REVIEW ARTICLE

Vasculo-Protective Cover: A Novel Action of Metformin

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ABSTRACT:
Type 2 diabetes is associated with multiple changes/complications in the body that affects almost every organ and system. In the cardiovascular system main pathology lies in the vascular endothelium leading to atherosclerosis and arteriosclerosis. Different treatment options are available for diabetes including both oral and injectable drugs. Oral drugs have better compliance like Sulfonylureas, Alpha glucosidase inhibitors, Glitazones and Maglitinides. These groups of anti-hyperglycemic drugs maintain blood glucose level, providing diabetics cost effective better life through a physiological route. However, it has been documented that these drugs do not delay vascular complications in diabetic patients. Metformin is the first line oral anti-diabetic drug from biguanide group used to treat type 2 diabetes mellitus. It is a euglycemic agent which decreases glucose levels and have additional benefit of decreasing the progression of vascular effects in multiple ways.

Keywords: Type 2 diabetes, Oral anti-diabetic drugs, Metformin ,Vasculo-protective effects, Endothelial dysfunctions

INTRODUCTION:

Diabetes Mellitus is a group of metabolic diseases characterized by increase in blood glucose levels. The pathophysiology of diabetes includes defects in insulin secretion, insulin action, or both. Chronic hyperglycemia of diabetes is associated with damage, malfunction and failure of various organs including eyes, kidneys, nerves, heart, and blood vessels[1].

Global prevalence of diabetes has increased up to 6.6% in recent years. Almost 285 million, people around the world are affected with this disease.142 million affected people are males and remaining 143 million are females. Out of 285 million approximately 108 million have age range of 60-79 years, 132 million 40-59 years and 44 million 20-39 years of age[2]. Pakistani nation is ranked 6th with diabetic burden in the population.[3] Changes in body due to hyperglycemia and hyperinsulinemia in diabetes can lead to athero-thrombic deposition as well as lethal changes in the vessels that causes 70-75% deaths in diabetic patients due to cardiovascular events[4,5] Multiple treatments have been used for patients of Type 2 Diabetes Mellitus. Oral drugs include several groups such as Sulfonylureas, Biguanides, Glitazones, Maglitinides, DPP-4 inhibitors etc. If control of hyperglycemia is not attained by oral drugs alone then injectable agent insulin is also prescribed. Some drugs which are common in use, are sulfonylureas and biguanide- metformin, have better compliance than others. Oral drugs maintain blood glucose level, providing diabetics cost effective better life through a physiological route. Metformin is the first line oral anti-diabetic drug used in type 2 diabetes. It is a euglycemic agent with additional benefit of decreasing the progression of vascular adverse effects caused by hyperglycemia[6]. Multiple electronic databases PubMed, Science direct, Google.com and Google scholar were searched by using key words, terminologies and phrases of diabetes type 2, oral hypoglycemic agents, metformin, euglycemic agent, metformin effects on vessels, vasculo-protective effects, endothelial dysfunction, atherosclerosis, fibrinolysis, carotid intima, and lipoprotein lipase. Literature search of abstracts, original articles, review articles and case studies published in past 13 years (September 2000 - September 2013) was carried out and is incorporated in the preparation of this review article after using the filter vasculo-protective effect.

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Received: 16-09-2015
Revised: 19-10-2015
Accepted: 21-10-2015

LITERATURE REVIEW:

The vascular endothelium is an important site for control of almost all vascular events and functions[7]. Many crucial vasoactive endogenous products like prostacyclin, thromboxane, nitric oxide, angiotensin, endothelium derived hyperpolarizing factors, free radicals, and bradykinins are formed in the endothelial cells of vessels to control the proper functioning of vascular smooth muscles and of circulating blood cells[8]. Many at times endothelial dysfunctions precede and predict clinical micro vascular diseases. Multiple studies have proven the fact that endothelium is both a target and mediator of atherosclerotic changes leading to cardiovascular diseases[9]. Different pathological events occurring with diabetes such as change in cholesterol levels, hypertension, increase in homocystine levels and visceral fat accumulation are also associated with endothelial dysfunction[10].Other risk factors for vascular diseases in diabetes could be increase in plasminogen activator 1, increase in clotting factor 7, decrease in HDL levels, increase in triglyceride levels and micro albuminuria[11] which further worsen the condition in vascular wall in type 2 diabetics. The most important of these vasoactive substances is nitric oxide which is a vasoprotective agent as it inhibits inflammation, oxidation and proliferation of vascular smooth muscles. Bioavailability of nitric oxide plays a very important role in regulation of events in vessels[12]. Early markers of endothelial dysfunction

can be decrease in amounts of nitric oxide leading to abnormal vasomotor response and subsequently micro and macro vascular pathology. Different studies have also indicated the fact that endothelial dysfunction can be induced by abnormality in the insulin signaling pathway, that can be a result of deprivation of endothelial nitric oxide synthase. When taken together it is evident that in type 2 diabetes, insulin resistance and endothelial dysfunction are related to each other. Treating these two previous issues would definitely improve the latter ones and therefore the functioning of vascular system[13.]

Metformin: Metformin is one of the important agents for controlling hyperglycemia in type 2 diabetes these days. It has a botanical source, obtained from Galegia Officianalis; known as goats rue and French lilac. It acts as a euglycemic agent by decreasing the carbohydrate absorption and increasing its utilization by decreasing the insulin resistance.[14]

Metformin is slowly absorbed from the gut with elimination half life of 3-6 hours which occur through kidneys. It does not increase the body weight and can be used as mono-therapy.[15] The side effects encountered with metformin are metallic taste, anorexia, nausea, flatulence, abdominal cramp, occasionally diarrhea and vomiting. All these features usually tend to disappear with the continuation of therapy. Rarely lactic acidosis can occur in patients with renal and hepatic insufficiency. This can be prevented to a large extent by having LFTs and renal profile of the patients before starting the therapy.

