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Review

# Protective effects of metformin on cardiovascular system

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**Summary** For several decades now, metformin has been a first medicine of choice in the treatment of diabetes mellitus type 2. As a monotherapy or combined with other anti – diabetic medications, metformin is widely used as diabetes therapy, unlike other medications, it does not threaten the occurrence of hypoglycemia since it does not stimulate the secretion of insulin in pancreaticβ- cells but it disposes of free insulin that has already been secreted. Besides its anti – diabetic effects, metformin demonstrates the pleiotropy of effects on various diseases and issues related to metabolism. For the last ten years, metformin has been greatly tested as a treatment of polycystic ovary syndrome, prediabetes, cardiovascular diseases, but also as a produce to destroy cancer cells and potential produce to prolong the life expectancy. It creates the antihyperglycemic effect by inhibiting gluconeogenesis in the liver and increasing the sensitivity of the tissue by stimulating its receptors for insulin. Besides, this medication increases the intensity of glycolysis, inhibits the effects of glucagon and stimulates the fatty acid oxidation. Certainly, the result of this effect is the reduction of the level of glucose in the blood and a reduction of fatty acid accumulation.

However, despite the benefits that metformin has in treating diabetes type II in the first place, and then other metabolic issues both related to insulin resistance and those beyond this framework, a chronic usage of metformin has proven in some research to have insufficient effectand to lead to the body becoming saturated therewith. Thorough survey into the effects of this medication shall be continued, in order to determine its place not only as an accessible and certain medicine for insulin resistance, but also as applicable in both prevention and treatment of a numerous other metabolic issues.

**Keywords:** Metformin, diabetes, cardiovascular protective effect, glucotoxicity, lipotoxicity

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## Introduction

Metformin is 1,1dimethylbiguanidecreated out of Leguminosae *Galega officinalis* and has been recorded as anti-diabetic medicine for the first time in 1957 (1). Based on its safety profile, metformin is anti-hyperglycemic first medicine of choice to treat diabetes mellitus type II accounting for more than 90% of diagnosed diabetes types (2). After approving its usage in 1958, in the United Kingdom and the United States

of America in 1995, metformin merged as one of the most commonly used medicines to treat insulin resistance in patient with diabetes II type insulin resistance in patient with dosages ranging from 500 to 2.500 mg/ per day (3).

Unlike other anti – diabetic medicines, metformin rarely exhibits contraindications such as hypoglycemia, hyperinsulinemia, B12 vitamin deficiency, peripheral neuropathy and rarely lactic acidosis, simultaneously being less connected to risk factors occurring with overweight patients. In many cases it has shown benefits by reducing the body weight (4,5).

Besides those mechanisms related to the treatment of diabetes type II and insulin resistance, its mechanisms in different conditions represent the objective of the research within many studies in last couple of decades. Numerous studies have shown that metformin, besides its basic role in treating insulin resistance, has many pleiotropic effects, the anti – carcinogenic and anti – aging characteristics among them, effects in treatment of polycystic ovaries syndrome, as well as protection characteristics for cardio – vascular and nervous system. Diabetes patients most commonly face greatest challenges due to complications happening as a consequence of impairing the cardio – vascular system, which may be divided into macrovascular complications (coronary artery disease, peripheral artery disease and cerebrovascular disease) and microvascuar complications (nephropathy, retinopathy and neuropathy) of which almost around 70% of patients die from heart conditions and macrovascular disease in their brain. (6).

Many studies have shown the benefits metformin has with such patients The United Kingdom Prospective Diabetes Study (UKPDS) was a first study conducted in 1998 determining that metformin considerably reduces the death risk and risk of acute myocardial infarction with overweight patients diagnosed with diabetes II type. Initial treatment implied the metformin dosage of 850mg on a daily basis, which doubled afterwards, until the maximum dosage was not reached of 2550 mg daily (5).

Compared to sulfonylurea and insulin therapy, metformin efficiently reduces the risk of myocardial infarction and death (7). A research conducted by Roumie at al. 2012. confirms the statement, since it has shown that metformin has less chances to develop a cardiovascular disease or death with patients diagnosed with diabetes type II compared to sulfonylurea therapy. Unlike metformin stimulates pancreatic beta cells in a way to synthetie more insulin thus reducing glucoses level, which is not done by metformin since it uses already syntetized insulin (8).

