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Review Article

A REVIEW ON THE ROLE OF PEROXISOME PROLIFERTOR-ACTIVATED RECEPTOR-γ AGONISTS AND HYBRIDS IN TYPE 2 DIABETES AND CARDIOMYOPATHY

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ABSTRACT

Type 2 diabetes mellitus (DM) is a chronic multiple metabolic disorders characterized by increase in blood glucose level and accompanied with a number of microvascular and macrovascular complications due to lifestyle factors, genetic factors related to impaired insulin secretion and insulin resistance and environmental factors. Cardiovascular complications are one of the main causes responsible for 80% mortality rate in Type 2 diabetic patients. Recently, amino acids and peptides are emerging as very good groups of antidiabetics as well as cardioprotective drugs, which may decrease the symptoms of DM as well as take care of cardiovascular complications. Synthetic analogs of amylin and incretin mimetics are becoming ideal adjuncts to diabetes therapy. To overcome the complications related to present day oral hypoglycemic agents which includes sulfonylureas, biguanide, thiazolidinediones etc., This study has been done to review the role of peroxisome proliferator-activated receptor-γ agonists, amino acids and hybrid compounds for activation of adenosine monophosphate-activated protein kinase receptors, which in turn plays important role in the treatment of Type 2 diabetes and cardiomyopathy.

Keywords: Peroxisome proliferator-activated receptor-γ agonists, Thiazolidinediones, Hybrid compounds, Adenosine monophosphate-activated protein kinase activation, Type 2 diabetes, Cardiomyopathy.

INTRODUCTION

Type 2 diabetes has affected 285 million people in 2010 and will affect 438 million by the year 2030 [1]. It is a progressive metabolic disorder associated with multiple microvascular and macrovascular complications. The microvascular complications include diabetic neuropathy, diabetic nephropathy, and diabetic retinopathy while the macrovascular complications include cardiovascular diseases. Thus, there is an urgent need for the synthesis of newer drug moieties or hybrid compounds, which can control both diabetes and related complications and decrease the medication cost for the Type 2 diabetes patients [2]. Diabetic complications are aggravated due to oxidative stress [3]. This led to the discovery of peroxisome proliferator-activated receptor (PPARs) and the PPAR agonists more specifically PPAR-γ agonists consisting of thiazolidinediones (TZDs). TZDs have become the most potential group of oral antidiabetic drugs being used, which has also reported to promote adipogenesis, insulin sensitization and inhibit pathogenesis of cardiovascular system (CVS) complications such as atherosclerosis [4], cardiac hypertrophy [5], Myocardial infarction [6] and diabetic cardiomyopathy [6,7]. A more recent concept of PPAR-γ agonists–hybrid moieties has been also reported, which serves multi-purpose therapeutic activities such as lowering blood glucose level, anti-inflammatory and cytoprotective effects, etc., [7].

PPAR receptors

The PPARs are a class of nuclear receptor super family comprised of PPAR subtypes PPAR-α, PPAR-δ and PPAR-γ [8-10]. All the three subtypes of PPAR family play an important role in the regulation of lipid metabolism, glucose homeostasis, inflammation, cytoprotection making PPAR transcription factors ideal targets for cure of hyperlipedimia, diabetes mellitus (DM) [9], cancer [10] and cardiovascular diseases [11,12].

PPAR-α is a transcription factor and mainly regulates lipid metabolism in the liver and is mostly expressed in liver, heart, and skeletal muscle. Activation of PPAR-α is primarily through ligand binding. Fibrate drugs are the synthetic ligands while fatty acids and various fatty acid-derived compounds are the endogenous ligands, which act as PPAR-α agonists [13].

PPAR-δ is expressed in comparable levels in almost all tissue and is involved mainly in fatty acid controlled differentiation of pre-adipocyte [14,15] response of white adipose tissues to nutritional changes [15] and also in the regulation of cholesterol changes [16]. PPAR-δ also acts as a hypolipidemic agent, which is still under investigation [17]. GW0742, another PPAR-δ agonists, has been reported to show prospective function on hepatic steatosis, which was confirmed in both Type 2 diabetes rat model and HepG2 cells [18].

