Ann Res Antioxid. 2018;3:e03 Review

Annals of Research in Antioxidants http annresantioxidants.com

Protective effect of metformin on diabetes mellitus, diabetic kidney disease and hepatocytes

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Received 20 October 2017
Accepted 14 January 2018
ePublished 23 January 2018

Keywords: Diabetes mellitus, Diabetic kidney disease, Liver diseases, Metformin

Abstract

Diabetes mellitus is a series of metabolic disturbances followed by high blood glucose levels associated with insulin deficiency. Critical long-time difficulties due to high blood glucose are nerve and kidney disorders, expansion of heart attack or stroke, serious vision impairment, and lesions of limbs. Suitable medicines used to treat diabetes include insulin and some oral medicines. Insulin injection is used to remedy type 1 diabetes and metformin as an available drug by mouth is used to remedy type 2 diabetes. Metformin can decrease the prevalence of type 2 diabetes mellitus by 31% after 3 years consumption and by 18% after 10 years consumption in people at risk for this disease. According to many studies, mechanisms of diabetic kidney disease are started by high production of reactive oxygen species (ROS) and apoptosis. For keeping safe renal tubular cells and podocytes, physicians recommended administration of medications that stop renin-angiotensin–aldosterone system such as angiotensin converting enzyme (ACE) inhibitor or medications that block the effect of angiotensin II. Among the problems of diabetes mellitus, you can refer to multiple diseases of the liver including sediment of glycogen, nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis, biliary disease, cholelithiasis, cholecystitis, and complications of therapy of diabetes. The results of taking metformin have proven the protective effects of this drug against heart failure, liver problems, and kidney disease.

Citation: Darabi S, Hasanvand A. Protective effect of metformin on diabetes mellitus, diabetic kidney disease and hepatocytes. Ann Res Antioxid. 2018;3:e03.

An introduction to diabetes mellitus

Diabetes mellitus is a series of metabolic disturbances followed by high blood glucose levels associated with insulin deficiency (1). Insulin as a significant hormone can keep glucose at a steady level in the body. This hormone provides glucose for different tissues including muscles, adipose, and liver from various ways. Insulin is able to stop the breaking of glycogen (gluconeogenesis), it can motivate the absorption of glucose by fat and muscle cells, and it can save glucose in the shape of glycogen in hepatocytes. Therefore, any deficiency of insulin can decrease the absorption of glucose by the body cells and prevent glucose storage in the liver and muscles. Finally, the outcome of deficiency of insulin is various metabolic disorders such as acidosis, decreased protein synthesis, and high blood glucose levels (2). Insulin deficiency is related to either the lack of enough insulin production by pancreas or inappropriate replication of body cells to the insulin (2). High blood glucose level can cause many symptoms including repeated urination, proliferated starvation (polyphagia), and proliferated thirst (polydipsia) (3). Critical long-time difficulties due to high blood glucose are injuries to the small and large blood vessels. Cardiovascular disease as a factor of 75% of mortality in patients with diabetes mellitus is the outcome of large blood vessels injuries. Expansion of heart attack or stroke is another disease due to large blood vessels injuries. Nerve and kidney disorders, serious vision impairment, and lesions of limbs are significant diseases associated with small blood vessels injuries (3,4).

Four significant kinds of diabetes mellitus

Core tip

Metformin is used in patients with type 2 diabetes and it is known as the selection of first-line therapy which can decrease blood glucose level and mortality. Metformin has also been shown to have protective effects on diabetes mellitus, diabetic renal failure and hepatocytes.

include (3,5);

1. Insulin-dependent diabetes mellitus (IDDM) known as type 1 diabetes mellitus commonly happens in youngsters. Disability of pancreas for unknown reason can cause this form of diabetes.
2. Insulin independent diabetes mellitus known as type 2 diabetes mellitus usually happens in adulthood. In this form, as body weight increases cells resist to respond to insulin correctly and finally a loss of insulin may also elaborate.

Gestational diabetes that happens in pregnant women without a prior precedent of diabetes is the third form of diabetes.