Results by Reduction of Atherothrombosis for Continued Health Registry (9) indicate that metformin, which was used as secondary protection device, was related to 24% reduced risk of death with patients suffering from atherothrombosis. This research has proven that metformin has cardiovascular protection effects which are not exclusively related to reducing level of glucoses in blood (9). According to Summary of Product Characteristics, metformin presents the contraindication to heart failure (HF) (10).

However, most recent research proves that metformin cannot actually cause a distinguished lactic acidosis and can be used with patients having early signs of HF (11).

It is precisely due to these discrepancies in results when it comes to contraindication of metformin in heart diseases why numerous research have been conducted to explain thoroughly the effects of metformin, and to determine whether it presents a safe choice in treatment of patients with diabetics who besides that issue face a cardiovascular issue, while those for HF are most emphasized.

Generally, effects of metformin on cardiovascular system are different. It primarily reduces the level of low-density lipoprotein (LDL) holesterol by activating adenosine monophosphate kinase (AMPK) thus improving the metabolism of lipoproteins (12). Metformin influences the reduction of weight by reducing the feeling of hunger, which results in lesser introduction of food generally (13). One of the most recent meta studies indicates that metformin may effectively lower systolic blood pressure with patients who are not patients with diabetes (14). One of the explanations for this mechanism may be that metformin, by reducing insulin in blood, deactivates adrenergic receptors. Metformin also reduces the concentration of calcium in cytoplasm whilw inhibiting sympathetic nervous system in situations when the amount of salt introduced is higer and increases glomerular filtration and

excretion (15). Previously explained effects may lead to a conclusion that it reduces oxidative stress as well as stimulates the function of epithelial cells (16, 17).

## Some of the mechanisms by which metformin has the effects onto cardiovascular system and its diseases

### *Glucoses and FFA Metabolism*

With a damaged heart, activation of metabolic pathways controlled by AMPK (activated by metformin) in cardiomyocytes is a mechanism enabling adaptation in conditions when the total energy has been reduced (18,19). Most research has been devoted to exploring the factors influencing the phosphofructokinase 1 (PFK – 1). Levels of AMP, ADP and non – organic phosphorus are the allosteric activators of PFK – 1, while its inhibitors are ATP, citrate and h+ ions (18). AMPK activates PFK -2 which leads to increased concentration of fructose 2, 6 – bisphosphate which is also one of PFK -1 activators being produced in cardiomyocytes (Figure 1) (20). AMPK activated by metformin leads to translocation of glucose transporter type 4 (GLUT-4) within cardiomyocyte membrane and performs the acceleration of glucose binding by insulin (18,21).

In vitro studies have shown that by adding metformin to an incubated medium, increased absorption of glucose happens since it stimulates phosphoinositide 3-kinase (PI 3 – K) – protein kinase B/Akt pathway and AMPK activation (20).This positive effect has been noted with cardiomyocytes that are resistant to insulin and with those that had normal sensitivity thereon (22). Consequently, it can be concluded that in patient with diabetes that face heart issues, which then causes deteriorated usage of glucose, metformin may help improve its usage.

In these patients (type II diabetics with heart damage), due to increased production of energy through intensifying oxidation of glucose, inhibition of β oxidation of fatty acids may occur thus leading to accumulation of free fatty acids (FFA) in cardiomyocytes and cardiac steatosis (excessive accumulation of lipid in heart cells) (20). Research have shown that overweight patients with diabetes type II have higher level of triglycerides in heart compared to healthy people, even with no symptoms of left atrium impairments (23). This is exactly why the issue of metformin in therapy for heart disease patients is disputable.

On the other hand, many in vitro research have shown that small quantities of metformin do not deteriorate the condition of heart diseases, but rather protect heart muscles from apoptosis caused by fats (20). However, high concentration of metformin may increase the number of cells which due to FFA accumulation start the process of apoptosis (24). In in vivo studies, chronic usage of metformin reduces FFA level in plasma and increases their oxidation in cardiomyocytes that do not belong to patients with diabetes (25).

