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Metformin protects renal tubular cells; mechanisms and new concepts

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ABSTRACT

Context: The prevalence of diabetes markedly increased in recent decades. It is well accepted that the risk of morbidity and fatality increases in patients with type 2 diabetes (T2DM).
Evidence Acquisition: An electronic search was performed to detect suitable studies, with keywords of metformin, prediabetes, diabetes Mellitus, Gentamicin and lactic acidosis.
Results: Metformin (biguanide) is widely used as the first pharmacological option in pre-diabetic subjects and patients with T2DM. Low-cost, long-term effect, low risk of hypoglycemia, and ease in utilization are considered as significant benefits of metformin compared with other therapies. Numerous studies have explored that medicinal intervention particularly metformin administration not only can decrease high blood glucose in patients with T2DM but also can avoid or postpone the beginning of clinical T2DM in pre-diabetic cases. Protective effect of metformin on renal cells by different mechanisms is described here. Gentamicin is an important factor that affects kidney function and structure. Nephrotoxicity is one of the serious side effects of gentamicin (an aminoglycoside antibiotic). Numerous investigation showed the protective effect of metformin against the gentamicin nephrotoxicity. On the other hand, lactic acidosis is known as an uncommon but serious side effect of metformin that should be mentioned. Signs of lactic acidosis are defined by plasma lactate levels higher than 5 mmol/L and pH smaller than 7.4.
Conclusions: Different small series and large experimental investigations have discovered the association between metformin and lactic acidosis summarized here.

Review

Implication for health policy/practice/research/medical education:
Although metformin is known as the most confident hypoglycemic medicine in patients with chronic kidney disease according to the benefits linked with reduction of metabolic disorder and protection against cardiovascular disease, present recommendations explain that it should be administrated with carefulness in glomerular filtration rate of lower than 60 mL/min. Other studies suggested an important clinical benefit for diabetes mellitus outcomes particularly myocardial infarction from metformin compared with other oral agents like sulfonylurea agents. Finally, elderly people may be at higher risk for lactic acidosis.

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1. Context

The prevalence of diabetes markedly increased in recent decades. It is well accepted that the risk of morbidity and fatality increases in patients with type 2 diabetes (T2DM) (1). The levels of glycosylated hemoglobin (HbA1c) or glucose in plasma are considered ways to diagnose diabetes. Metformin (biguanide) is usually used as the first pharmacological option in pre-diabetic subjects and patients with T2DM mellitus in the Europe, United States, and Australia. Low cost, long-term effect, low risk of hypoglycemia, and ease of utilization are considered significant benefits of metformin compared with other therapies (2). Lower overall mortality and minor risk of serious infection/acidosis are other important benefits of metformin in contrast with medication with insulin and too alternative oral hypoglycemic agents. This drug can decrease high blood glucose in patients with T2DM and prevent the alteration of prediabetes to clinical T2DM by different pharmacologic mechanisms (3). Metformin decreases primarily the production of hepatic glucose by increasing the function of insulin in the hepatocytes (3,4). Amelioration in insulin acceptation in skeletal muscle as a major therapeutic action of metformin helps to the removal of non-oxidative glucose. Enhanced anaerobic metabolism in the gastrointestinal wall is similarly known as a significant mechanism of metformin on removing high blood glucose (3). Moreover, metformin can increase the glucagon-like peptide-1 (GLP-1) levels in blood by raising the excretion of GLP-1 and/or by reducing the activation of dipeptidyl peptidase-4 (DPP4), the enzyme accountable for making inactive of GLP-1 (3). Furthermore, Metformin may also increase the expression of GLP-1 receptors on the surface of β-cells in the pancreas (5). Metformin remarkably reduces the risk of both myocardial infarction (MI) and mortality due to diabetes mellitus. In addition, most drugs used to treat diabetes cause weight gain but it is not seen in the use of metformin (3).

According to recent trials, non-diabetic increased levels of blood glucose including increases in fasting or postprandial plasma glucose are strongly considered as a high risk of expanding T2DM (6). Disruption of glucose metabolism, which is a primary cause of T2DM, occurs long before the diagnosis of diabetes. Insulin resistance, in which disruption of glucose metabolism happens, is considered as the pathogenesis of prediabetes. In the early stages, insulin resistance is countered by high insulin secretion. However, advanced damage of β-cell mass and function restricts the ability of the pancreas to control the presence of glucose in the blood by rising insulin secretion (7). The first obvious sign of hyperglycemia due to prediabetes is impairment of postprandial glucose control but normal and/ or impaired fasting plasma glucose.

