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ISSN: 0975-7538
Research Article

Altered metabolism of diabetes mellitus and its metabolic blockers

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ABSTRACT

The treatment of diabetes will not be perfect when it controls merely hyperglycemia. Hence, there are many multi dimensional approaches accelerated in diabetes research. In recent years, considerable progress has been made towards understanding the biochemical mechanisms leading to diabetic complications. Some of such path ways and drugs discovered for blocking such metabolism from chemical and herbal sources are conferred in this paper. To describe biochemical mechanisms and new treatment modalities being explored in current scenario. As the discovery of drug and clinical trials take several years to achieve their goal it is necessary to observe the developmental process taking place worldwide. The papers reviewed here in this decade will help us to predict the trend of the next decade. There are many drugs have proved its efficacy in *in-vitro* assays and animal models. Some of them are underway in clinical trials. Altered path ways responsible for secondary complications of diabetes are illustrated. A possible mechanism for higher rate of free radical production in diabetes is also proposed. There are hundreds of plant based medicines found to have better antioxidant metabolites and trace elements that play vital role in degenerative diseases though their specific mechanism could not be established, but they are proved by scientific evaluations. There are many metabolic blockers under clinical trials, when outcome of these trials demonstrate unsafe for the usage, drug modification may be the potential area for research or else the process of chemical synthesis may have such potential. As this task is the major thirst area for research, it is presented for exploration.

Keywords: Metabolic rearrangements; Diabetic complications; Diabetic therapy

INTRODUCTION

Diabetes mellitus (DM) is a common medical condition characterized by both microvascular and macrovascular complications. Microvascular complications affecting the eye (retinopathy), the kidneys (nephropathy) and feet (neuropathy) are unique to the diabetic condition. However, macrovascular complications, including an increased risk of coronary heart disease, cerebral vascular disease and peripheral vascular disease, account for 75% of mortality, and occur at a much younger age compared to the non-diabetic population, (Hall and Davies, 2008). Although tight control of blood glucose greatly reduces the incidence of these complications, a significant fraction of diabetic patients with good glycemic control still develop these diseases. Therefore, it is imperative to understand the underlying mechanisms of these diseases such that effective treatment or preventive methods can be developed to augment euglycemic control (Chun and Chung 2005).

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Received on: 05-06-2012
Revised on: 19-07-2012
Accepted on: 26-07-2012

Early assessment, diagnosis and management of patients are essential for reducing the incidence of diabetes and also minimizing the complications. In recent years there has been a huge increase in the number therapeutic options (Hall and Davies, 2008).

Metabolic rearrangement and Alternative pathways in Diabetes

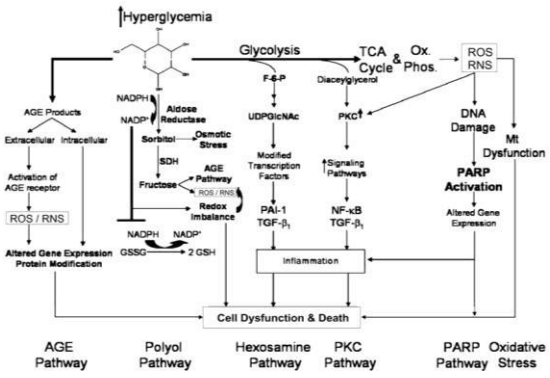


Figure 1: Metabolic rearrangement and Alternative pathways in Diabetes

The figure-1 shows various unusual alterations in metabolite flow in hyperglycemia associated with diabetes. All of these pathways end with inflammations and cell death.

A small note about these path ways are given here (Adopted from James *et al.,*2008).

Advanced glycation end products pathway: Non-enzymatic reactions between reducing sugars and proteins/lipids result in advanced glycation endproducts (AGEs). AGEs are modified intracellular and extracellular heterogeneous biomolecules. Those molecules alter the function of both protein and DNA. It causes defect in cellular transport and responds to induce sensitivity for vascular damage in endothelial cells.

Polyol pathway: The enzyme aldose reductase (AR) reduces glucose to sorbitol and sorbitol dehydrogenase (SDH) oxidizes sorbitol to fructose Both of these enzymes are abundantly expressed in tissues prone to diabetic complications. Hyperglycemia activates the aldose reductase pathway primarily by mass action: Increased flux through the AR pathway causes increased intracellular sorbitol.