PPAR-γ is mostly expressed in the adipose tissue and skeletal muscles. Natural ligands include the arachidonate metabolite and related metabolites, which induce adipogenesis, dietary polyunsaturated fatty acids and eicosapentanoic acids. Endogenous PPAR-γ include oxidized low density lipoproteins particles 9-HODE, 13 HODE. Artificial or synthetic ligands include TZDs and newer moieties such as GI262570, GW1929, and GW7845 [19].

PPAR-γ agonists

PPAR-γ plays a very critical role in the glucose homeostasis and is the most important target for the TZD class of compounds, generally known as glitazones [20]. Lipid lowering and blood glucose lowering activity was first studied in AL-294 by the Sohda *et al.* in obese diabetic mice followed by discovery of AL-231 [21]. This was followed by a number of modifications and structure-activity relationship (SAR) studies which finally led to the discovery of ADD-3878 in 1982, commonly known as ciglitazone [21,22]. Consequently troglitazone (CS-045) was discovered in 1988, but withdrawn from the market due to severe liver toxicity [23,24]. In the same year another drug BRL-4965 (rosiglitazone) was introduced which was effective at lower doses (1 mg/kg) compared with ciglitazone (150 mg/kg) [25,26] followed by the development of AD-4833 (pioglitazone) [25,26]. At

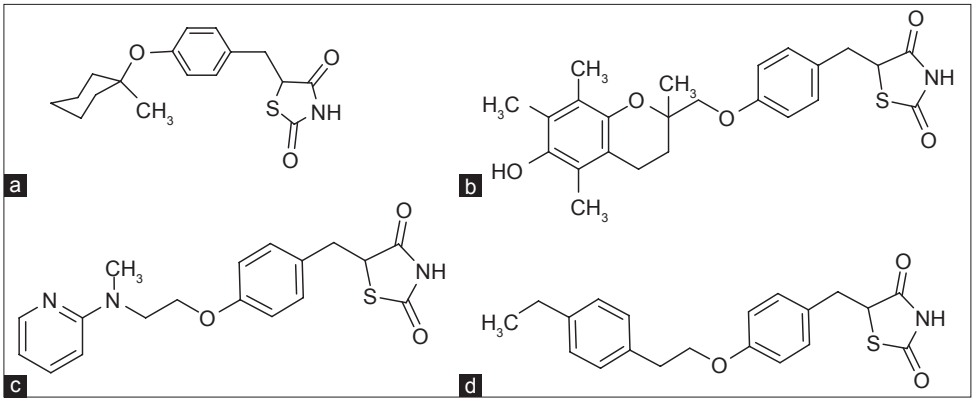


Fig. 1: Chemical structures of different thiazolidinediones, (a) ciglitazone (ADD-3878), (b) troglitazone (CS-045), (c) rosiglitazone (BRL 4965), (d) pioglitazone (AD-4833)

present, rosiglitazone and pioglitazone have been approved by U.S FDA as the two glitazones for the treatment of Type 2 diabetes [27]. Fig. 1 shows the chemical structure of the different TZDs. Balaglitazone is a selective partial PPAR-γ agonist. Balaglitazone has excellent antidiabetic and hypolipidemic properties, but shows less adipogenic activity.

Ragaglitazar, muraglitazar, tesoglitazarial reached the clinical trial phase 3 in 2006, but was withdrawn due to side effects such as anemia induction, urothelial cancer, edema and adverse cardiovascular events. Only aliglitazar showed improved safety. Novel PPAR pan agonists (PX204, GW-625019, and GW-677954) are being still investigated for both Type 2 diabetes and cardiovascular complications. Several thiazolidinedione and non-thiazolidinedione like PPAR-γ partial agonists for example balaglitazone (DRF-2593), or neoglitazone (MCC555) are in the process of development for clinical use [28]. Fig. 2 shows the chemical of different non-TZDs (Table 1).

The PROSactive pioglitazone clinical trials in macrovascular events (PROactive study) indicated that pioglitazone has protective action against mortality due to the macrovascular complications in Type 2 DM (T2DM) [29].

