Editorial
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Metformin beyond Diabetes

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Metformin (MTF) is a 1, 1 dimethylbiguanide derivative of legume *Galega officinalis* and was first reported as an antidiabetic drug in 1957[1]. It is one of most commonly used oral agent for treating diabetes because of its efficacy, safety and wide availability[2]. Type 2 Diabetes Mellitus is characterized by insulin resistance in liver, muscle, adipose tissue and other insulin resistant tissues which leads to hyperglycaemia and secondary hyperinsulinemia[3]. MTF acts primarily by inhibiting gluconeogenesis. It has specific action on mitochondrial respiration that increases the AMP. Experimental evidence supports activation of Adenosine Mono-Phosphate (AMP) dependent protein Kinase (AMPK), leading to stimulation of hepatic fatty acid oxidation, glucose uptake, and nonoxidative glucose metabolism and reduction on gluconeogenesis and lipogenesis. It also inhibits mitochondrial glycerol phosphate dehydrogenase, there by changing redox state of cell. More recent evidence implicates other mechanisms, including blunting the effects of glucagon, inhibiting conversion of lactate and glycerol to glucose, and shifting liver towards negative lipid balance[4]. Several pre-clinical studies show promising results in non-diabetic use of MTF as an anti-inflammatory agent, antioxidant, weight reducing agent and antineoplastic.

Study conducted by Vasamsetti et al., showed that MTF can act as an anti-inflammatory agent by inhibiting monocyte to macrophage differentiation which is AMPK dependent. It reduces Signal Transducer Activator of Transcription (STAT) proteins activity and inhibits Phorbol Myristate Acetate (PMS) induced STAT-3 phosphorylation in T-Helper 1 cells and reduces the production of pro-inflammatory cytokines such as TNF-a, so its potential use can be in chronic inflammatory conditions[5]. MTF is thought to ameliorate the atherosclerosis and vascular senescence in mice by decreasing the expression of Angiotensin 1 Receptor induced by high fat diet[6]. It is also proposed that metformin confers cardio protection by inhibiting mitochondrial complex 1 and inhibiting AMP deaminase which increases the AMP: ATP ratio. This activates AMPK causing the phosphorylation of Endothelial Nitric Oxide synthase, an integral part of Reperfusion Injury Salvage Kinase (RISK) pathway. MTF reduces the systemic production of tissue plasminogen activator, Von Willebrand factor and Plasminogen Activator Inhibitor[7]. Furthermore, increased AMP: ATP facilitates the extracellular diffusion of adenosine and its subsequent activation of RISK pathway via G-protein coupled receptor. RISK pathway inhibits Mitochondrial Permeability Transition Pore (MPTP) opening which mitigates the detrimental effects of calcium influx and ROS generation at reperfusion

Hyperglycaemia induces the oxidative stress so MTF is thought to act as an antioxidant as hypotheses explains lowering the reactive oxygen species by inhibiting complex 1 electron transfer complex chain and upregulation of uncoupled protein-2 in fat cells activates AMPK system which further induces glutathione reductase, superoxide dismutase and catalase[8].

Metformin is not a weight reducing agent on its own but it stops the weight gain caused by diabetes related medications like insulin, thiazolidinediones, sulfonylureas and antipsychotics[9, 10]. Mechanism behind it is reduction in carbohydrate uptake in gut as well as modulation of insulin resistance, reduction in leptin levels and increase in Glucagon like peptide-1 on fat cells[11].

In a study conducted on subjects with already existing hypothyroidism whether they are on treatment or not and euthyroid, there was significant difference in the level of

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TSH in diabetic who were on metformin while the level of T3 and T4 remain unchanged and in euthyroid also, TSH remain unchanged[12].

Metformin is thought to play a crucial role in Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis by activation of AMPK pathway as brain cells are dependent on glucose for survival and insulin leads to amyloid deposition. The AMPK stimulation induces autophagy and decomposes the beta amyloid and improves the neurological changes related to Alzheimer's disease[13].

Antiretroviral agents lead to insulin resistance, dyslipidaemia, lipodystrophy and worsening of blood glucose levels. MTF when added to lifestyle modification can effectively prevent all these effects. In addition to it, metformin can improve immune function and it can change the composition of bacteria in the gut which may improve inflammation[14].

MTF downregulates mitochondrial metabolism which helps in tumor modulation[15]. It also modulates the Adenosine A1 receptor (ADORA1) expression in human colorectal cancer[16]. Direct affect of AMPK pathway plays a cardinal role in exerting its antioneoplastic effect by inhibiting LKB1 and Mtor, which are linked to cancer predisposition, so MTF is useful in Liver cancer, Pancreatic cancer, Prostate cancer, Breast cancer, Renal cell Cancer, Cervical cancer.

In nutshell, metformin is one of most widely prescribed oral hypoglycaemic agent. Being gold standard in type 2 Diabetes Mellitus, it is worth doing some more research to confirm these pleiotropic effects of metformin.

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