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## Lipid Peroxidation Alterations in Type 2 Diabetic Patients

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**Abstract:** It was studied that type 2 diabetes mellitus is connected with increased plasma lipid peroxidation (lipid peroxidation expressed as malondialdehyde). This review aimed to evaluate the state of lipid peroxidation among type 2 diabetic subjects. Present finding showed that lipid peroxidation increased in type 2 diabetes mellitus. Increased lipid peroxidation maybe is associated with some diseases such as cancer, cardiovascular diseases and diabetes mellitus. Lipid peroxidation has an important role in the pathogenesis and the complications of diabetes. Antioxidants have been found to prevent the progression and occurrence of diabetes. There are several mechanisms that may cause lipid peroxidation affront in diabetic subjects, although, their precise contributions are not completely clear. We proposed that production of free radicals can be reduced by preventing high blood glucose levels and by the control of instabilities in blood glucose levels. A contributor to these instabilities in blood glucose is glycaemic control by using of fast blood sugar test. Furthermore, the earlier assessment of the advancement of diabetes that firmly control of blood glucose can be obtained; the greater will be the decrease in diabetic complications. Patients with type 2 diabetes may have very high physiological antioxidants requirements.

**Key words:** Lipid peroxidation, type 2 diabetic patients, disease

### INTRODUCTION

It is well known that either insufficiently of secretion or resistance to the insulin action which is partly due to disorder of insulin receptor eventually will end to the well known abnormality called diabetes mellitus, which a metabolic disorder in carbohydrate metabolism. In this disease blood sugar increased, due to what was mentioned above. Viral infection, autoimmunity and other ethological factors can be considered as a common reason for the onset of diabetes. On the base of latter statement the exact cause of diabetes mellitus still in matter for further studies (Kataoka *et al.*, 1983; Like *et al.*, 1979; Paik *et al.*, 1982; Sandler *et al.*, 2000; Shewade *et al.*, 2001). It is commonly linked with ecological factors such as food habit, physical activity and obesity. These factors can increase, decrease or prevent the side effects of DM (Veghari *et al.*, 2007). There are different reports on the state of incidence of type 2 Diabetes Mellitus (DM) over the worlds. The prevalency can be varied from 1.2 to 14.6, 4.6 to 40 and 1.3 to 14.5 % in Asia, Middle East and Iran, respectively (Azizi *et al.*, 2003a, b). Cardiovascular, cerebrovascular and peripheral vascular diseases are among the typical disorder related to the diabetes mellitus. Among other abnormality associated with diabetes, in eye vision with subsequent blindness, amputations and end stage renal disease are among other disorder associated with diabetes mellitus (International Diabetes Federation).

Lipid peroxidation results from a lack of balance between the productions of oxygen radicals and antioxidants in the organism. It should be mentioned that the peroxidation of membrane lipids alter the lipid structure with biological membrane and the physiological process of the membrane will be influence adversely through peroxidation caused by free radicals (Niki *et al.*, 2005; Stark, 2005). Polyunsaturated fatty acids are the main substances to be changed structurally and on the base of above alteration, which caused by peroxidation of lipids. The by-product of latter chemical change is the malondialdehyde (MDA) formation. Thiobarbutiric acid reactive substance (TBARS) is the by-product of MDA and due to toxicity of MDA, the alternative substance, which is thiobarbutiric acid, is mostly used to assess the lipid peroxidation (Flemming *et al.*, 1997; Del Rio *et al.*, 2005). Free radicals have tendency to attack different kinds of unsaturated fatty acids and lipids (cholesterol and low density lipoprotein) that their productions are undesirable oxidized products causing to starting and development of the disease (Valko *et al.*, 2007; Johansen *et al.*, 2005). In the study, we determined that malondialdehyde (MDA) levels and superoxide dismutase activities were increased and decreased in the 41-45 age groups of healthy individuals. We think that malondialdehyde levels seem to be effected by age in healthy individuals. The results indicate that the balance between antioxidant and prooxidant factors in free radical metabolism shifts

