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## ROLE OF MITOCHONDRIA IN DIABETES AND ITS COMPLICATIONS

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**ABSTRACT:** It has been reported that mortality associated with diabetes is about 2.9 million cases in World. The most common diabetes complications consist of cardiovascular disease, renal failure and blindness. The increase of lipid oxidation and reduction of antioxidants in mitochondrial dysfunction were showed. The role of investigation on mitochondria damage is requiring for evaluation of insulin resistance. In this study, we reviewed the relationship between mitochondrial function to diabetes and its complications according to latest study during 2011 - 2015 using databases such as pubmed, science direct and web of science.

**INTRODUCTION:** Increased blood sugar due to reduction or dysfunction insulin leads to diabetes mellitus. The type 1 often seen in children due to failure of the pancreas for insulin secretion and its type 2 is a multi-factorial disease, especially due to obesity and genetic disorders <sup>1, 2</sup>. This disease is linked to many problems such as end stage renal disease (ESRD), diabetic macular edema (DME), and cardiovascular disease (CVD) <sup>1, 3 - 5</sup>. The increase of diabetes prevalence created serious problems in today's societies, so that dispel them required to spend many costs <sup>6</sup>. A conducted research in 2000 was showed that the prevalence of diabetes would increase by 37% in the future 30 years <sup>7</sup>.

Statistics were determined that according to collected data from 130 countries in 2013, there are 382 million diabetic patients and possibly will reach to 592 million by 2035 <sup>8</sup>. Today although, there are antidiabetic drugs, but mainly intention is to the use of herbal medicine <sup>9 - 11</sup>. It has been estimated about 2.9 million mortality attributed to diabetes in 2000 (mainly associated with type II diabetes).

In 2004, it has been mentioned the increase of death heart disease and stroke associated with diabetes in the United States <sup>12</sup>. There is mitochondria in the cytoplasm of all eukaryotic cells and has a key role in the oxidative phosphorylation, glycolysis, oxidation of fatty acids and energy homeostasis <sup>12, 13</sup>. The effect of mitochondrial dysfunction in the development of type II diabetes should be checked because there are differences of opinion on this matter and has not yet determined cell's response to mitochondrial dysfunction and its released signal <sup>14, 15</sup>. In line with our recent studies on diabetes complications

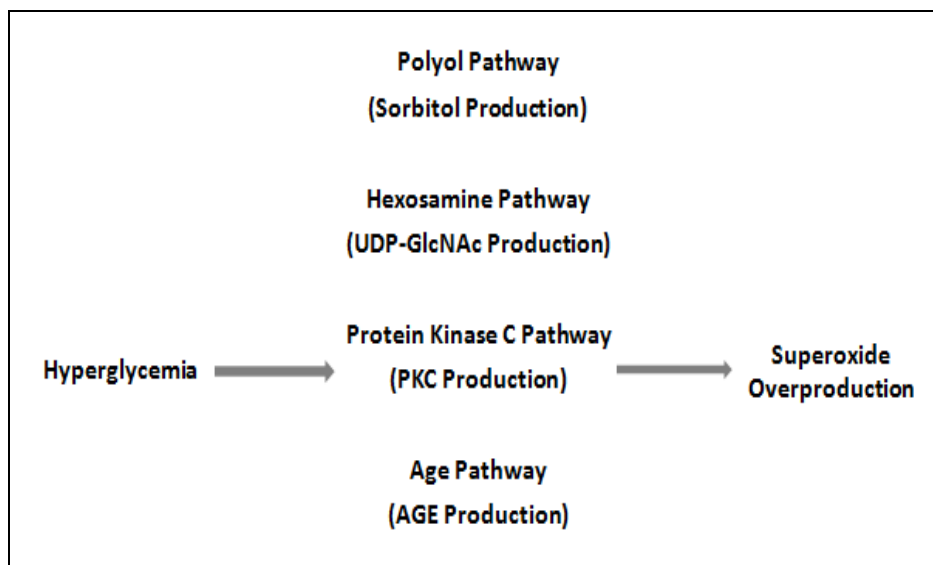
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<sup>16</sup>, peroxidane / antioxidant imbalance <sup>17</sup>, heart failure <sup>18</sup>, trace element changes <sup>19</sup>, as well as on the mechanisms of plant ingredients in the treatment of diabetes mellitus <sup>20</sup>, this study designed. The role of mitochondria in the development of complications associated with diabetes was viewed.