Hexosamine pathway: The hexosamine pathway was associated as an additional factor in the pathology of diabetes-induced oxidative stress and complications. Fructose-6 phosphate is a metabolic intermediate of glycolysis. However, during glucose metabolism some fructose-6 phosphate is shunted from the glycolytic pathway to the hexosamine pathway. Here, fructose-6 phosphate is converted to glucosamine-6 phosphate by glutamine fructose-6 phosphate amidotransferase. Glucosamine-6 phosphate is then converted to uridine diphosphate-N-acetyl glucosamine (UDPGlcNAc), a molecule that attaches to the serine and threonine residues of transcription factors.

Protein kinase C pathway: The protein kinase C (PKC) pathway is an additional mechanism by which hyperglycemia causes injury in complications-prone tissues. Elevated glucose levels stimulate diacylglycerol (DAG), which in turn activates PKC. Increased production of the PKC,, PKC-β-isoform in particular has been implicated in overexpression of the angiogenic protein vascular endothelial growth factor (VEGF), PAI-1, NF-κB, TGF-β and the development of diabetic complications.

Poly (ADP-ribose) polymerase pathway: PARP found in Schwann, endothelial cells, and sensory neurons are also involved in glucotoxicity. PARP is a nuclear enzyme closely associated with oxidative–nitrosative stress: free radicals and oxidants stimulate PARP activation.

Oxidative stress and apoptosis: Hyperglycemia increases production of reactive oxygen species (ROS) in mitochondria. NADH and $FADH_2$ produced from the tricarboxylic acid cycle transfer electrons to the mitochondrial membrane-associated redox enzyme complexes. These electrons (e^-) are shuttled through oxidoreductase complexes until they are donated to molecular oxygen, forming water and ATP. Synthesis of ATP utilizes energy from proton gradient between the outer mitochondrial membrane and the inner mitochondrial membrane. This potential is crucial for mitochondrial viability, function, and normal metabolism. As electrons are passed from different electron carriers ROS are produced as byproducts. The levels of ROS produced during normal oxidative phosphorylation are minimal, and they are detoxified by cellular antioxidants such as glutathione, catalase and superoxide dismutase. The hyperglycemic cell, on the other hand produces increased levels of radicals. Accumulation of these radicals, or ROS, is severely detrimental to mitochondrial DNA, mitochondrial membranes and the whole cell. Development of agents to prevent mitochondrial oxidative damage will be the focus of intense study (Green *et al.,* 2004). A possible mechanism for higher rate of free radical production in diabetes is proposed in the Figure- 2.

The figure- 3 shows the free radical production by ETC (Electron transport chain) and its impact on mitochondria.

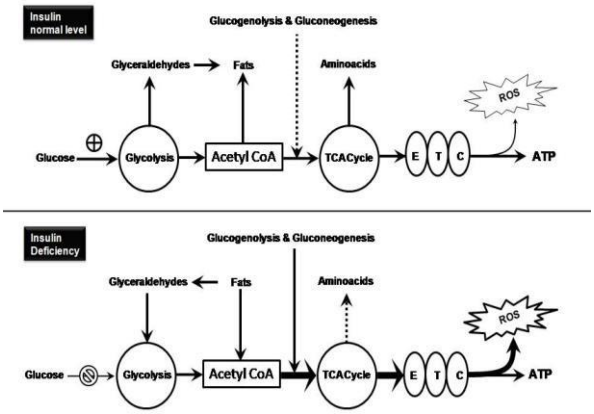


Figure 2: Free radical production influenced by Diabetes mellitus

Figure-2. The arrows indicate pathway flow direction. Continues line represents normal flow. Bold line represents triggered flow of metabolites. Dotted lines show the diminished flow of metabolites.