towards increased lipid peroxidation with advancing age (Marjami, 2005). There are several animal and human studies proposing that free radicals motivate and happen faster the additional problems in type 2 diabetes mellitus (Anabela and Carlos, 2006; Joseph *et al.*, 2002; Paul *et al.*, 2004; Bhatia *et al.*, 2003). Lipid peroxidation plays an important role in the progression of complications of diabetes. Some studies have been showed increased levels of lipid peroxidation, as a consequence of free radical activity, in both type 1 and type 2 diabetes (Griesmacher *et al.*, 1995; Jennings *et al.*, 1991) but some other studies failed to detect any elevation in lipid peroxidation in diabetic subjects, (Velazquez *et al.*, 1991) probably because of differences of the patient population. It was studied that type 2 diabetes mellitus is connected with increased plasma lipid peroxidation (Gopaul *et al.*, 1995). Another study showed that (Davi *et al.*, 1999) diabetes mellitus is associated with enhanced lipid peroxidation. Our interest in present study was to explain the state of lipid peroxidation among type 2 diabetes mellitus patients. In this study, it was reviewed with a number of related articles on lipid peroxidation among type 2 diabetes mellitus patients.

**Lipid peroxidation in diabetes mellitus:** There is the evidence for oxidative damage in diabetic subjects as reported by Satoa *et al.* (1979). They showed that the level of lipid peroxides was higher in diabetic subjects than in normal subjects. The high levels of lipid peroxide in plasma may make an increase in lipid peroxide levels in the inner membrane of the blood vessel, which may then begin atherosclerosis. Lipid peroxidation has been involved in the pathogenesis of many disorders (Armstrong *et al.*, 1982) including naturally occurring (Nishigaki *et al.*, 1981) and chemically induced diabetes mellitus (Rerup, 1970; Higuchi, 1982). Mechanisms in the formation of lipid hydroperoxides and other biologically active metabolites, together with their effect on cellular structure and function are becoming of increasing importance to the study of diabetogenesis (Crabbe, 1987). On the other hand, lipid peroxide levels in plasma of diabetic patients have been showed to be higher than in healthy subjects (Kaji *et al.*, 1985). Satohb (1978) showed an increase in thiobarbituric acid reaction in diabetic subjects specifically in uncontrolled diabetic and diabetic subjects with angiopathy. This elevation maybe caused by organ or tissue degeneration. Higher levels of thiobarbituric acid reactive substances (TBARS), which provide an indirect measurement of lipid peroxidation and decreased erythrocyte antioxidant enzyme activities, have been showed in serum of adult diabetic patients (Arai *et al.*, 1987; Sharma *et al.*, 2000). Type 2 diabetic

patients have an increase in oxidative stress and inflammation. Increased oxidative stress in type 2 diabetes is indicated by an increase in Reactive Oxygen Species (ROS) generation; increased lipid peroxidation (Nishigaki *et al.*, 1981), protein carbonylation (Aljada *et al.*, 1995), nitro-tyrosine formation (Aydin *et al.*, 2001) and DNA damage (Dandona *et al.*, 1996).

**Alterations of lipid peroxidation in diabetes mellitus:**

Some studies showed that in diabetes mellitus patients lipid peroxidation has been increased (Griesmacher *et al.*, 1995; Velazquez *et al.*, 1991; Satoa *et al.*, 1979; Collier *et al.*, 1992; MacRury *et al.*, 1993; Neri *et al.*, 1994; Niskanen *et al.*, 1995; Santini *et al.*, 1997; Cederberg *et al.*, 2001) and also increased oxidized low density lipoprotein or Vulnerability to oxidation has also been shown in diabetes (Collier *et al.*, 1992; Neri *et al.*, 1994; Griesmacher *et al.*, 1995; Santini *et al.*, 1997). Lipid peroxidation may cause the beginning and progression of diabetes (Van Dam *et al.*, 1995; Giugliano *et al.*, 1996). There are controversy informations about whether the increased oxidative stress is merely associative rather than causal in diabetes mellitus. We have observed that the levels of malondialdehyde (MDA), a lipid peroxidation product and a marker of oxidative stress, is increased significantly in male as well as in female diabetic patients (Marjania *et al.*, 2010). This shows that diabetic patients are exposed to an increased oxidative stress via lipid peroxidation. Some other researchers have also reported elevated lipid peroxidation products in the blood samples of type 2 diabetic patients. Several studies have shown that lipid peroxidation is increased in diabetes, particularly in type 2 diabetes mellitus (Atli *et al.*, 2004; Marjami *et al.*, 2007; Maharjan *et al.*, 2008). Jain (1989) demonstrated that hyperglycemia stimulates the lipid peroxidation of RBC and (Kannan and Jain, 1994) later showed that it increases oxidative stress in cells in vitro. Contrary to our findings and to that of others, there are studies which did not find increased oxidative stress in type 2 diabetes mellitus patients (Singh *et al.*, 2007). In an animal study, Midaoui and Champlain (2005) suffered the rat from type 2 diabetes mellitus and examined oxidative stress in the model of rat. They observed that hyperglycemia alone does not cause oxidative stress unless it was accompanied by insulin resistance; thereby, implying that the involvement of reactive oxygen species is selectively related to insulin resistance (Houstis *et al.*, 2006).

