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Review

Role of Protein Oxidation, Lipid Peroxidation and Antioxidant Defense Systems on Diabetes Mellitus

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Abstract: Diabetes; is a chronic disease whose prevalence has been increasing day by day in the world. Several mechanisms have been causing the formation of diabetes. One of these mechanisms is the oxidative stress that occurs in cells and tissues. Oxidative damage which is caused by reactive oxygen species; has an important role in the formation of complications due to diabetes. Hyperglycemia caused by diabetes increases free radical formation. The antioxidant defense system tries to balance the toxic effects of reactive oxygen species. A, C, E vitamins and glutathione is Non-enzymatic antioxidants, and superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase is enzymatic antioxidants against reactive oxygen species. In this study; the balance between antioxidants and free radicals, the role of oxidative stress in diabetes and possible therapeutic effects will be examined.

Key Words: *Malondialdehyde, Oxidative damage, Free radicals, Antioxidant defense.*

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Introduction

Diabetes is one of the most important diseases that cause cellular damage in living organisms and cause deaths after advanced cell damage. According to the research conducted by the International Diabetes Federation, there are 387 million diabetic patients in the world. This ratio is expected to exceed 600 million in 15 years (Fernandes et al., 2014). The most important biomarker of diabetes is the rise of fasting blood glucose. If the fasting blood glucose is greater than 126 mg / dl or the HbA1c result is more than 6.5 mg, it indicates the presence of diabetes in the patients. Moreover, the most important cause of diabetes can be considered as the total or partial suppression of the amount of insulin. Disruption in insulin production; some biomolecules (lipid, protein and carbohydrate) may cause inadequate metabolic functions (Gezginci et al., 2009). Inability to control hyperglycemia can lead to many diseases such as diabetic retinopathy, diabetic nephropathy in the kidneys, diabetic neuropathy in the nerves, myocardial infarction in the heart,

and atherosclerosis in the veins (Jeffcoate, 2004). In this study; biochemical effects of oxidative stress and antioxidant defense system on diabetes mellitus were examined.

1. Some Free Radicals and Reactive Oxygen Derivatives

There is a need for molecular oxygen in all living things to maintain vital activities. About 2% of the oxygen is converted to reactive oxygen derivatives by metabolism. Reactive oxygen derivatives can cause toxic effects in living organisms causing oxidative damage (Seifried et al., 2007; Sugeçti et al., 2016; Sertçelik et al., 2018). Reactive oxygen derivatives that occur in vivo can cause oxidative damage on many biomolecules. Reactive nitrogen causes cellular damage together with reactive oxygen species. Most of the cellular damage occurs on the cell membrane. Many diseases like cancer, cellular aging, and diabetes can occur occurred as a result of this damage.

1a. O^{2-} (Superoxide)

O^{2-} radical is produced as an intermediate step in the reduction of radical molecular oxygen. The molecular oxygen atom (O_2) forms a superoxide radical as an unstable structure with an electron-losing consequence. The O^{2-} radical does not directly cause damage to living cells. It causes significant cell damage when it is used as a source of H_2O_2 (Hydrogen Peroxide). However, the optimal amount of O^{2-} radical plays an important role in many helpfull reactions in living organisms. The most important ones are bactericidal activity of neutrophils, apoptosis, regulation of inflammation and vascular functions. In the cells, increased O^{2-} radical is tried to be reduced by superoxide dismutase (SOD) enzyme by converting O^{2-} radical into hydrogen peroxide and oxygen. O^{2-}radicals production occurs in the presence of glucose at high levels as a result teh cellular metabolic activity. This is one of the most important triggers of diabetes. (Rosen et al., 1998, Maritim et al., 2003, Memişoğluları et al., 2003).

1b. H_2O_2 (Hydrogen Peroxide)

Peroxide accures as a result of the oxygen molecule receives 2 electrons from a different molecule, H_2O_2 occurs when this structure reacts with two hydrogen molecules. H_2O_2 can also be produced as a result of exchange with SOD, an important antioxidant enzyme. The H_2O_2 can easily pass through the cell membrane, penetrates the cytosol and can lead to cell damage. Compared to the O_2 molecule, H_2O_2 is associated with more oxidative damage (Vincent et al., 2004).

1c. OH (Hydroxyl Radical)

The Hydroxyl Radical is the most reactive radical that can easily react with many biochemical substances (such as amino acids, organic acids, nucleic acids and sugars) Among free radicals, OH gives the most damage (Ayala et al., 2014). The increase in OH radicals is known to produce new radicals by causing a proton degradation in many molecules such as thiols and fatty acids in vivo. As a result of these reactions, cell damage occurs. This damage can trigger cancer and aging, especially diabetes (Yin et al., 2011).