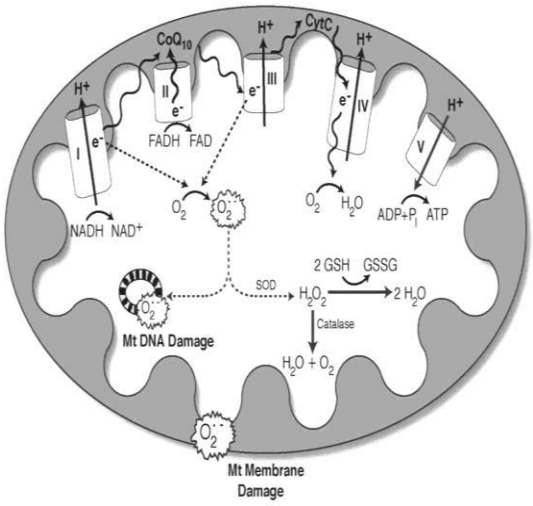


Figure 3: Mt Membrane damage

Figure - 3. Abbreviations: Cyto-*c*, cytochrome *c*; CoQ10, coenzyme Q10; e^-, electrons; GSH, glutathione; GSSG, oxidized glutathione; H_2O_2, hydrogen peroxide; $O_2^{\bullet-}$, superoxide; P_i, phosphate; SOD, superoxide dismutase.

Inflammation: Inflammatory agents including C-reactive protein and TNF-α are present in the blood of both Type I DM and Type II DM. Higher levels of these proteins correlate with the incidence of neuropathy.

Growth factors: Growth factors promote the growth and survival of neurons and direct neurite outgrowth. Given that diabetic neuropathy is characterized by neuronal degeneration and damage to supporting Schwann cells, alarms in growth factors such as nerve growth factor (NGF), insulin-like growth factor (IGF), and neurotrophin 3 (NT-3) have been suggested to be involved in the pathogenesis of diabetic neuropathy.

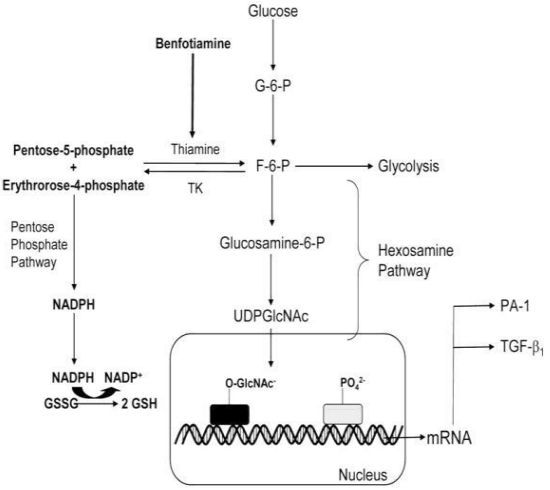
Diagnosis of Diabetes complications

All the intermediate metabolites of these alternative pathways are estimated only in the research laboratory against the treated and untreated groups of experimental objects. The development of diagnostic kits and the specificity are to be well established. In the current scenario the tissue /organ specific profiles mostly based on symptoms are measured as indices of severity. The advanced gycation end product pathway such as HbA_{1C} , Fructosamine and the glucosamine for the hexosamine pathways are available in the clinical diagnostic market but latter two are least popular.

Management of Diabetic complications

Inhibitors of advanced glycation end products (AGE): Chronically increased amounts of glucose amplify the physiological process of non-enzymatic protein glycosylation (glycation). In this glycation glucose forms labile links with the N terminal side-chain lysine radicals within proteins. Such links tend to turn into stable products (AGE) leading to degradation of both structural and functional proteins which accelerating aging and cell death. Aminoguanidine, a compound that prevents AGE formation proved promising effect in the prevention. Aspirin reduces glycation *in vitro*, in animal experiments, potentially by acetylation of amino groups (Blakytny & Harding, 1992). Aminoguanidine (also called pimagedine) is a nucleophilic hydrazine compound and has received the most attention as a potential anti-glycation drug (Thornalley, 2003). Phenacylthiazolium bromide a compounds capable of cleaving AGE cross-links described the possibility of reversing diabetic complications. These compounds include N-phenacylthiazolium bromide (PTB), which can cleave AGE cross-links by a mechanism which is still unclear. (Cooper *et al.,* 2000).

Inhibitors of Polyol pathway: (Aldose reductase inhibitors - ARI) Chronic hyperglycemia increases the metabolic flux through the polyol pathway, leading to the conversion of glucose into sorbitol through the key enzyme aldose reductase, so that studies with aldose reductase inhibitors that possess better bioavailability could still yield interesting results (Massimo and Attilio 2004). The drugs which are under clinical trial or need modification for least toxicity are quoted as examples. Sorbinil is ARI (Judzewitsch *et al.,* 1983), Zopolrestat (Arezzo *et al.,* 1996) it is a carboxylic acid analog, Myo-inositol (Sima *et al.,* 1997) it is a naturally occurring secondary messenger. Evidence suggests that dietary myo-inositol supplements might slow diabetic neuropathy progression, though further study is needed to assess efficacy.