PPAR-γ agonists activate the PPAR-γ and improve the insulin sensitivity, decreases inflammation decreases the plasma levels of free fatty acids (FFA) and also decreases the blood pressure, which in turn inhibits the atherogenesis, improves the endothelial function and reduces CVS complications [30] have beneficial effect on lipid profile and coagulation. TZDs thus show a wide spectrum of activities. Both rosiglitazone and pioglitazone improve the endothelial function and restore impaired acetylcholine induced relaxation in angiotensin II infused rats. TZDs decrease vascular DNA synthesis, vascular cell adhesion, platelet and endothelial cell adhesion expression in mesenteric arteries [31]. Rosiglitazone is also seen to normalize nicotinamide adenine dinucleotide phosphate-oxidase NAD (P) H oxidase activity, which is a downstream effect or of angiotensin II in the vasculature and improves *in vivo* re-endothelization capacity of endothelial progenitor cells [32,33]. TZDs also activate adenosine monophosphate-activated protein kinase (AMPK), suppress high glucose induced hyperactivity of NAD (P) H oxidase [34].

AMPK activation and its effect on cardiovascular complications

Garret and Melvin in 2004 [20] studied that AMPK is an important regulatory protein involved in a number of diseases related to energy metabolism, including T2DM, obesity, and cardiovascular complications. Major effects of AMPK activation are carbohydrate and lipid metabolism, appetite regulation, cell growth and differentiation, vascular function and basic cellular functions. In 2010 [35] reported

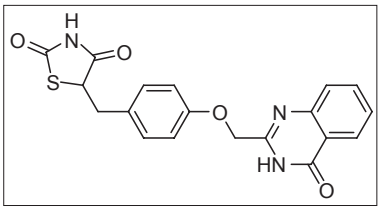


Fig. 2: Balaglitazone (DRF-2593)

that AMPK promotes cardiovascular homeostasis by ensuring an optimum redox balance on the heart and vascular tissues. AMPK senses the increase in AMP: Adenosine triphosphate (ATP) ratio by binding AMP to the Y subunit thus activating it and improving the vascular endothelium, inhibits inflammatory responses in the endothelium, causes nitric oxide (NO) bioavailability, enhancement of FFA oxidation and inhibition of reactive oxygen species (ROS). NO bioavailabity causes vasodilatation and thus muscle relaxation. Gruzman *et al*., [36] reported that two oral antidiabetics, which activate AMPK were metformin and TZDs. In 2010 Shirwany and Zou [37] studied that TZDs activate AMPK by inhibiting mitochondrial oxidation in the muscle protecting cardiac structure and function by increasing the autophagy in diabetic rats.

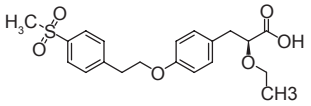
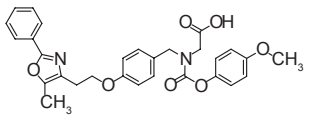
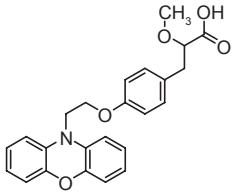
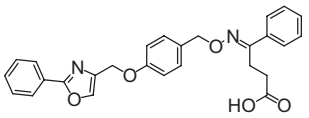
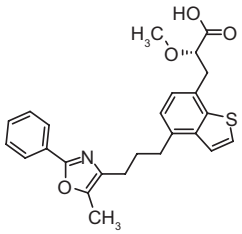
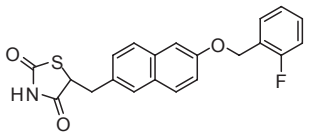
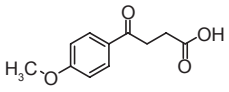
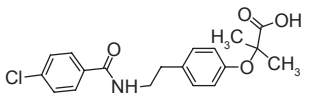
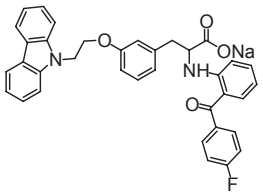
Diabetic cardiomyopathy