**MATERIAL AND METHODS:** To evaluate of new studies, we used databases such as pubmed, science direct, and web of science from 2011 to 2015.

**Mitochondria and Complications of Type II Diabetes:** Increase of NEET protein activity makes maintain fat reserves and energy homeostasis and it

has well been known that reduction of NEET protein in the mitochondria resulted in appearance of symptoms pre-diabetes such as impaired glucose metabolism <sup>14</sup>. Our results on the evaluation of oxidation and peroxidation in women with type 2 diabetes showed that lack of balance in the oxidation and peroxidation seen in these patients. We examined the levels of superoxide dismutase, malondialdehyde and catalase and found that significant changes in these parameters occur in diabetes <sup>17</sup>. When mitochondria is under high oxidative stress condition during early stages of diabetes, mitochondrial dysfunction is evident **Fig. 1**; on the other hand, to normal insulin function occurs followed by decreased lipid oxidation <sup>21</sup>.



**FIG. 1: THE ROLE OF HYPERGLYCEMIA IN MITOCHONDRIAL SUPEROXIDE OVERPRODUCTION DURING EARLY STAGE OF DIABETES** <sup>22</sup>

We in a case study on 60 patients with type 2 diabetes found that imbalance of essential elements such as zinc and copper occur under diabetes so that it is associated with decrease and increase in zinc and copper respectively <sup>19</sup>. Diabetes is often associated with obesity that probably it is main reason disruption of energy homeostasis and resulted from mitochondrial dysfunction <sup>23</sup>. The comparison between different animal models of diabetes were determined that mitochondrial dysfunction there was only in models with high-fat diet (models for diabetes type 2) <sup>24</sup>. Perhaps Hsp60 is main factor relationship between diabetes and obesity. Studies were shown that in mice with knockout Hsp60 were occurred hypothalamic mitochondrial dysfunction and lead to the development of insulin resistance.

Moreover, the lack of leptin regulation during obesity resulted in reduction of Hsp60 production and development of type 2 diabetes. These event scan be reversible by weight loss <sup>25</sup>. Neuropathy is one of the complications of type 2 diabetes. During diabetes the transfer of BAX and cytochrome C from mitochondria to the cytoplasm lead to apoptosis in the hippocampus neurons and ultimately loss of spatial memory <sup>12</sup>. Evidence suggests that diabetes can be one of the main factors of Alzheimer's disease. In addition, it has well been known that mitochondrial dysfunction can be associated with Alzheimer's disease <sup>26</sup>. A survey conducted on patients with type 2 diabetes was shown that there was a link between endothelial dysfunction and impaired mitochondrial function.