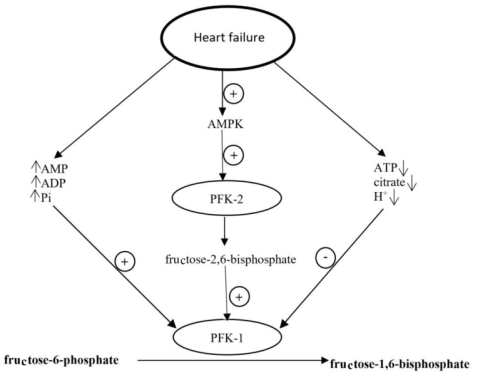


**Figure 1. Regulation of PFK activity in heart failure.**ADP, adenosine diphosphate; AMP, adenosine monophosphate; AMPK, AMP activated protein kinase; ATP, adenosine triphosphate; PFK-1, phosphofructokinase 1; PFK-2, phosphofructokinase 2; and Pi, inorganic phosphate. Circles with "+" and "–" represent stimulatory and inhibitory effects, respectively. ↓ and ↑ represent increase and decrease in the concentration of specific compound, respectively. (20)

### *Inhibition of protein synthesis*

In vitro studies have shown that the activation of AMPK protects hearth muscles from hypertrophy by inhibiting the synthesis of protein (26, 27). It has been determined that there are two key pathways in the synthesis of protein: eEF – 2 (eukaryote elongation factor 2) and p70S6 (ribosomal protein S6) kinase path (27). eEF – 2 regulates the movement of ribosomes along the mRNA through the process of elongation (28), while p70S6 kinase phosphorylases eEF-2 kinase (29) and ribosomal protein S6 (30). Chan and associates (27) have proven that by activating AMPK by metformin, it inhibits the synthesis of protein by

increasing the levels of phosphorilated inactive eEF-2 proteins and reduces the phosphorylation p70S6 kinase, which leads to activation of eEF – 2 kinase as well as to the inhibition of ribosomal S6 protein (26).

### *Improving the functions of mitochondria*

Another mechanism explaining the benefits of metformin is the improvement of the function of mitochondria in cardiomyocytes. By activating AMPK phosphorylation and expression of endothelial nitric oxide synthase (eNOS) and PGC - 1α peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) in an experiment carried out in mice during 4 – week time, small dosage of metformin considerably improved the operation of left ventricle and a survival of the animals for 47% (31). eNOS and PGC-1α are important regulators of biogenesis and functions of mitochondria and their activation improves the oxidative metabolism in cardiomyocytes by increasing the synthesis of ATP and returns the normal relation of its oxidation and synthesis (32, 33).

### *Synthesis of collagen and glycation*

In patients suffering from diabetes, the most important mechanism leading to the damage of the heart is an interstitial accumulation of collagen and process of glycation (non-enzymatic reaction causing covalent attachment of protein or lipid molecules to sugar molecules, fructose or glucose without enzymes) and metformin may inhibit both processes (34).

In periclinical research carried out on mice that had an issue with increased blood pressure in left ventricle, the results achieved showed that metformin inhibits the synthesis of collagen in myocardium, which then results in reduction of the size of left ventricle and considerable reduction of diastolic pressure therein (20). The way metformin achieves this is by inhibition of synthesis of transforming growth factor (TGF) - β1 in myocardium.

Whereas for the non – enzymatic glycation, it may cause various structural and functional disorders in the heart of patients with diabetes (20). This process leads to binding of carbonyl groups from sugar for free amino groups from proteins or for nucleic acids or phospholipids (36, 37), which results in creation of reactive compounds (glyoxal, methylglyoxal, etc.) which in the end covalently binds for the proteins, thus forming glycation end products advanced glycation end products (AGEs) (38). These products do not dissociate and are permanently accumulated in proteins such as collagen in myocardium and in blood vessels which increases its callosity thus disrupting their usual work (Figure 2) (37,39).

Collagen glycation increases its resistance for the dissolution by enzymes, which leads to its accumulation and fibrosis (formation of excess of connective tissue) (40-42). Metformin has the capacity to inhibit the creation of AGEs by neutralizing reactive compounds that are created in the process, by binding the guanine group for α- dicarbonyl group of methylglyoxal (20).