In 2010 Shirwany and Zou reported that in 1972 for the first time death of diabetic patients was observed due to diabetic cardiomyopathy [37]. Anatomical dissection of the hearts showed left ventricular (LV) hypertrophy and fibrosis without coronary artery atheroma or another substrate pathology [38]. It basically effects the myocardium of the heart in diabetic patients leading to LV hypertrophy and systolic and diastolic dysfunction or may be a combination of all these. The mechanistic approach of diabetic cardiomyopathy mostly includes metabolic disturbances (depletion of glucose transporter 4, increased FFA, carnitine deficiency, changes in calcium homeostasis), myocardial fibrosis (association with increase in angiotensin II, IGF-I, and inflammatory cytokines), small vessel disease (microangiopathy, impaired coronary flow reserve, and endothelial dysfunction), cardiac autonomic neuropathy (denervation and alterations in myocardial catecholamine levels), and insulin resistance (hyperinsulinemia and reduced insulin sensitivity). All these bring changes in the cellular level, which lead to structural abnormalities causing cardiomyopathy (Poornima *et al.* 2006, Fang *et al.* 2004, Nesto *et al*. 2004, Wang *et al*. 2003) [39-42].

PPAR-γ agonists: Its effect and activation of AMPK

PPAR-γ agonists, more specifically TZDs especially rosiglitazone apart from insulin-sensitizing fat and skeletal muscles, increase the

Table 1: The chemical structures, indication, side effects and causes of side effects and their present status in the development process [29]

Name	Structure	Indication	Side effect	Remarks
PPAR α/γ dual agonists				
Tesaglitazar		Hyper-lipedemia	Anemia, leucopenia, renal failure, fibrosarcomas	Discontinued in 2006
Muraglitazar			Heart failure, myocardial infarction and stroke	Discontinued in 2006
Ragaglitazar			Anemia, oedema, and urinary tract-cancer in rodents	Discontinued in 2006
Imiglitazar			Liver dysfunction	Suspended in 2004
Aleglitazar			Bone fractures heart failure, and gastrointestinal bleeding (Roche *et al.* 2013)	No longer in Phase III clinical trials
Netoglitazone		Obesity	Not reported	
PPAR δ/γ modulators				
Propionic acid derivatives		T2DM, hyperlipedemia		
PPAR α/γ/δ modulators				
Benzafibrate		T2DM, hyperlipedemia, atherosclerosis		
Chiglitazar		T2DM	None reported	Currently in Phase II

T2DM: Type 2 diabetes mellitus, PPAR: Peroxisome prolifertor-activated receptor

expression and function of glucose transporters in the heart leading to increased glucose metabolism and reduce the non-esterified fatty acids (NEFA) utilization by myocardium. This protects against myocardium injury [38,43].

Fryer *et al.* in 2002 studied that TZDs activate AMPK through a mechanism involving an increase in the AMP: ATP ratio. They inhibit mitochondrial fuel oxidation in skeletal muscles, which causes changes in nucleotide level affecting the cellular adenine nucleotide levels producing an increase in the level of AMP: ATP level. Also, AMPK promotes cardiovascular homeostasis and protection by ensuring an increase in the AMP: ATP ratio [44].

Viollet *et al.* in 2012 reported that metformin acts on the heart by promoting myocardial preconditioning, reduction in cardiomyocyte metabolism [45]. Benes *et al.* also reported that metformin normalized the serum NEFAs and modified the cardiac lipid/glucose ratio [43]. Studies by Young in 2003 showed that TZDs, besides decreasing

the blood glucose levels, increases the expression and function of glucose transporters in the heart, which causes improved glucose metabolism and also reduce the NEFAs utilization by myocardium thus protecting the myocardium from myocardial injury. The key mechanism responsible for the development of diabetic cardiomyopathy was dysregulation autophagy and metformin was found to restore impaired autophagy and prevented heart damage in OVE26 diabetic mice making metformin play an important role in the treatment of diabetes related cardiovascular diseases [38]. Thus metformin has complex properties on endothelial function, ROS production and cardiomyocyte functionality [41].

Amino–acids and peptides

Various natural chemical moieties such as alkaloids, flavonoids, etc., are known to be effective in the treatment of DM [46]. About more than 700 amino acids have been discovered in nature, and most of them are α amino acids, which form the basic unit of peptides and polypeptides. Small chain peptides form an integral part of the human body, which maintains its various vital functions and health. Recent advances in peptide chemistry is showing that if their biological activity are properly understood, improved and synthesized upon in the laboratory, they can become promise an enormously attractive candidate as a new generation of medicines. Like proteins, peptides are expected to be highly target specific. Peptides can also target intracellular proteins. Appropriate modifications can be added to make the peptides less susceptible to proteolysis.

