Type II Diabetes Mellitus and Oxidative stress

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Abstract: Type II Diabetes Mellitus (TYIIDM) is a well-known global challenge. It affects a large population of the world and has become a major concern in recent years. It is commonly observed in young adults ageing from 24-40. Majority of adults beyond the age of 40 suffer from this metabolic disorder. Oxidative stress (O.S) is the first step that can lead to any disease condition. This also holds true for TYIIDM. We will look at the molecular mechanisms that leads to an increase in the O.S of the person suffering from TYIIDM. We will also look how alternative pathways of glucose oxidation other than glycolysis is a key factor in generating ROS and RNS. The switching of this pathway from glycolysis is the main focus of this review article.

Index Terms – Type II Diabetes Mellitus, oxidative stress, reactive oxygen species, reactive nitrogen species, glucose metabolism glyceraldehyde-3-phosphate, fructose-6-phosphate, dihydroxyacetone phosphate.

I. INTRODUCTION

Type II Diabetes Mellitus(TYIIDM) is a serious health concern. This disorder impairs the glucose metabolism [1],and is often connected to oxidative stress cell dysregulation and insulin resistance [3].The overall metabolism of the diseased person is affected in many ways [2]. Previous literature on the topic suggest thatlack of physical exercise, sedentary habits, irregular sleep, high carbohydrate-rich diet, mental stress and several environmental and genetic factors may lead to this disorder. Obese people whose BMI (Body Mass Index) >35 in case of females and > 40 in case of males are at a higher risk of developing this disorder. Previous works suggest that obesity is often the primary root cause of TYIIDM. Diabetic patients are often immuno-compromised and at a higher risk of developing the disease as oxidative stress is often high in these individuals [2,3]. Oxidative stress is defined as the imbalance between the generation of free radicals and their quenching by antioxidants [4,5]. Free radicals are defined as ionic species that have unpaired electrons. Most common free radicals include ROS (reactive oxygen species) and RNS (Reactive Nitrogen Species) [5]. Free radicals are often quenched by antioxidants like GSH (glutathione) SOD (superoxide dismutase) CAT (catalase). Generation of free radicals and their quenching by antioxidants is a normal process that keeps the body under homeostasis. This includes the immune response to pathogens by destroying their cell wall and cell membrane, several signaling cascades, cross-talks between different cells of thesame tissue. The counter effects of free radicals and antioxidants are one of the most important prerequisites for the proper functioning of cells in synchrony [7]. However diabetic patients generate a large number of free radicals that create an imbalance and often damage the cellular machinery [8,9]. This is often done by those unpaired electrons of free radicals that react with membrane lipids and causes lipid oxidations. Proteins which are composed of a basic amino group and a carboxylic acid group are often oxidized by these free radicals which hampers their tertiary structure and thereby effects proper folding of such proteins and eventually disturb its functions [10]. Oxidative stress also makes such individuals more prone to pathogenic invasions and is the root cause of early ageing and sometimes even death.

II. OXIDATIVE STRESS AND RELATED COMPLICATIONS

O.S is one of the key players in diabetic patients. Here we will look at some of the important processes that cause severity in the disease –

1–Advanced Glycation of End products (AGE) –

Proteins play a central role in maintaining the homeostasis of the cell. Any change in the protein structure can hamper the normal process and functioning of the cell. Intracellular and extracellular proteins are negatively modified to AGE as their amino acids react with AGE precursor [13-15]. Reduced Carbohydrates (Glyoxal, methylglyoxal deoxyglucosone) act as AGE precursors [16,17]. These AGE precursors bind to AGE receptors like AGE R1, AGE R2, AGE R3, RAGE. AGE precursors can also react with the components of E.C.M and promote ROS generation thereby promoting O.S. Lipids Nucleic Acids Carbohydrates and E.C.M. are modified to AGE [18]. Hyperglycaemia which is the characteristic feature of TYIIDM has shown an increase in these AGE products [19]. The mechanism involves autooxidation of glucose to glyoxal [16,17]. Triose phosphates like Glyceraldehyde 3-phosphate (G-3-P) and dihydroxyacetone phosphate (DHAP) are dephosphorylated in a nonenzymatic manner to produce methyl glyoxal. Formation of amadori product is also linked to O.S in diabetic patients. Amadori product is formed when 1 amino 1 deoxy fructose lysine is broken down [20]. AGE products and their binding to AGE receptors also increase O.S by increasing peroxidative stress pathway like the PKC pathway [21].

2- Di-Acyl Glycerol formation and PKC activation-

PKC Protein Kinase C phosphorylates different cellular proteins and acts as their modulator. This modulation is done by phosphorylating certain enzymes that can activate them or deactivate them. The enzyme plays a key role in the signalling involving Ca^{+2} ions and Di-Acyl-Glycerol (DAG) [22].Reports and literature on PKC suggest that at-least 11 isoforms of PKC are found in living systems. They belong to Serine Theorine kinase family. Increase in G-3-P Dehydrogenase (G-3-PD.H) in hyperglycaemic condition leads to an increasing in the level of DHAP [8]. DHAP which is converted to G-3-P by the action of isomerase reacts with fatty acids and lead to the *denovo* synthesis of Di-Acyl Glycerol (DAG) [8]. Increased cellular levels of DAG which may also be a product of the breakdown of phospholipids such as phosphatidylcholine (PC) and Phosphatidylserine (PS) may induce the PKC pathway [24]. This induction of pathway may be contributing to the interaction of AGE with extracellular receptors (RAGE) [18].The PKC pathway increases ROS generating enzymes like NADPH oxidase and lipoxygenase which results in an oxidative environment [25].