Metformin mode of action:

Metformin reduces blood glucose level without increasing the production of insulin, and has greater glucose lowering efficacy as compared to other anti-diabetic agents.[16] The anti hyperglycemic effect of metformin is explained by several mechanisms that collectively balance insulin resistance and improve glucose homeostasis.[17, 18] The two main mechanisms are inhibition of gluconeogenesis, and improvement in glucose uptake by decreasing insulin resistance.[19] Metformin along with some life style modifications and weight reduction can be useful for improving the endothelial function and decreasing the risk of CVS diseases in diabetics.[20, 21]

1. Effect of Metformin on smooth muscles :

Many studies have proven the fact that defective insulin signaling is a factor for vascular problems in type 2 diabetic patient. In insulin resistance this pathway gets disturbed and finally there is no nitric oxide dependent relaxation of vascular smooth muscles leading to stiffness and shortening of diameter in these vessels. Metformin has shown vasculo-protective effects by inhibiting these above mentioned mechanisms. Metformin improves the skin capillary reactivity, functional capillary density and also stimulates slow wave arteriolar vasomotion.[22,23] Different animal studies have shown improvement in nitric oxide activity and probable relaxation of pre-contracted aortic ring in streptozotocin induced diabetic rats.[24,25] Administration of metformin in the rat tail arteries causes arterial relaxation due to decrease in activity of intracellular calcium ions. Metformin potentiate the production of nitric oxide by increasing local nitric oxide synthase which again decreases the response of calcium ions in the smooth muscles of the vessels. Finally metformin decreases constriction and enhances the post ischemic perfusion of capillary beds.[26]

2. Effect of metformin on vascular endothelium:

Other than vascular smooth muscles in vessels, endothelium is also an important part where vascular deformity is noticed at an early stage in diabetics. In recent years insulin resistance and endothelium has been of great interest to the researchers due to a strong relationship between diabetics and endothelial abnormalities. Metformin increases endothelial dependent vasodilation, independent of its glycemic control properties. The main mechanism behind this effect is the increase in nitric oxide synthase and nitric oxide precursor L-arginine which is an amino acid.

3. Effects of metformin on monocyte adhesion:

Metformin also inhibits monocyte adhesion to the endothelium which is one of the factors causing arthrosclerosis in the vessels. It decreases the adhesion molecule expression in the endothelium including Vascular Cell Adhesion Molecule 1 (VCAM 1), Intracellular Adhesion Molecule 1 (ICAM 1) and E- selection[27.]

4. Effects of Metformin on haemostatic factors:

In patients with type 2 diabetes, metformin improves the markers of endothelial dysfunction and inflammatory activity including von-willebrand factor, selectin tissue type plasminogen activators and plasminogen activator inhibitor 1.[6, 28] It is also found to improve the endothelial regulators of hemostasis (vWf), leukocyte adhesion molecules (SE selectin , VCAM 1) and fibrinolytic agents (tPA, PAI).[29]

5. Effects of Metformin on platelets:

The anti atherosclerotic and cardio protective effects of metformin by its action on platelets have recently been confirmed in both prospective and retrospective studies. Metfomin has direct effect on two important component of an arterial thrombus that is fibrin and platelets. It acts by inhibiting two important platelet activating factors; PAF4 and B7G thus causing decrease in platelet plug formation.[30,31]

6. Effects of Metformin on fatty acids:

The storage of free fatty acids in the endothelium is increased in insulin resistance state. Metformin in turn promotes free fatty acid oxidation in the endothelial tissue by its ability to activate endothelial AMP protein kinase.[5, 32] Metformin decreases lipoprotein lipase production and thus decrease the breakdown of LDL into VLDL, accounting for further vasculoprotective effects. LDL is taken up by liver due to presence of its receptors on hepatocytes thus decreasing VLDL in blood. It also reduces endothelial permeability and edema and thus improves capillary functions[33.]

7. Effects of Metformin on inflammation:

Metformin along with other effects, also decreases inflammatory mediators such as tissue plasminogen activator (tPA), antigen factors 7 and 13, and C-reactive protein (CRP) levels[34].

8. Additional effects of Metformin:

Type 2 diabetes mellitus patients being treated with metformin have shown slowing of annual progression of carotid intima indicating that this drug decreases the normal carotid changes in these patients.[35] It has been documented that metformin treatment produces significant reduction in multiple factors leading to decrease in brachial artery diameter at base line; brachial artery diameter after reactive hyperthermia, abnormal flow mediated dilation and increased intima media thickness.[36, 37] In addition, plasma concentration of endothelin 1 which is one of the main biological markers of endothelial function is significantly altered in polycystic ovarian syndrome patients, has been found to decrease with metformin therapy.[38] At cellular level specifically in mitochondrial chain, it also prevents apoptosis, which is another mechanism to explain the long term vascular protection afforded by metformin.[39] A study on obese insulin resistant cases has documented that metformin promotes a prolonged post prandial fall in the plasma levels of the gut hormone "ghrelin" which stimulates food intake and encourages adiposity .Thus metformin decreases caloric intake and helps in total weight reduction in type 2 diabetes.[40]

CONCLUSION:

Metformin provides vasculo-protective cover and delays the vascular changes in type 2 diabetic patients in addition to provision of good control of glycemic levels with least side effects. These vasculo-protective effects make metformin a novel drug in the class of oral anti-diabetics.

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