Barrlett and Elmore (2004) studied that small molecules like peptides have been the drug of choice because of its ease and low cost of synthesis and stability and therefore longer half life [47]. Kim *et al*. (2011) studied that a hexapeptide (Gly-Ala-Gly-Val-Gly-Tyr) showed improvement in glucose transport and also exerts beneficial lipid metabolic effects [48].

In 2007, Sulochana and Ge [49] studied the advantages of small peptides over proteins for therapeutic application, due to their stability, solubility, increased bio-availability and lack of immune response in the host cell. Further Ghosh *et al.* [50] studied the extensive research on peptides, which revealed that they have a therapeutic potential for the treatment of DM for example exenatide (Incretin mimetics), pramlintide (amylin derivatives).

Setter and Neumiller in 2011 [51] concluded that exenatide is an incretein mimetic and mostly used as adjunctive therapy for patients whose T2DM is not well controlled by metformin. It normalizes blood glucose level by decreasing the fasting and postprandial glucose concentrations through different mechanisms, which include enhanced glucose dependent insulin secretion, regulation of glucagon, delayed gastric emptying and decreased food intake. The amino acid sequence of exetanide is as follows:

H–His-Gly-Glu-GLY-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Ly-Gln-Met-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Lue-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2.

Pramlintide is the first amylinomimetic compound and is a synthetic analog of the human hormone amylin, which is a 37 amino acid peptide. Pramlintide's peptide sequence differs from amylin by replacing proline at positions [25,28,29]. Pramlintide has a disulfide bridge between C2 and C7. The amino acid sequence of pramlintide is as follows:

H-Lys-Cys-Asn-Thr-Ala-Thr-Cys-Ala-Thr-Gln-Arg-Leu-Ala-Asn-Phe-Leu-Val-His-Ser-Ser-Asn-Asn-Phe-Gly-Pro-Ile-Leu-Pro-Pro-Thr-Asn-Val-Gly-Ser-Asn-Thr-Tyr-NH2 acetate salt (S-S Bond) [52].

In early 1950's the first peptidic analogue pepstatin was discovered. In the late 1980's tetrapeptide-like agents (enalkiren, remikiren, and zankiren) were developed, which could be orally administered. Later on, the active agent aliskiren, was successfully tested for preclinical and clinical evaluation after a few years, despite its non-cost effective synthesis [53].

Recent extensive research on peptides has revealed that they have a therapeutic potential for the treatment of DM and also as cardioprotectives.

Hybrid compounds

In 1997 Tomkinson *et al.* designed and synthesized a library of TZD-fatty acid hybrid molecules to understand the relationship between natural and synthetic PPAR ligands initiating the concept of the use of TZD-hybrid compounds. Prabhakar *et al.* in 1998 [54] synthesized TZD-nabumetone (anti-inflammatory) hybrid compounds most important being 6-methoxy-2-napthylacetic acid derivative of TZDs. Similarly, a unique hybrid class of lipoic acid-TZD derivatives were designed, synthesized and biologically evaluated, and some were found to be effective in the nanomolar range.

In 2006 Chittiboyina *et al.* [55] reported the design, synthesis and biological evaluation of a unique class of lipoic acid-thiazolidinedione hybrid compounds some of which were effective in nanomolar range (Chittiboyina *et al*. 2006). Neogi *et al.* in 2003 designed and studied the structural and functional features of cinnamic acid-TZD hybrid molecules that could facilitate the binding of small molecules to PPAR-γ receptor and find new series of thiazolidinedione hybrid PPAR-γ agonists [56]. Flora (2009) studied that lipoic acid has beneficial effects some being antioxidant and free radical scavenger, anti-inflammatory activity, cytoprotective activity along with beneficial effects on glucose metabolism [57].

In 2011 Prasantha *et al.* studied theSAR of some hybrid TZD-amino acid [58]. The anti-hypergycemic activity of some new TZD-sulfonylurea hybrid molecules have been designed and studied by Jawale *et al.* in 2012 [59]. Mohler *et al*., (2012) developed both solid phase and solution phase synthesis of peptide substituted thiazolidinedione to study the importance of the structural and functional features that facilitate the binding of small molecules to the PPAR-γ receptors and serve as potent PPAR-γ agonists [60]. Thus, it is observed that the hybrid-compounds are gradually being exploited to be established as novel antidiabetics and also taking care of related complications.