2. Cell Damage and Diabetes Caused by Oxidative Damage

Reactive oxygen derivatives damage to the most important biomolecules which are necessary for the survival of vital activities in living organisms. These molecules are proteins and lipids. Possible sources of oxidative damage in diabetic patients are glucose oxidation, reduced glutathione and low E vitamins. Also; inadequate antioxidant defense system triggers oxidative stress in diabetic patients. Especially; the reduction of superoxide dismutase and catalase activity in tissues significantly increases the oxidative damage (Haskins et al., 2003; Khan et al., 2017). In previous research it has been found that vascular cells produce reactive oxygen derivatives in the hyperglycemic state. It has been suggested that oxidative damage plays an important role in the pathogenesis of nephropathy. However, the mechanism of action of oxidative stress on diabetic complications is not fully understood. The results of the investigations showed that lipid peroxide and 8-hydroxydeoxyguanosine levels were increased in diabetic rats. The increase in the amount of this substance is one of the most important indicators of oxidative tissue damage (Ha and Kim, 1999). In another study; increased amounts of glucose in extracellular and intercellular media caused oxidative stress (Giugliano et al., 1995; West, 2000). Another research shows that oxidative stress over endothelium and beta cells have a negative effect and cause functional disorders. Damage in beta cells; is highly proportional to the high concentration of glucose and increased fatty acid levels found in the medium (Evans et al., 2003). The antioxidant enzymes found in beta cells are very few. For this reason, it is highly sensitive to reactive oxygen species (Tiedge et al., 1997). Oxidative stress on beta cells can cause damage to mitochondria and in this case insulin release can be significantly reduced (Drews et al., 2010).

2a. Protein Oxidation

Increase in protein carbonyl (PCO) levels and decreased protein thiol levels are used as a biomarker for oxidative protein damage in vivo. PCO products are formed as a result of damage to many amino acid residues or peptides that cause reactive oxygen species to react with proteins. Measuring the amount of PCO is one of the most important indicators of oxidative protein damage (Levine et al., 1994,). Also; free radicals cause oxidative protein damage as a result of damage to thiol groups in proteins (Büyükgüzel, 2013). Damage over proteins can happen directly by reactive oxygen species or indirectly by reaction of seconder products, which occur as a result of oxidative stress, and proteins. The increase in damaged proteins due to oxidative stress leads to damage to cells and tissues (Butterfield et al., 1998). Proteins; are less sensitive to free radicals than unsaturated oils. They do not suffer damage as long as there are not too many free radicals in the environment (Chesemann and Slater, 1993). Free radicals' effects over proteins can also cause peroxides. The advanced level of protein oxidation can lead to diabetes and cardiovascular diseases, especially cancer. In a study showing the association of protein oxidation with diabetes; it has been found that the total protein content of the blood sera from diabetic rats decreases significantly. A reduction in protein oxidation or mRNA damage resulting in protein synthesis has been suggested as the reason for this (Peavy et al., 1985).