**TABLE 1: THE PERFORMED STUDIES ON MITOCHONDRIA AND COMPLICATIONS OF TYPE 2 DIABETES**

Type of study	The country of study design setting	Experiment result(s)	Author(s)
<i>In vivo</i> (the designing of mouse model with altered adipocyte expression of mito NEET)	USA	The maintenance of fat reserve by increase of NEET protein activity	Kusminski <i>et al.</i> , 2012
Human study (the evaluation of oxidation and peroxidation conditions in women with type 2 diabetes)	Iran	The confirmation of imbalance in the oxidation and peroxidation during diabetes	Barari <i>et al.</i> , 2014
<i>In vivo</i> study (diabetes induction with streptozotocin injection in rat)	USA	The decrease of lipid peroxidation resulted in improvement of insulin function	Noriega-Cisneros <i>et al.</i> , 2013
Human study (the evaluation of trace element during diabetes)	Iran	The observation of imbalances in zinc and copper during diabetes	Mahdizadeh <i>et al.</i> , 2014
<i>In vitro</i> study (hyperglycemia effects on human fibroblasts and endothelial cells)	Sweden	In the human with type 2 diabetes occur mitochondrial dysfunction	Moruzzi <i>et al.</i> , 2014
<i>In vivo</i> (mouse model with Knockdown of Hsp60)	USA	There is hypothalamic mitochondrial dysfunction in mice with knockout Hsp60 and ultimately the development of insulin resistance	Kleinridders <i>et al.</i> , 2013
<i>In vitro</i> study (the study on middle frontal gyrus, superior and middle temporal gyri, and frontal cortex from human brain)			
Human study (the use of brachial artery ultrasound and digital pulse amplitude tonometry methods)	USA	There is the connection between endothelial dysfunction with impaired mitochondrial function in diabetic patients	Kizhakekuttu <i>et al.</i> , 2012
<i>In vivo</i> study (the induction of type 2 diabetes with high-fat diet and STZ in mice)	USA	the main reason of coronary arteries dysfunction is SOD2 ubiquitination and expression reduction by ROS	Cho <i>et al.</i> , 2013
<i>In vitro</i> study (the measurement of ATP synthesis rate and ROS generation in mitochondria isolated from NGT obese and 11 T2DM subjects)	USA	The poor performance of skeletal muscle by ATP production reduction during insulin resistant	Daniele <i>et al.</i> , 2014
<i>In vitro</i> study (the effect of high glucose concentrations in bovine retinal endothelial cells and the evaluation of retinopathy in obtained retina from STZ-induced diabetic rat and mice and human donors)	USA	The activation of RAC1-NOX2 signaling in retinal cells resulted in mitochondrial damage	Kowluru <i>et al.</i> , 2014
Human study (the evaluation of 94 urine metabolites by gas chromatography-mass spectrometry)	USA	The reduction of expression of OAT1 and OAT3 by reduction of PGC1 $\alpha$ production and mitochondrial DNA during nephropathy	Sharma <i>et al.</i> , 2013
<i>In vitro</i> study (the use of renal cortices from db/db mice for biochemical factor measurement )	Australia	The presence of oxidized CoQ10 mitochondria is one of the main reason of nephropathy	Sourris <i>et al.</i> , 2012

In this study, measurement of the inner mitochondrial membrane potential, mitochondrial mass and mitochondrial superoxide production was showed that there was dramatically damage, which was districted as endothelial dysfunction<sup>27</sup>. Increase of ROS production resulted in SOD2 ubiquitination and reduction of SOD2 expression in mitochondria is the main causes of coronary arteries dysfunction<sup>28</sup>. One of the events that occur under conditions of insulin resistance is reduction of ATP production in skeletal muscle due to their

poor performance. There is a significant correlation between the increase of free fatty acids in plasma and decrease of ATP production in mitochondria to increment of oxidative stress in patients with obese NGT and T2DM<sup>29</sup>. Likely mitochondrial damage resulted from increase of ROS production in the cytosol is due to activation of RAC1-NOX2 signaling in retinal cells and eventually causes retinopathy<sup>30</sup>. Impairment of mitochondrial metabolism determines by nephropathy.

In a study was showed that diabetics patients with nephropathy was lowered expression of OAT1 and OAT3 and this results were confirmed by reduction of PGC1 $\alpha$  production and mitochondrial DNA, which indicates a lack of regulation of mitochondrial metabolism in diabetes<sup>31</sup>.

In another study was mentioned that the presence of oxidized CoQ10 mitochondria is other reason neuropathy. It was shown that diabetic mice treated with CoQ10, was improved mitochondria function because normalized of ATP production and level of oxidative stress<sup>32</sup>.

**CONCLUSION:** In this study, we reviewed the role of mitochondria in complication of diabetes. Our review indicated that damages of mitochondria could be important in development of diabetes such as cardiomyopathy, nephropathy, and retinopathy.

Also insulin resistance in diabetes can be associated with alzheimer probably due to dysfunction of mitochondria. Therefore, we need to separate plant compounds and examine their effects on diabetes.

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