Correlation between AMPK activation, metformin, TZDs and diabetic cardiomyopathy

Both metformin and TZDs (rosiglitazone) belongs to most widely used oral hypogycemics. Brunmair *et al.* in 2004 reported that and TZD and metformin inhibit complex I of the respiratory chain and impair both mitochondrial function and cell respiration. This in turn causes the hypoglycemic effects of metformin [61]. Glitazones inhibit respiratory complex I similar to metformin, also activates AMPK (Viollet *et al*. 2012) [44]. The flow diagram in Fig. 3 shows the correlation between AMPK activation, metformin, TZDs and diabetic cardiomyopathy.

CONCLUSION

From this review it can be concluded that the PPAR-γ agonists especially glitazones and metformin inhibit the complex I in respiratory chain and also activate AMPK. Activation of AMPK in turn further provides cardiovascular homeostasis and protects the myocardium of the heart. Amino acids and peptides have also shown promising effect both as antidiabetics and also as cardioprotectives eliciting their importance and significance as cytoprotective, antidiabetic, cardioprotective agents along with other important biological functions, giving a rise to new era for the establishment of new series of TZDs-amino acid/peptide hybrid compounds, which may help to rejuvenate the organ cells and restore back the normal body physiology for patients suffering from T2DM and cardiomyopathy.

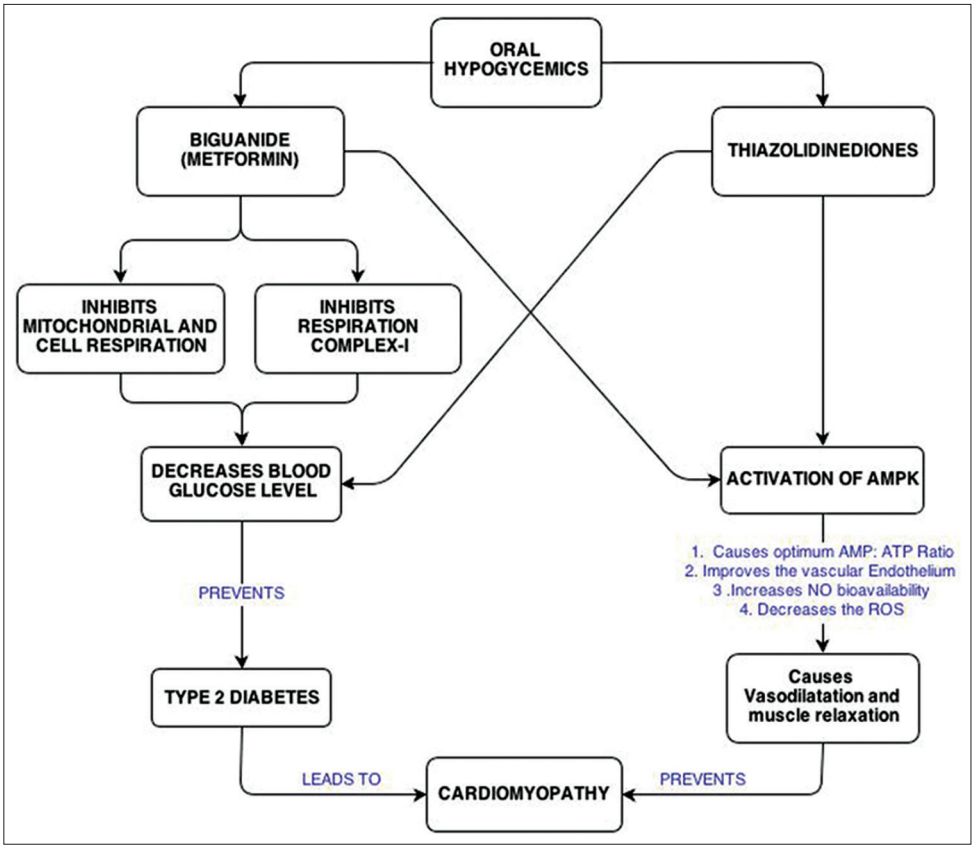


Fig. 3: Correlation between adenosine monophosphate-activated protein kinase activation, metformin, thiazolidinediones and diabetic cardiomyopathy

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