Numerous studies have explored that medicinal intervention particularly metformin usage by pre-diabetic cases can avoid or postpone the beginning of clinical T2DM (3). Planned cell death showed by cell shrinkage (apoptosis) and high production of free radicals such as reactive oxygen species (ROS) are considered as injurious factors of kidney disease in patients with diabetes mellitus. In diabetic patients, hyperglycemia can break nucleic acids into small parts and increase apoptosis. The production of these injurious factors by mitochondria in tubular cells can cause apoptosis in epithelial cells of different parts of the body including proximal tubules and podocytes (8,9). Protective effect of metformin on renal cells is exhibited by different mechanisms. One mechanism is reducing albumin excretion by inhibiting renin-angiotensin–aldosterone system in diabetic patients. Another mechanism of metformin is stimulating of adenosine monophosphate kinase (AMPK) in different tissues. Finally, many studies demonstrated that metformin is able to inhibit the oxidative stress by decreasing free radicals' production for example ROS and reactive nitrogen species (RNS) (10).

2. Evidence Acquisition

For this review, we used a variety of sources including PubMed, Embase, Scopus and directory of open access journals (DOAJ). The search was conducted by using combinations of the following key words and or their equivalents; metformin, type 2 diabetes mellitus, hyperglycemia, prediabetes, diabetes, gentamicin, lactic acidosis, type 2 diabetes, insulin, hepatocytes, glucagon-like peptide-1, Insulin resistance, apoptosis, free radicals, reactive oxygen species, kidney disease, mitochondria, acute kidney injury, tubular cells, epithelial cells, proximal tubules, podocytes, renin-angiotensin–aldosterone system, adenosine monophosphate kinase (AMPK), oxidative stress, free radicals, Renal toxicity, reactive nitrogen species, nephrotoxicity, oxidative phosphorylation, acute renal failure, antioxidant systems, glomerular filtration rate, renal plasma flow, and renal blood flow.

3. Metformin and nephropathy induced by gentamicin

Nephrotoxicity is one of the serious adverse effects of gentamicin antibiotic (an aminoglycoside) administered in the treatment of gram-negative bacterial infection. Renal toxicity induced by gentamicin is based on both tubular and glomerular effects (11,12). Some trials demonstrated that gentamicin can decrease the levels of adenosine triphosphate (ATP) in renal tubular cells by inhibiting oxidative phosphorylation. In fact, these studies showed that free radicals could have a key role in the progress of

the renal injuries. Therefore, gentamicin can cause acute kidney injury (AKI) by increasing ROS formation in renal cells and subsequently apoptosis of proximal tubular cells (11,12). AKI is verified by increased creatinine release and exclusion of *N*-acetyl-β-D-glucosaminidase. Previously, Morales et al investigated the protective effect of metformin treatment in rats with gentamicin toxicity. They reported that the biochemical mechanism of metformin involved in the renal protection was related to a low activity of *N*-acetyl-β-D-glucosaminidase, reduce in lipid peroxidation, and increase of antioxidant systems. Moreover, gentamicin-induced histological damages after six days were also prevented by metformin. Furthermore, administration of metformin in treated animals by gentamicin also increased glomerular filtration rate (GFR), renal plasma flow (RPF), and renal blood flow (RBF) (13).

4. Metformin and lactic acidosis

Lactic acidosis (LA) is known as an uncommon but serious side effect of metformin. Plasma lactate levels higher than 5 mM and pH lower than 7.4 are defined as signs of LA, and it is associated with a high risk of death (14,15). Two significant types of LA are anaerobic and aerobic versions. Increased production of lactate for regeneration of ATP in the absence of oxygen is considered as the main cause of anaerobic LA. This type of LA is usually related to the impairment in the function of specified bodily systems particularly neurologic and cardiovascular. Stupor, coma, and seizures are consequences of neurologic system dysfunction and the results of cardiovascular system dysfunction are hypotension and ventricular fibrillation. Aerobic version of LA can be caused by the underutilization of lactate, and is associated with liver disease, gluconeogenesis prevention, vitamin B1 deficiency, diabetes, cancer, and metformin intoxication. Different small and large experimental studies have discovered the association between metformin and LA summarized here (16).

Recent studies suggested a high risk of either LA or increased plasma lactate levels in patients received metformin. A cohort study from Denmark investigated the effect of metformin in contrast with sulphonylureas on 168 443 patients with T2DM. This study demonstrated that metformin was related to a 50% elevated risk of acute dialysis compared with sulphonylureas (17).

In some series, normal or elevated levels of metformin measured in patients hospitalized with lactic acidosis were not associated with the degree of acidosis (18,19). Furthermore, some believed that diabetic state is a risk factor for LA instead metformin administration. In another series, high levels of metformin were correlated with decreased death. In these studies (19,20) the greater number of cases with LA induced by metformin had normal kidney function. This finding demonstrated that the prescribing restriction of metformin based on renal factors is not certainly considered as a preventative agent for LA. One study evaluated the prevalence of metformin-induced LA (MILA) in 204 patients intoxicated by metformin. For this purpose, they divided patients into two groups. Around 55 patients were in group 1 received metformin alone and 149 were in group 2 received multi-drug including metformin. According to results, acidosis was observed in sixteen cases in group 1 and 52 patients in group 2. Only four patients belonged to group 1 required dialysis, and two patients (1%) belonged to group 2 died (21).