**Biomarker of lipid peroxidation:** Lipid peroxidation expressed as malondialdehyde (MDA) is certainly the most used to estimate the peroxidation processes. This aldehyde is produced by the radical breakdown of

hydroperoxides resulting from poly unsaturated fatty acid peroxidation containing at least two double bonds (Hecker *et al.*, 1987). MDA is generally measured in biological fluids (e.g., urine, serum and plasma) as well as in isolated cells after reaction with thiobarbituric acid (TBA) or diethyl TBA, which are purified by HPLC and measured by absorbance at 532 nm, or by fluorimetry (Guichardant *et al.*, 1994; Berger and Chioléro, 1995).

**The measurement of serum malondialdehyde:** To 0.5 mL serum, 2.5 mL of trichloroacetic acid is added and the tube is left to stand for 10 min at room temperature. After centrifugation at 3500 rev./min for 10 min, the supernatant is decanted and the precipitate is washed once with sulfuric acid. Then 2.5 mL sulfuric acid and 3 mL thiobarbituric acid (TBA) in sodium sulfate are added to this precipitate and the coupling of lipid peroxide with TBA is carried out by heating in a boiling water bath for 30 min. After cooling in cold water, the resulting chromogen is extracted with 4 mL of n-butyl alcohol by vigorous shaking. Separation of the organic phase is facilitated by centrifugation at 3000 rev./min for 10 min and its absorbance is determined at the wavelength of 530 nm (Satoh, 1978).

**Mechanisms for lipid peroxidation in diabetes mellitus:**

The mechanisms behind the increased oxidative stress in diabetes are not completely clear. There is some evidence that point to a number of mechanisms, increasing production of free radicals such as superoxide (Nath *et al.*, 1994; Ceriello *et al.*, 1991; Wolff *et al.*, 1991; Dandona *et al.*, 1996) or decreasing antioxidant status (Asayama *et al.*, 1993; Tsai *et al.*, 1994; Ceriello *et al.*, 1997; Santini *et al.*, 1997). Superoxide can eliminate by enzyme superoxide dismutase. Zinc as a cofactor of enzyme Cu-Zn superoxide dismutase is an important element for activity of this enzyme. The function of zinc in the body metabolism is based on its enzymatic affinity, such as a zinc-enzyme complex or Zinc metalloenzyme. In humans and animals, diabetes maybe results in disturbance of these vital trace elements (Kinlaw *et al.*, 1983). In most mammals, insulin is stored as zinc crystals and is probably secreted in zinc form. Zinc has important role in regulating the defense system and its dysfunction in diabetes mellitus may be related in part to the status of zinc (Mocchegiani *et al.*, 1989). Lack or inadequate supply of zinc produces functional defect and can result in disease. The clinical importance and evaluation of zinc in regard to different diseases, including diabetes mellitus remains conflicting as well as controversial. A lot of questions still remain unanswered. Many scientific reports emphasize the role of micronutrient status in