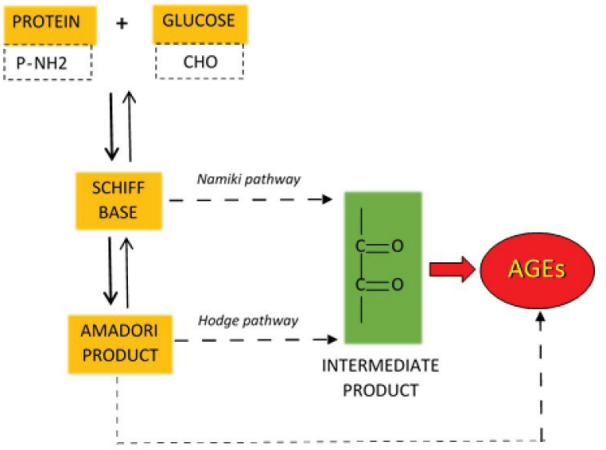


**Figure 2. Maillard reaction.** Carbonyl groups of glucose respond with amino gatherings of proteins (both in dabbed outlines) to frame Schiff bases (yellow) which at that point are unexpectedly changed over to Amadori items (yellow). Them two add to development of low atomic weight receptive dicarbonyls (middle of the road items, green) which tie to proteins framing advacned glycation final results (AGEs, red). Consistent and spotted bolts speak to one-and various advance responses, individually (20).

### *iNOSactivity and transport of $Ca^{2+}$*

There are three isoform of NO – synthase (NOS) in the heart tissue: endothelial (eNOS), neural NOS (nNOS) and inducible NOS (iNOS) (20). The eNOS is located in endothelial cells and cardiomyocytes and is key source of molecules of nitrogen – monoxide; nNOS is located in cardiomyocytes while the existence of iNOS is found in immune system cells, car-

diomyocytes and activated fibroblasts (43). Increased expression of iNOS is considered to be the cause of development of different complications in muscle tissue such as congestive heart insufficiency (the condition of insufficiency when greater quantity of blood reaches the heart than the heart can actually pump) (44). Too high synthesis of NO molecule caused by iNOS contributes to the deterioration of systolic and diastolic pressure in left ventricle (20). Compared to eNOS which synthetizes small nanomolar quantities of nitrogen – monoxide, iNOS produces nitrogen – monoxide in micromolecular concentrations, which is sufficient for the disorders in heart (45).

High concentrations of NO via secondary messenger cyclic guanosine – monophosphate (cGMP), activate protein kinase G (PKG) and cGMP – activated phosphodiesterase; PKG further blocks L-type $Ca^{2+}$ ion channels and reduces the density of calcium in cell cytosol, while phosphodiesterase uses cAMP (46). These changes, happening because of the increase in nitrogen – monoxide molecules by the activities of iNOS, reduce intracellular density of $Ca^{2+}$ and cAMP density which contributes to myocardial contraction, finally leading to serious impairments of myocardia, since these conditions may initiate the process of cell apoptosis (46, 47).

iNOS activity is regulated by genetic expression mainly of the proinflammatory cytokine such as inteleukin-1β (IL-1β) but also of the lipopolysaccharide induction iNOSmRNK expression in macrophage (20,48). Metformin inhibits both activators. In vitro studies have shown that metformin inhibits IL-1β in activated macrophages through AMPK activity. (49). Besides, metformin also inhibits TGF-β1 which is the main growth factor and causes the occurrence of fibrosis in cardiovascular system of myocardia (50).

### *Apoptosis*

Apoptosis is one of the basic mechanisms useds to express its pleiotropic effects, most commonly leading to initiation of this process, especially if we talk about cancer cells. However, speaking of apoptosis with cardiovascular diseases, we actually focus on the capacity of metformin to inhibit this process in cardiomyocytes. Sasaki and associates established that metformin inhibits the process of apoptosis during the incubation of cardiomyocytes with hydrogen peroxide ($H_2O_{2)}$ (19). In one of the in vivo studies carried out on dogs who had heart problems, metformin showed positive results in reduction of the number of dead cardiomyocytes, as well as the improvements in the works of left ventricle; this is explained by AMPK dependent mechanism of metformin, consequently activating the eNOS expression, thus resulting in the increased NO synthesis (19).

### *Metformin therapy for HF (heart failure)*

Numerous research have shown that metformin may improve the HF condition. Hence, in the study carried out with patients having heart insufficiency and type II diabetes, metformin, either as a monotherapy or in combination with sulphonylurea, has demonstrated a significant reduction in the number of deaths and hospitalization when compared to therapy consisting only of sulphonylurea alone (51). Metformin has proven, both in monotherapies and poly therapies, to be a better solution when compared to traditional treatment that implied, besides other things, the change of a diet and generally a lifestyle, even when prescribed in greater quantity (20). The effect of metformin in research has been independent of glycemic index and total body weight (52).