Other specific types: prediabetes is a state of diabetes in which glucose levels increase in the blood. However, it may take years so that blood glucose reaches as high as the state of type 2 diabetes. Another form of diabetes happens when type 2 diabetes mellitus isn't detected in adults and this issue can cause the development of type 1 diabetes mellitus named latent autoimmune diabetes of adults (LADA). Another appearance of diabetes is related to a kind of genetic deficiency in the secretion of insulin. Eventually, the consumption of high doses of glucocorticoids can lead to another figure of diabetes mellitus named steroid diabetes (6).

It is estimated that almost 1.5 to 5.0 million mortality happened by diabetes every year from 2012 to 2015 (7). Among all of the countries in the world, India has the highest proportion of people with diabetes so that statistics estimate approximately 62 million Indian diabetics with the average age of 42.5 years. Of the Indians with diabetes, one million patients die each year (7). There are some solutions to prevent and treat diabetes mellitus. Type 1 DM cannot be prevented but type 2 diabetes will be prevented by holding a healthy diet such as polyunsaturated fats, which are usually of plant origin and healthier in the diet than saturated fats, losing body weight, and high physical activity that decreases the risk of diabetes by 28% (8). The aim of treatment is lowering blood glucose level and keeping HbA1C level at 6.5% (9). Suitable medicines used to treat diabetes include insulin and some oral medicines. Insulin injection is used to remedy type 1 diabetes and metformin as an available drug by mouth is used to remedy type 2 diabetes. Preserving blood pressure and foot care are other important managements that must be performed by people with diabetes mellitus (10).

Cardiovascular disease is a very significant problem due to diabetes mellitus. Therefore, the administration of medicines that decreases blood pressure (such as medications that inhibit angiotensin converting enzyme [ACE]) and medicines that are effective on heart attacks and strokes like aspirin are suggested for people with cardiovascular disorders (11). When patients suffer from drastic problems of type 1 diabetes, transplantation of organs such as pancreas or kidney is recommended (12). Sometimes weight loss by surgery in patients with type 2 diabetes or obesity can decrease blood sugar levels without taking any medicines (13).

Materials and Methods

For this review, we used a variety of sources including PubMed/Medline, EBSCO, EMBASE, Web of Science, Google Scholar, Scopus and directory of open access journals (DOAJ). The search was conducted by using combinations of the following key words and/or their equivalents; Diabetes mellitus, type 2 diabetes mellitus, reactive oxygen species, angiotensin converting enzyme (ACE) inhibitor, glycogen, nonalcoholic steatohepatitis, fibrosis, cirrhosis, biliary disease, cholelithiasis, cholecystitis, metformin, heart failure, liver, kidney disease, Insulin-dependent diabetes mellitus, gluconeogenesis, glycogen lysis, gluconeogenesis, glycogen synthesis, adenosine monophosphate kinase enzyme, hypoglycemia, myocardial infarction, sulfonylurea agents, reactive oxygen species, apoptosis, free radicals, proximal tubules, podocytes, renin-angiotensin–aldosterone system, end-stage renal disease, oxidative stress, inflammation, gestational diabetes and lactic acidosis.

Metformin and diabetes

Among several groups of drugs suggested for treatment of type 2 diabetes (such as insulin, glibenclamide, chlorpropamide, and metformin), metformin is known as the first choice of treatment which can reduce blood glucose level and mortality by thirty percent (14). According to trials, when metformin is administrated in patients with type 2 diabetes over a 10-year treatment period, weight increase is lower than when sulfonylureas (glibenclamide and chlorpropamide) and insulin are used. Minus weight increase can aid patients to control their blood glucose better (15). Sulfonylureas act by raising insulin extrication from pancreatic gland and making the body more sensitive to insulin (16). The therapeutic effect of the sulfonylureas is not verified in patients with insulin inadequacy such as patients with type 1 diabetes. In contrast, helpful effect of these drugs is proven in patients with type 2 diabetes and newborn diabetes.

