinase (MAPK) and extracellular-signal-regulated kinase (ERK) pathways that alter gene expression, as well as in coordination with superoxide dismutase initiates cell death (Cho and Wolkenhauer, 2003). For instance, RNS produced by neurons act as neurotransmitters and those generated by macrophages act as mediators of immunity. These are also responsible for leukocyte adhesion, thrombosis, angiogenesis and vascular tone. Similarly ROS is involved in gene transcription, single transduction and regulation of other activities in cell (Fang *et al*., 2002)[18].

Both T2D and PDM groups had lower plasma TAC compared with the NG subjects. Hyperglycaemia induces the excess ROS generation thus depleting the plasma TAC in T2D and PDM [19–22]. T2D and PDM subgroups with poor glycaemic control had depleted plasma TAC compared to the NG similar to previous studies [20,25]. T2D and PDM subjects exhibited higher levels of the plasma lipid peroxidation marker, MDA. The rise in plasma MDA among T2D has been previously reported similar to our fifindings [27,28]. Hyperglycaemia promotes ROSmediated lipid peroxidation via nonenzymatic and autoglycation pathways [23,24]. Hyperlipidemia experienced by the T2D and PDM could be one of the reasons for increased production of lipid peroxides [24]. Although we could not obtain signifificantly difffferent MDA levels in T2D with good and poor glycaemic control, previous authors have demonstrated raised MDA levels among T2D with poor glycaemic control [28,29]. It also highlights the presence of lipid peroxidation and systemic inflammation that contributes to the metabolic imbalance even in well-controlled T2D as suggested by previous authors [30, 31]. Hence, depleted plasma TAC and increased MDA represent the presence of oxidative stress in T2D and PDM of the present study. MDA levels of T2D and PDM were positively correlated with fasting plasma glucose and HOMA-IR and therefore show the association of hyperglycaemia with oxidativestress. It further

verifiies that persistent hyperglycaemia promotes ROS production, leading to lipid peroxidation and depletion of endogenous antioxidants demonstrating the increased oxidative stress in T2D [32]. Differences in sample sizes of T2D and PDM and use of oral hypoglycaemic agents only by the T2D might have contributed to the identical HbA1c levels in T2D and PDM of the present study. Erythrocyte GPx activity has elevated in T2D and PDM and particularly the T2D and PDM with poor glycaemic control. GPx responses in T2D were controversial [33, 34–36]. Our findings on GPx activity are in agreement with previous authors [34, 35]. GPx is thought to represent the initial protective response required for adjusting hydrogen peroxide concentration in normal physiological conditions and after oxidative insult [37]. In the present study, the rise of erythrocyte GPx activity in T2D and PDM was parallel to that of MDA. Therefore, we can hypothesize that the excess hydrogen peroxide generation resulted from lipid peroxidation in T2D and PDM, which may have stimulated the GPx activity. Further, T2D and PDM with poor glycaemic control showed the higher GPx activity parallel to the MDA levels. T2D with poor glycaemic control had the highest GPx activity in the present study. As the primary function of GPx is to achieve the hydrogen peroxide balance, once the hydrogen peroxide production is exaggerated via the lipid peroxidation pathway, GPx activity would have been raised. It suggests an adaptive response against the excess lipid peroxidation and accumulation of hydrogen peroxide in a dysglycaemic state [38]. Therefore, the T2D with poor glycaemic control tend to exhibit the higher GPx activity among all groups. Positive correlations existed between HbA1c and GPx activity; FPG and MDA of T2D further verify the above findings [39]. In the present study, control group and study finding reviewed similar results.

CONCLUSION

Most of the studies have shown relationship between elevated level of lipid peroxide and diabetes along with their complications related to heart, liver kidney and eye. Thus, lipid peroxidation indicates hazardious in metabolic disorders specially type 2 diabetes. It is characterized by disruption in glucose homeostasis and defects in insulin action on many target tissues including liver, muscle, pancreas and adipose. Patients with type 2 diabetes mellitus have a significant risk of lipid peroxidation.

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