2b. Lipid Peroxidation

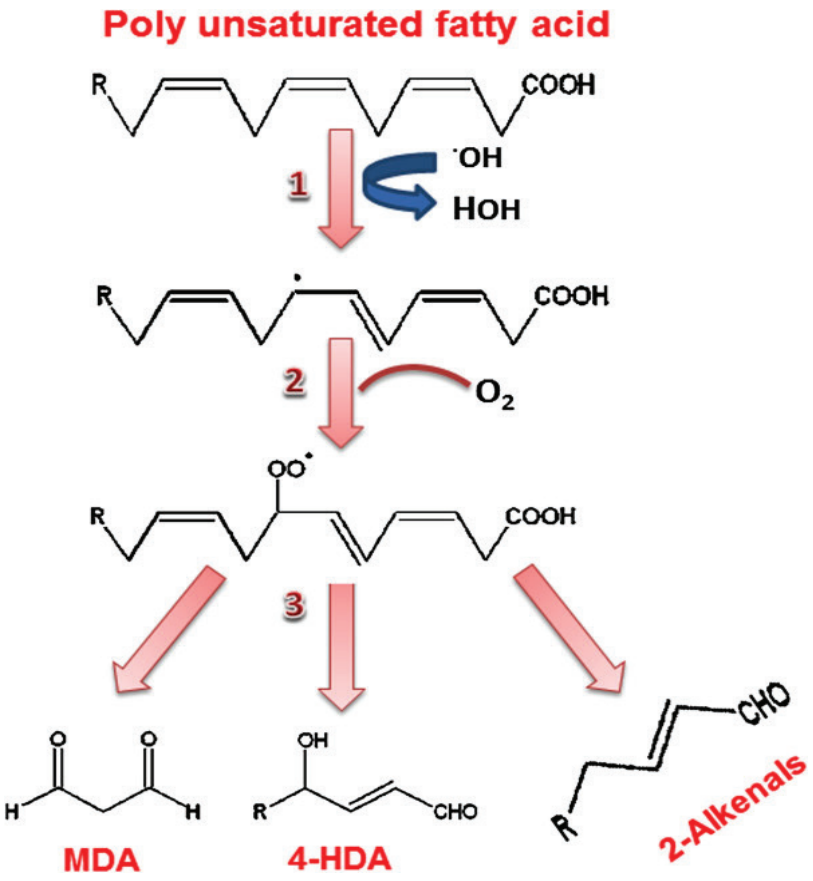
Studies have shown that oxidative damage from free radicals is directly linked to diabetes. Occurence of reactive oxygen species is determined as a result of lipid damage with glycation which accurues with diabetes. (Wolf, 1993; Rosen et al., 1998). The polyunsaturated fatty acids of the organic molecules such as phospholipids and glycolipids present in the cell membrane are converted to a variety of by-products such as peroxides, alcohols, aldehydes by free radicals. This chain of reactions is called lipid peroxidation. Malondialdehyde (MDA) is the most commonly used oxidative stress biomarker for lipid peroxidation and lipid oxidation. In addition, lipid oxidation can occur in end products such as the resultant 4-hydroxy nonenal (Figure 1). These products, which are the result of lipid oxidation, as a result of reaction with protein and DNA can cause damage. The amount of MDA can be measured by spectrophotometric methods. The amount of MDA increases in proportion to the lipid damage. (Young and Woodside, 2001; Niki et al., 2005; Masella et al., 2005). Many studies have found links between diabetic complications and lipid peroxidation (Vincent et al., 2004, Memişoğulları and Bakan, 2004). In many studies, it has been found that LDL oxidation increases in diabetic patients (Mowri et al., 2000; Julius et al., 2005). Damaged lipids; accumulates in the cell membrane, preventing receptors from functioning actively (Cai and Harrison, 2000). Therefore, prevention of lipid damage is very important for diabetics.

3. Antioxidant Defense System and Diabetes

Antioxidant mechanisms that provide protection against free radicals in living organisms are divided into enzymatic and non-enzymatic antioxidants. The most important non-enzymatic antioxidants against free radicals are Vitamins A, C and E, glutathione, albumin, and uric acid. The most important enzymatic antioxidants found in living organisms are; catalase, glutathione peroxidase, superoxide dismutase and glutathione reductase. All antioxidants are normally tried to prevent oxidative stress caused by free radicals. Antioxidants can be used in the treatment of many diseases such as cancer, diabetes and heart diseases caused by reactive oxygen species (Maritim et al., 2003, Sugeçti and Büyükgüzel, 2017).

There are many studies investigating the effect of antioxidant treatment on diabetic patients. In patients with type 1 diabetes, who were given vitamin C at certain concentrations, many complications of diabetes were seen to decrease. It has also been found that vitamin C lipid metabolism affects positively in patients with type 2 diabetes (Cunningham et al., 1994; Eriksson et al., 1995). Oxidative damage has been shown to be reduced in type 2 diabetes patients who are given a certain dose of vitamin E (900 mg / day) (Paolisso et al., 1993). In another study on diabetic rats; the effects of vitamins A, C and E and ω-3 fatty acid on the antioxidant defense system were investigated. In the final results; it has been found that SOD enzyme and catalase enzyme activity in the liver are decreased statistically in the heart of diabetic rats given no substance. Catalase enzyme activity increased statistically in the heart of rats given A, C and E vitamins. It has been determined that omega-3 fatty acid does not have any effect on the antioxidant enzyme activity of diabetic rats (Tabei et al., 2015). In another research; it has been found that nonenzymatic antioxidants (vitamin E, lipoic acid, and vitamin C) applied to diabetic patients increase oxidative stress during methemoglobin synthesis and decrease hemoglobin levels (Coleman et al., 2003).

Figure 1. Chemical reactions of lipid peroxidation (Shah et al., 2014).



Conclusion

It is thought that oxidative damage due to reactive oxygen species play an important role in the development of diabetes. But the mechanism of interaction between oxidative damage and diabetes has not yet been resolved. Lipid peroxidation and protein damage are thought to be increased in diabetic patients. It is thought that these antioxidants can be used in the treatment of many diseases such as cancer, diabetes, and cardiovascular disease, where oxidation of lipids and proteins can be prevented by using antioxidant protectors.

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Conflict of Interests

Authors declare no conflict of interests

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