3-Hexosamine Pathway –

This pathway is rarely seen in normal individuals. In normal individuals, glucose is broken down to simple sugars and enters the Krebs cycle and Electron Transport Chain (ETC) to generate ATP for cellular activity. However, this is not the case with people suffering from TYIIDM. Individuals that suffer from hyperglycaemia and TYIIDM switch to another pathway known as the hexosamine pathway. The key intermediate of this pathway if fructose-6-phosphate (F-6-P) [26]. This pathway is controlled by the activity of a rate-limiting enzyme known as the Glucosamine fructose amidotransferase (GFAT) [27]. In the reaction, the F-6-P is converted into Glucosamine-6-P. The intermediate of this reaction is Uridine-N-acetyl Glucosamine (UDP-Glu-Nac). This reaction is mediated by Uridine-N-acetyl Glucosamine synthase. Uridine-N-acetyl Glucosamine is a vital compound for the formation of glycosyl chains of proteins and lipids. It has been reported that in hyperglycaemic patients GFAT increases which increase the levels of UDP-Glu-Nac. This is also related to an increase in the activity of O-Glucosamine-N transferase [28,29]. This leads to an increase in the activity of TGFα and TGFβ. This is linked to the inhibition ofmesangial cells mitogens.TGFα and TGFβ also causes the proliferation of collagen matrix and basement membrane thickening [30-32]. Toxic and pro-oxidative role of the hexosamine pathway is linked to severe diabetes complications and nephropathy [27].

4- The Polyol Pathway —

This pathway is a minor pathway which is seen in glucose metabolism. The reason is that the key enzyme that triggers glucose to follow this pathway has a very high Km i.e., has a very low affinity towards glucose. Glucose is converted to Sorbitol through this pathway and the key enzyme aldol Reductase (AR) uses NADPH as a cofactor [8]. In normal condition, sorbitol is rarely formed and glycolysis is the major pathway. In case of hyperglycaemic condition large amount of glucose is diverted to follow this pathway leading to increase in the condition of the sorbitol which in turns increases the NADPH consumption as NADPH is the cofactor for this pathway [30,33-34]. The increase in the consumption of NADPH affects the redox cycle of the cell and thereby complicating the symptoms. NADPH is used as a cofactor for the synthesis of cellular antioxidants like GSH and GPx [34-35]. An increased in the consumption of NADPH through the polyol pathway makes it difficult for the cell to regenerate such antioxidants. Thus, creating an imbalance in the cell by increasing the concentration of ROS and RNS which in turn leads to OS in the cell and thus making the cell more prone to oxidative damage [35].

5- Hyperglycaemia induced O.S inhibits the pathway of Insulin signaling-

The uptake and release of glucose are mediated by insulin secretion and insulin action [11]. In normal condition when the blood glucose level increases insulin secretion and action bring back glucose level to normal [38]. In patients suffering from hyperglycaemia and TYIIDM often lack this regulatory mechanism. The β cells of pancreas sense glucose by the enzyme glucokinase. This enzyme has a low affinity for glucose. Thus, the pancreas can only sense glucose when the concertation of glucose is high. This results in uptake of glucose by pancreas through the action of insulin which is initiated by glucokinase. Glucose is broken down to pyruvate which then enters the Krebs cycle and ETC in the cell of the pancreas. All these process leads to an increase in the ATP production. The increase in the concentration of ATP tends to shut down ATP sensitive K$^+$ channels [39-40]. ATP sensitive K$^+$ channels promote Na$^+$ the influx and Na$^+$/K$^+$ channel is disturbed. The influx of Na$^+$ ions causes the depolarization of the cell membrane of the pancreas and opens voltage T type voltage-gated Ca^{+2} channels. This leads to an influx of Na$^+$/Ca^{+2} channels which further cause membrane depolarization [41]. High Ca^{+2} ions lead to the fusion of insulin secreted granules with the plasma membrane (PM) of the β cells of the pancreas that lead to the release of insulin [42-44]. Insulin secretion leads to insulin action that metabolizes the glucose and helps to maintain a normal blood glucose level [45]. It is seen that in diabetic patients suffering from hyperglycaemia the O.S of the cell activates uncoupling protein 2 (UCP-2) thereby decreasing ATP: ADP ratio [46]. The decrease in this ratio affects the ATP dependent release of insulin. Oxidative damage to the β cells of the pancreas also affect the quantity and quality of insulin release. Mitochondrial dysfunction that is a result of O.S also reduces ATP production and thus interferes the ATP dependent release of insulin [47]. O.S also affects the activity of GLUT-4 which is the major glucose transporter in adipocytes. Transport of glucose is thus affected and glucose remains high in the bloodstream [47,48].

III. CONCLUSIONS

After understanding the molecular mechanisms of O.S generation in the patients suffering from TYIIDM it is quite evident that O.S is one of the major factors in the development of diabetes. The alternative pathways mentioned in the text gives an overall approach of the fate of glucose in diabetic individuals. These pathways not only disrupt the glucose homeostasis in the blood but also affect insulin secretion and action. Most of the pathways also generate ROS and RNS thereby increasing the oxidative stress of the cell.

IV. REFRENCES

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