(Adopted from Hammes *et al.,* 2003)

Figure 4: Inhibitors of hexosamine pathway

Figure-4 shows the effect of benfotiamine on biochemical pathways in diabetic complications. Excess glucose activates flux through hexosamine pathway creating UDPGlcNAc from F-6- P. UDPGlcNAc modifies transcription factors which lead to inflammation. Addition of benfotiamine, a thiamine analog activates transketolase (TK) which diverts substrate away from the hexosamine pathway and into the pentose phosphate pathway.

Inhibitors of Protein kinase C pathway: Ruboxistaurin is a PKC-β competitive inhibitor that has effectively managed many complications of diabetes in clinical trials. It has been particularly successful in reducing the progression of diabetic retinopathy, endothelial vasodilation, and (to a lesser extent) nephropathy (Ishii *et al.,* 1996; Beckman *et al.,* 2002; Tuttle *et al.,* 2005; Aiello et al 2006).

Poly (ADP-ribose) polymerase inhibitors: As PARP mediates both neuronal dysfunction and inflammation, inhibition of PARP holds the potential of improving two aberrant causeways in diabetic neuropathy, making it a promising target. PARP inhibitors such as 1,5-isoquinolinediol and 3-aminobenzamide have successfully improved these PARP-mediated dysfunctions in STZ-induced diabetic rats (Li *et al.,* 2005; Obrosova *et al.,* 2005; Ilnytska *et al.,* 2006).

Growth factors: Insulin-like growth factors (IGFs) I and II have profound effects on nervous systemdevelopment and survival, mediated through activation of the IGF-I receptor (IGF-IR) (Leinninger & Feldman, 2005; Fernandez *et al.,* 2007).

Anti-inflammatory drugs : Non-steroidal anti-inflammatory drugs. Non-steroidal anti-inflammatory drugs (NSAID) are a class of medications that inhibits cyclooxygenases, and thus prevent the formation of prostaglandins. It is commomly used symptomatic therapy in diabetic polyneuropathy. (James *et al.,* 2008).

Antioxidants: The secondary complications of diabetes and this alternative pathway are mostly depending on ROS/RNS in addition to mitochondrial oxidative stress. Hence antioxidant therapy will play a crucial role to keep the complications under control. Nicotinamide (AKA vitamin B3) is a weak PARP inhibitor, antioxidant, and calcium modulator. effective in experimental diabetes and currently in a type 1 diabetes patient trial. (Eriksson *et al.,* 1999; Bonnefont-Rousselot, 2004; Stevens *et al.,* 2007). Minerals Metal ions including vanadium, chromium, magnesium, zinc, selenium, and copper contribute to antioxidant defense. They may become depleted in diabetic patients and should be included in the diet. (Bonnefont-Rousselot, 2004). There are many antioxidants like U83836E, A synthetic ROS scavenger, effective against oxidative stress (Sayyed *et al.,* 2006), Dimethylthiourea a hydroxyl radical scavenger, prevents diabetes-induced blood flow deficits. (Cameron *et al.,* 2001) all are under clinical trials.

Herbal remedies: Root part of the plant Salacia species have multi target activities such as, PPAR α luciferase activation, suppression of angiotension II induced mRNA expression, inhibition of aldose reductase, pancreatic lipase etc reported by Yuhao Li, *et al.,* (2008). Bhavna Sharma *et al.,* (2009) demonstrated the hypoglycemic effect of *Commiphora mukul* resin contains Guggulsterone significantly improved PPARγ expression and activity in *in-vivo* and *in-vitro* conditions and suggested that the guggulsterone has both hypoglycemic and hypolipidemic effect which can help to cure type II diabetes. Apart from this there are hundreds of plant based medicines found to have better antioxidant metabolites and trace elements that play vital role in degenerative diseases though their specific mechanism could not be established, but they are proved by scientific evaluations.

CONCLUSION

There is lack of progress, despite intense research, suggests that a new paradigm is needed. Though there are many inhibitors under clinical trial some of them are being terminated as because of toxicity. Hence a strong knowledge in synthesizing new derivative of these drugs or modification required to minimize the dose and dose dependant toxicity with high specificity and efficiency.

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