Nevertheless, regardless of numerous evidence, metformin is not recommended to patients suffering from both diabetes and heart insufficiency due to the risk of lactic acidosis (20). However, there are still no clinical studies clearly indicating the connection of metformin with lactic acidosis, but it is mainly considered that the latter one represents a condition that occurs as a result of different illnesses and the risk of its occurrence is not considerably changed depending on whether the metformin is used or not (51, 53).

## Conclusion

Based on the data presented, it may be concluded that metformin has a positive effect on protection of cardiovascular system. It has the capacity to either improve many impairments or to prevent their further

deterioration. Although it is not recommended in patients with HF due to the risk of lactic acidosis, the results showing that metformin is not a direct cause and usage does not increase the risk actic acidosis compared to other medicines against hyperglycemia. Metformin is actually recommended as a first medicine of choice with patients with diabetes type II and those having heart insufficiency, but also with those who do not have diabetes.

## Statement on conflict of interests

The authors of the paper claim that the manuscript has not been published elsewhere as a whole or partly. We agree with the content of the manuscript and approve about its publication in Progress in Nutrition. These are no financial problems that might lead to a conflict of interest. The authors declare no conflicts of interest.

## References


1. Bailey C.J. Metformin: Historical overview. Diabetologia 2017; 60: 1566–1576.
2. Maruthur NM, Tseng E, Hutfless S, Wilson L.M, Suarez-Cuervo C, Berger Z, et al. Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis. Ann Intern Med 2016; 164: 740–751.
3. Scarpello JH, HowlettHC. Metformin therapy and clinical uses. DiabVasc Dis Res 2008; 5(3): 157-167.
4. Gupta K, Jain A, Rohatgi A. An observational study of vitamin b12 levels and peripheral neuropathy profile in patients of diabetes mellitus on metformin therapy. Diabetes Metab Syndr 2018; 12: 51–58.
5. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 854–865.
6. Benjamin EJ, Blaha MJ, Chiuve SE, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation 2017; 135(10): e146–e603.
7. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359(15): 1577–1589.
8. Roumie CL, Hung AM, Greevy RA, et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. Ann Intern Med 2012; 157(9): 601–610.
9. Roussel R, Travert F, Pasquet B, et al; Reduction of Atherothrombosis for Continued Health (REACH) Registry Investigators. Metformin use and mortality among patients with diabetes and atherothrombosis. Arch Intern Med 2010; 170(21): 1892–1899.
10. Rojas LBA, Gomes M.B. Metformin: An old but still the best treatment for type 2 diabetes. Diabetol Metab Syndr 2013; 5: 6.
11. Kappel BA, Marx N, Federici M. Oral hypoglycemic agents and the heart failure conundrum: Lessons from and for outcome trials. Nutr Metab Cardiovasc Dis 2015: 25: 697–705.
12. Xu T, Brandmaier S, Messias AC, et al. Effects of metformin on metabolite profiles and LDL cholesterol in patients with type 2 diabetes. Diabetes Care 2015; 38(10): 1858–1867.
13. Adeyemo MA, McDuffie JR, Kozlosky M, et al. Effects of metformin on energy intake and satiety in obese children. Diabetes ObesMetab 2015; 17(4): 363–370
14. Zhou L, Liu H, Wen X, Peng Y, Tian Y, Zhao L. Effects of metformin on blood pressure in nondiabetic patients: a meta-analysis of randomized controlled trials. J Hypertens. 2017; 35(1): 18–26.
15. Thomopoulos C, Katsimagklis G, Makris T. Metformin and blood pressure lowering: a questioned association. J Hypertens 2017; 35(1): 27–28.
16. Wan X, Huo Y, Johns M, et al. 5′-AMP-activated protein kinase activating transcription factor 1 cascade modulates human monocyte derived macrophages to atheroprotective functions in response to heme or metformin. Arterioscler ThrombVasc Biol 2013; 33(11): 2470–2480.
17. Isoda K, Young JL, Zirlik A, et al. Metformin inhibits proinflammatory responses and nuclear factor-kappaB in human vascular wall cells. ArterioscIerThrombVasc Biol 2006; 26(3): 611–617.
18. Nascimben L, Ingwall J.S, Lorell B.H, Pinz I, Schultz V, et al. Mechanisms for increased glycolysis in the hypertrophied rat heart. Hypertension 2004; 44: 662–667.
19. Sasaki H, Asanuma H, Fujita M, Takahama H, Wakeno M, Ito S, et al. Metformin prevents progression of heart failure in dogs: Role of AMP-activated protein kinase. Circulation 2009; 119: 2568–2577.
20. Dziubak A, Wójcicka G, Wojtak A, Bełtowski J. Metabolic Effects of Metformin in the Failing Heart. Int J Mol Sci 2018; 19: 286-299.
21. Young M.E, McNult P, Taegtmeyer H. Adaptation and maladaptation of the heart in diabetes: Part II:Potential mechanisms. Circulation 2002; 105: 1861–1870.
22. Bertrand L, Ginion A, Beauloye C, Hebert A.D, Guigas B, Hue L, et al. AMPK activation restores the stimulation of glucose uptake in an in vitro model of insulin-resistant cardiomyocytes via the activation of protein kinase B. Am J Physiol Heart Circ Physiol 2006; 291: H239–H250.
23. McGavock JM, Lingvay I, Zib I, Tillery T, Salas N, Unger R, et al. Cardiac steatosis in diabetes mellitus: A 1H-mag-