patients with type 1 or 2 diabetes mellitus (Mooradian *et al.*, 1994; Anderson, 1995; Chaumer, 1998; Anderson *et al.*, 1997; Ravina *et al.*, 1999). Zinc maybe makes normalize glycemia and a restored zinc status in type 2 diabetic patients may work against the harmful effects of oxidative stress and helping to prevent many complications associated with diabetes. In people with diabetes, the vulnerability to oxidative damage maybe partly associated with deficient antioxidant micronutrient status. Impairment of zinc status has been reported as an exacerbating factor in the progression of diabetes (Walter *et al.*, 1991; Bolstein-Fujii *et al.*, 1997; Ruiz *et al.*, 1998; Chaumer, 1998). Zinc may affect the processes collaborated with oxidant stress, the importance of its status have not been studied widely (DiSilvestro, 2000). A possible explanation for this is that there is loss of a large amount of Zn from the body via urine. The source of the Zn that being excreted remains unresolved. There is a simultaneous zinc decrease in blood and in tissue Zn stores. It is not clear if this is the result of hyperzincuria, or from an independent occurrence, an insulin or hyperglycemia related induced loss of Zn from tissue stores. Zinc would then be released into the plasma and after that excreted. Present finding showed that in patients with type 2 diabetes plasma lipid peroxidation was significantly increased and that zinc levels were decreased compared with control subjects (Marjani, 2006). Some of the previous studies are also showed the increased lipid peroxidation and decreased Cu-Zn superoxide dismutase activity in patients with type 2 diabetes (Vanizor *et al.*, 2001; Cigremis *et al.*, 2003). Sundaram *et al.* (1996) studied type 2 diabetic patients showed an increase in lipid peroxidation from the onset of disease. Study of Nourooz-Zadeh *et al.* (1997) showed that alterations in lipid peroxidation having relationship with the underlying metabolic abnormalities in type 2 diabetic subjects rather than to the onset of complications. Some studies describe that plasma Zn in type 2 diabetes mellitus patients is decreased (Walter *et al.*, 1991; Evliaoglu *et al.*, 2002), whereas, others show no significant differences (Evliaoglu *et al.*, 2002; Zargar *et al.*, 1998) compared to controls. Present finding showed that in type 2 diabetes mellitus patients, erythrocyte Cu-Zn superoxide dismutase activity is decreased (Marjani, 2006). Other studies have reported that erythrocyte superoxide dismutase activity in this type of patients was either decreased (Palanduz *et al.*, 2001; Turk *et al.*, 2002), increased (Hunt and Wolff, 1991) or no significant differences were observed (Sumovski *et al.*, 1992). Possible explanations include reduced antioxidant protection in type 2 diabetes mellitus and/or extremely increased amounts of free radicals that overpower the defense system. Other explanations

include decreased activity of Cu-Zn superoxide dismutase related to either increased free radical production causing oxidation and then denaturation of the enzyme, or alternatively glycation of the enzyme and then inhibition of enzymatic activity (Obrosova *et al.*, 2002). Zinc is a required cofactor for different antioxidant enzymes, especially superoxide dismutase. Changes of zinc metabolism and reduction of zinc might be expected contribute to tissue damage observed in diabetes (Horie *et al.*, 1981). Increased lipid peroxidation, decreased plasma zinc and reduced erythrocyte Cu-Zn superoxide dismutase activity may make sensitive patients with type 2 diabetes to cardiovascular complications. Free radicals are formed in diabetic patients by glucose autooxidation, polyol pathway and non-enzymatic glycation of proteins (Memisogullari *et al.*, 2003). High levels of free radicals and simultaneous decrease of antioxidant defense systems can lead to the damage of cellular organelles and enzymes, increased lipid peroxidation and development of complications of diabetes mellitus (Maritim *et al.*, 2003). Hypoinsulinaemia in diabetes increases the activity of the enzyme fatty acyl coenzyme A oxidase, which begins  $\beta$ -oxidation of fatty acids, resulting in lipid peroxidation (Acworth *et al.*, 1997). Increased lipid peroxidation damages membrane function by decreasing membrane fluidity and changing the activity of membrane-bound enzymes and receptors. The products of lipid peroxidation are harmful to most cells in the body and are associated with different kind of diseases, such as atherosclerosis and brain damage (Fujiwara *et al.*, 1989). Hyperglycemia can load the cells with more free radicals (Atalay and Laaksonen, 2002). Increased oxidative stress has been shown to be increased in type 2 diabetes mellitus and it could cause impaired insulin production, release, or function in type 2 diabetes (Bonfont-Rousselot *et al.*, 2000; West, 2000).

### CONCLUSIONS

Uncontrolled blood glucose levels in type 2 diabetic patients can cause to a lot of pathological situations that in the end result in microvascular and macrovascular complications. Prevention of lipid peroxidation may help to hinder the development of diabetic complications. These states of affairs may play an important role in progress of cardiovascular abnormality in type 2 diabetic patients. We propose that production of free radicals can be reduced by preventing high blood glucose levels and by the control of instabilities in blood glucose levels. A contributor to these instabilities in blood glucose is glycaemic control by using of fast blood sugar test.

Furthermore, the earlier assessment of the advancement of diabetes that firmly control of blood glucose can be obtained; the greater will be the decrease in diabetic complications. Patients with type 2 diabetes may have very high physiological antioxidants requirements. Supplementation with free radical scavengers has the potential to boost antioxidant defenses and in the end these important factors up-grade the patient's quality of life and prevent sudden silent myocardial infarction.

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