Metformin as a medication from biguanide class with trade name of glucophage is administrated in the treatment of some various diseases including polycystic ovary syndrome, female infertility, and different form of diabetes (type 2 diabetes, prediabetes, and gestational diabetes). Although this drug is not allowed to be administrated in patients with renal impairment or liver disorder however, the results of taking metformin have proven the protective effects of this drug against heart failure, liver problems, and kidney disease (17). Many various mechanisms are known for metformin in decreasing of blood glucose level. During a mechanism, metformin enhances insulin effects without the involvement of the pancreas. Metformin can also stop the production of insulin from the liver by decreasing the measure of gluconeogenesis and somewhat glycogenolysis. Metformin can inhibit major liver enzymes associated with gluconeogenesis and

glycogen synthesis by stimulating of AMPK (adenosine monophosphate kinase) enzyme (18). Moreover, metformin prevents hypoglycemia by increasing the peripheral glucose discarding into skeletal muscle. This characteristic makes metformin special among other medications administrated for treatment type 2 diabetes (19). According to a trial in the United States, metformin can decrease the prevalence of type 2 diabetes mellitus by 34% after three years consumption and by 18% after ten years consumption in individuals with elevated risk of diabetes mellitus (20). Other trials demonstrated that women who take metformin during pregnancy are healthier than women who take insulin (21).

Lactic acidosis is known as an important side effect of metformin. Various signs of lactic acidosis are vertigo, intense sleepiness, and pain in muscles, fatigue, thrill, blue skin, breathing hardly, slow/irregular heartbeat, stomachache, diarrhea, and regurgitating. Metformin usually doesn't induce hypoglycemia. However, when metformin is administrated with other anti-diabetic drugs, hypoglycemia may happen. The incidence of gastrointestinal intolerance as side effect of metformin is more than lactic acidosis. Myocardial infarction (MI) is also an important outcome of diabetes mellitus that its incidence in patients treated with metformin is lower than those treated with sulfonylurea agents. Finally, older adults may be at greater risk for side effects such as low blood sugar or lactic acidosis (22).

Metformin and kidney cells

Many studies demonstrated that metformin may have protective effects on kidney cells against the factors that cause toxicity in the kidney such as nephropathy caused by diabetes mellitus (22). According to many studies, mechanisms of kidney disease due to diabetes are started by high manufacture of reactive oxygen species (ROS) and apoptosis (scheduled cell death showed by cell shrinkage) (23). High blood glucose increases apoptosis and breaking nucleic acids such as DNA into small or separate parts. Production of apoptotic signaling molecules and free radicals like ROS by mitochondria in tubular cells related to high blood glucose can cause apoptosis in different body cells including epithelial cells of proximal tubules and podocytes (24). Thus any drug that can keep renal tubular cells and podocytes safe by stopping or decreasing apoptosis is the best therapeutic choice in patients with diabetic kidney disease. For this purpose, physicians recommended the use of medications that stop renin-angiotensin–aldosterone system (those that inhibit angiotensin converting enzyme) or medications that stop the effect of angiotensin II by blocking the receptors of angiotensin in different tissues. The use of these drugs with exact control of lipid, blood pressure, and glucose in patients with diabetic nephropathy demonstrated a reduction in albumin excretion and progress of end-stage renal disease (ESRD) (25). Metformin has been widely used as the best choice for these patients. Metformin exhibits different mechanisms in protecting renal cells. One mechanism is related to decreasing albumin excretion in patients with diabetes mellitus. Another therapeutic efficacy of metformin is stimulating of AMP (adenosine monophosphate) kinase in various tissues (liver, skeletal muscle, and brain). Many studies explain protective effect of metformin on tubular and podocytes harm through reducing intracellular ROS which asserts metformin effect against oxidative stress (26). According many trials on rats, metformin not only prevents nephropathy caused by diabetes mellitus but also has beneficial and ameliorative effects against nephrotoxicity caused by gentamicin (27).