netic resonance spectroscopy study. Circulation 2007; 116: 1170–1175.
24. An D, Kewalramani G, Chan JKY, Ghosh S, Pulinilkunnil T, Abrahani A. et al. Metformin influences cardiomyocyte cell death by pathways that are dependent and independent of caspase-3. Diabetologia 2006; 49: 2174–2184.
25. Benes J, Kazdova L, Drahota Z, Houstek J, Medrikova D, Kopecky J. et al. Effect of metformin therapy on cardiac function and survival in a volume-overload model of heart failure in rats. Clin Sci 2011; 121: 29–41.
26. Chan AY, Soltys CL, Young ME, Proud CG, Dyck JR. Activation of AMP-activated protein kinaseinhibits protein synthesis associated with hypertrophy in the cardiac myocyte. J Biol Chem 2004; 279: 32771–32779.
27. Chan AY, Dolinsky V.W, Soltys CL, Viollet B, Baksh S, Light PE, Dyck JR. Resveratrol inhibits cardiac hypertrophy via AMP-activated protein kinase and Akt J Biol Chem 2008; 283: 24194–24201.
28. Gal-Ben-Ari S, Kenney JW, Ounalla-Saad H, Taha E, David O, Levitan, D, et al. Consolidation and translation regulation. Learn. Mem 2012; 19: 410–422.
29. Wang X, Li W, Williams M, Terada N, Alessi DR, Proud CG. Regulation of elongation factor 2 kinaseby p90 RSK1 and p70 S6 kinase. EMBO J 2001; 20: 4370–4379.
30. Proud, C.G. p70 S6 kinase: An enigma with variations. Trends Biochem. Sci. 1996, 181–185.
31. Gundewar S, Calvert JW, Jha S, Toedt-Pingel I, Ji SY, Nunez, D, et al. Activation of AMP-activated protein kinase by metformin improves left ventricular function and survival in heart failure. Circ Res 2009; 104: 403–411.
32. Chang JC, Kou S.J, Lin WT, Liu CS. Regulatory role of mitochondria in oxidative stress and atherosclerosis. World J Cardiol 2010; 2: 150–159.
33. Vettor R, Valerio A, Ragni M, Trevellin E, Granzotto M, Olivieri M, et al. Exercise training boosts eNOS-dependent mitochondrial bio-genesis in mouse heart: Role in adaptation of glucose metabolism. Am J Physiol Endocrinol Metab 2014; 306: E519–E528.
34. Jyothirmayi GN, Soni BJ, Masurekar M, Lyons M, Regan TJ. Effects of metformin on collagen glycation and diastolic dysfunction in diabetic myocardium. J Cardiovasc Pharmacol Ther 1998; 3: 319–326.
35. Xiao H, Ma X, Feng W, Fu Y, Lu Z, Xu M, et al. Metformin attenuates cardiac fibrosis by inhibiting the TGF β 1-Smad3 signalling pathway. Cardiovasc Res 2010; 87: 504–513.
36. Ashraf JM, Ahmad S, Rabbani G, Hasan Q, Jan AT, Lee EJ, et al. 3-Deoxyglucosone: A potential glycating agent accountable for structural alteration in H3 histone protein through generation of different AGEs. PLoS ONE 2015; 10: e0116804.
37. Singh VP, Bali A, Singh N, Singh JA. Advanced glycation end products and diabetic complications. Korean J Physiol Pharmacol 2014; 18, 1–14.
38. Brings S, Fleming T, Freichel M, Muckenthaler MU, Herzig S, Nawroth PP. Dicarbonyls and advanced glycation end-products in the development of diabetic complications and targets for intervention. Int J Mol Sci 2017; 18: 984.