Many investigators in their observational studies did not estimate consistent correlation between metformin and LA. Patients receiving metformin in spite of renal failure in these observational analyses may be in good health, and this can clarify the low-risk of LA. However, it is difficult to conclude from these observational studies about relation of metformin and LA in patients with renal failure and large-scale studies are needed (18-20). In a minor study, 35 patients with T2DM on automated dialysis received 0.5–1.0 g metformin every day. At this study, they investigated the factors measured during treatment period including the levels of HbA1c, blood sugar, plasma lactic acid, plasma metformin and lactate. Investigators did not observe an association between plasma metformin and lactate because a plasma lactate level above 5 mM in none of the patients recorded. These findings also showed that metformin is efficient and harmless even in serious renal failure. Investigators suggested that dialysis may be a protective factor against LA in these patients because it can cause a rapid removal of lactate. Thus it may be not accompanied by mortality for patients under hemodialysis, however, it requires further investigation (22).

However, it is proven that the benefits of metformin on cardiovascular disease and mortality, in contrast with insulin, persevered in subjects were classified by renal function. Those with a GFR less than 30 ml/min and in those with a GFR ≥60 mL/min may still benefit from metformin. In many studies is recommended that metformin in GFR ≤30 mL/min should be stopped, in GFR ≥60 mL/min, there is not significantly hazard and threat for prescribing metformin, and 30≤GFR≤60 mL/min is controversial and has been intensely debated with conflicting evidence. Ameliorated glycemic control is a significant reason for the metformin use in patients with renal dysfunction. Stop of metformin is often related to an increase in the levels of HbA1c (23). Metformin remains a beneficial treatment even in patients treated with insulin and if metformin is stopped in these patients, glycemic control decreases

(23). Suitable glycaemia control in insulin-treated patients has been shown to prevent end-stage kidney disease in diabetic patients with renal failure. Plasma metformin dose <10 mg/L would be to maintain in diabetic patients with stable renal function. The suggested dose for metformin in dialysis patients is dependent on the level of renal failure (23). Another important subject is whether to stop metformin administration in patients at high risk of AKI. An immediate reduction in GFR to lower than 5 mL/min in patients would quickly increase plasma metformin levels accessing 20 mg/L, and potentially the patient exposes to risk of LA. Since metformin-related LA in patients with normal renal function is so rare, metformin administration does not need to be stopped (23,24). In patients with renal failure (GFR <60 mL/min), early detection of renal failure after a possibly nephrotoxic abuse is crucial. The use of new biomarkers in urine sample (almost 12 hours after abuse) may supply a quick identification for AKI (25). One logical suggestion for metformin dose is first monitoring of plasma lactate and creatinine at 24 and 48 hours after procedure, and thus stop of metformin if creatinine is increasing (>10%) or lactate exceeds 3.5 mmol. This function would simplify the preservation of glycemic control. It seems that factors incresing the risk of LA such as errors in the estimation of renal function or indefinite aggravating factors that may decrease metformin exclusion, should be envisaged (23).

In T2DM patients, regardless of metformin therapy, the incidence of LA was between 9.7 and 16.9 among 100 000 patients every year (16). Since the mentioned incidence of metformin-associated LA (MALA) changes from 0–9.7 (average 6.3) (16). Therefore LA can be almost reported in all patients with diabetes, regardless of metformin treatment. In patients that used metformin, plasma levels of lactate are twofold of the level of healthy people (16). Therefore, the risk of MALA should be compared with this basic risk. Reduction of blood flow in patients with heart disorder and decreased hepatic metabolism of lactate in patients with hepatic failure are main causes of LA particularly in diabetic patients. Recently, an investigation demonstrated no increase in lactate levels in patients treated by metformin (16). Analysis of 347 controlled studies enveloping 70 490 patients received metformin determined no correlation between metformin and LA and no important change in plasma levels of lactate (26). Two investigations demonstrated that the prevalence of LA associated with sulfonylureas is more than that of MALA (27,28). Notice to contraindications, mainly in chronic kidney disease (CKD) cases, may be the cause of this low incidence.

According to studies, metformin level is not related to plasma lactate in MALA. On the other hand, only a few cases of MALA could be attributed to metformin. Therefore, scientists suggested that the term MALA should be divided into metformin-unrelated LA (MULA) and MILA (16,29). According to the recent data, the mortality rate from MALA is parallel with the risk of dying in traffic accident or anaphylaxis shock at time of penicillin therapy.

Conclusions

Although metformin is known as the most confident hypoglycemic medicine in patients with CKD according to the benefits linked with reduction of metabolic disorder and protection against cardiovascular disease, present recommendations explain that it should be administrated with carefulness in GFR of lower than 60 mL/min (30). Other studies suggested an important clinical benefit for diabetes mellitus outcomes particularly MI from metformin compared with other oral agents like sulfonylurea agents. Finally, elderly people may be at higher risk for LA (23).

Authors' contribution

MB and SB participated in conceptualization and preparation of the manuscript. MK, LM and MB prepared the literature review. MD and ND revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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.

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