Metformin and hepatocytes

Although diabetes mellitus and its problems are related to insulin persistence, pancreas injury, and autoimmune disorders but a large part of problems are associated with the liver. Liver as a body complex organ does a significant function in controlling sugars and starches and provides enough energy for body function. When blood glucose increases, it causes that liver stores supplemental glucose in the form of glycogen. When blood sugar levels decrease, it causes glycogen decomposition to glucose. Among the problems of diabetes mellitus, you can refer to multiple diseases of the liver including sediment of glycogen, nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis, diseases due to bile or the bile ducts, inflammation of the gallbladder, and difficulties of therapy of diabetes. The glycogen reposition in the liver, which is seen in 80% of diabetic patients, can be noted to the defect of long-standing insulin that practically simplifies, the acting of synthase and developed gluconeogenesis (28). High changes in glucose condensation and repeated insulin dosing can be accounted as mechanisms for glycogen sediment in the cytoplasm. According to studies conducted by Ehrlich in 1883, nuclear glycogen sediment is observed in various disease including sepsis, tuberculosis, cirrhosis, and diabetes mellitus. Mechanism of this glycogen deposit is not specified and has been found in 60%–75% of patients with diabetes mellitus (29). Another problem due to diabetes mellitus is cirrhosis. The prevalence of cirrhosis increases with diabetes and obesity. These two factors increase the risk of steatohepatitis which can prosper to cirrhosis. Obesity lonely can lead to cirrhosis without the presence of diabetes (30). According to reports, accumulation of fat in the liver is seen in 40–70% of patients with type 2 diabetes without paying attention to blood glucose control. Inversely, there isn't any correlation between type 1 diabetes and fat accumulation in the case of blood glucose control. CT scan and ultrasound are known as sensitive tests and liver biopsy is known as the best method in order to detect the accumulation of fat in the liver (31). In addition to the injurious effects of liver, diabetes also leads to increased liver enzymes. According to some studies on rats, the administration of metformin, 1α,25(OH)$_2$D3, or both of them in rats with diabetes improve liver enzymes.

This improvement is related to the control of a series of factors in the body by these two medications including glucose, lipid, Ca^{2+} with a significant reduction in NF-κB, p65 and caspase 3 and increased PPAR-α, and PCNA expression. Therefore, results achieved from histological studies prove not only beneficial and protective effects of 1α,25(OH)$_2$D3 and metformin on hepatocytes in patients with diabetes but also more powerful effects of 1α,25(OH)2D3 compared with metformin. Other important protective effects of metformin and 1α,25(OH)$_2$D3 on hepatocytes in patients with diabetes are preventing oxidative stress caused by apoptosis and motivating a rapid increase in numbers of liver cells (32). In addition, metformin can stop the dispensation of PARP induced by menadione. According to some studies on rats, menadione can cause apoptosis due to activation of caspases-3, 6, and 9. In these studies, they also showed that metformin is able to prevent the activity of caspase-9, -6, and -3 by increasing the cleavage of these caspases (33). Mechanism of metformin in decreasing of apoptosis isn't associated with insulin-resistance but it is related to the infusion of heme oxygenase-1 (HO-1) and bcl-xl and making c-Jun N-terminal kinase (JNK) activation stop. Metformin will be able to decrease phosphorylation of an important enzyme that is reactive to stress motivation (c-Jun N-terminal kinase) induced by oxidative stress. In this mechanism, metformin acts on isoforms of JNK p54 more powerful than isoforms of p46 (33). HO-1 is a factor that protects cells against oxidative stress. In a study on rats, scientists motivated the expression of HO-1 by menadione and then investigated the effect of metformin. They demonstrated that metformin can increase the expression of HO-1, though it isn't able to motivate HO-1 expression lonely (33). Bcl-xl is another protective factor of cells against apoptosis. Expression of this factor is associated with HO-1 motivation.

Conclusion

According to investigations, metformin will be able to increase the expression of bcl-xl factor; remarkably it can stimulate the expression of bcl-xl in hepatocytes lonely (34).

Authors' contribution

SD and AH contributed equally to search the literature and wrote the manuscript. Both authors signed the final paper.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

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