39. Dei Cas A, Spigoni V, Ridolfi V, Metra M. Diabetes and chronic heart failure: From diabetic cardiomyopathy to therapeutic approach. Endocr Metab Immune Disord Drug Targets 2013; 13: 38–50.
40. Nowotny K, Jung T, Höhn A, Weber D, Grune T. Advanced glycation end products and oxidative stress in type 2 diabetes mellitus. Biomolecules 2015; 5: 194–222.
41. Dhingra R, Vasan RS. Diabetes and the risk of heart failure. Heart Fail Clin 2012; 8: 125–133.
42. Miki T, Yuda S, Kouzu H, Miura T. Diabetic cardiomyopathy: Pathophysiology and clinical features. Heart Fail Rev 2013; 18: 149–166.
43. Ritchie RH, Drummond GR, Sobey CG, De Silva TM. Kemp-Harper BK. The opposing roles of NO and oxidative stress in cardiovascular disease. Pharmacol Res 2017; 116: 57–69.
44. Saito T, Hu F, Tayara L, Fahas L, Shennib H, Giaid A. Inhibition of NOS II prevents cardiac dysfunction in myocardial infarction and congestive heart failure. Am J Physiol Heart Circ Physiol 2002; 283: H339–H345.
45. Förstermann U, Kleinert H. Nitric oxide synthase: Expression and expressional control of the three isoforms.Naunyn. Schmiedebergs. Arch Pharmacol 1995; 352: 351–364.
46. Yang B, Larson DF, Watson RR. Modulation of iNOS activity in age-related cardiac dysfunction. Life Sci 2004; 75: 655–667.
47. Falcão-Pires I, Leite-Moreira AF. Diabetic cardiomyopathy: Understanding the molecular and cellular basis to progress in diagnosis and treatment. Heart Fail Rev 2012; 17: 325–344.
48. Tsujino M, Hirata Y, Imai T, Kanno K, Eguchi S, Ito H, Marumo F. Induction of nitric oxide synthase gene by interleukin-1 beta in cultured rat cardiocytes. Circulation 1994; 90: 375–383.
49. Bułdak Ł, Łabuzek K, Bułdak RJ, Kozłowski M, Machnik G, Liber S, et al. Metformin affects macrophages' phenotype and improves the activity of glutathione peroxidase, superoxide dismutase, catalase and decreases malondialdehyde concentration in a partially AMPK-independent manner in LPS-stimulated human monocytes/macrophages. Pharmacol Rep 2014; 66: 418–429.
50. Wang XF, Zhang JY, Li L, Zhao XY, Tao HL, Zhang L. Metformin improves cardiac function in rats via activation of AMP-activated protein kinase. Clin Exp Pharmacol. Physiol 2011; 38: 94–101.
51. Eurich DT, Majumdar SR, McAlister FA, Tsuyuki RT, Johnson JA. Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. Diabetes Care 2005; 28: 2345–2351.
52. MacDonald MR, Eurich DT, Majumdar SR, Lewsey JD, Bhagra S, Jhund PS, et al. Treatment of type 2 diabetes and outcomes in patients with heart failure: A nested case–control study from the U.K. General Practice Research Database. Diabetes Care 2010; 33: 1213–1218.

53. Holstein A, Stumvoll M. Contraindications can damage your health—Is metformin a case in point? Diabetologia 2005; 48: 2454–2459.
54. Gilbert RE, Krum H. Heart failure in diabetes: Effects of antihyperglycaemic drug therapy. Lancet 2015; 385: 2107–2117.
55. Seferovi´ c PM, Petrie MC, Filippatos GS, Anker SD, Rosano G, Bauersachs J, et al. Type 2 diabetes mellitus and heart failure: A position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2018; 20: 853–872.