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Renoprotective impacts of metformin with insulin in type 1 diabetes; role of its antioxidant efficacy

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ARTICLE INFO

Article type:
Commentary

Article history:
Received: 10 April 2018
Accepted: 18 May 2018
Published online: 3 June 2018

Keywords:
Diabetic kidney disease, Type 2 diabetes, Insulin, Diabetic nephropathy, Type 1 diabetes, Atherosclerosis

Implication for health policy/practice/research/medical education:

Chronic complications of diabetes mellitus are directly related to high blood glucose levels. Increasing blood glucose results in non-enzymatic glucose binding to proteins inside and outside the cell. Several biochemical and molecular factors such as increased blood glucose, oxidative stress, increased concentrations of ultimate glycosylated products, inflammation can affect nephropathy. Metformin is another treatment for diabetes which mainly used as the first treatment in patients with type 2 diabetes (T2D). Insulin is a peptide hormone produced by pancreatic beta cells and plays a major role in regulating carbohydrate and fat metabolism in the body.

Please cite this paper as: Babaenezhad E, Hasanvand A. Renoprotective impacts of metformin with insulin in type 1 diabetes; role of its antioxidant efficacy. J Nephrologist. 2018;7(3):217-219. DOI: 10.15171/jnp.2018.45.

Diabetes is the most common endocrine disorder in the world. Type 1 diabetes (T1D) or insulin dependent diabetes mellitus often occurs in children and young people. In this type of diabetes, the pancreatic beta cells that are responsible for making the insulin hormone in the body completely disappear or become inactive (1). Chronic complications of diabetes mellitus are directly related to high blood glucose levels. Increasing blood glucose results in non-enzymatic glucose binding to proteins inside and outside the cell (2). People with long-term diabetes mellitus have kidney failure, eye damage, heart failure and vascular and central nervous system failures (3). Irreversible complications of diabetes are the result of end products of non-enzymatic glycation, which, due to changes in the composition of biomolecules, such as albumin, collagen and hemoglobin, provides the basis for some complications such as atherosclerosis, nephropathy and retinopathy (4). Diabetic kidney complications are known as diabetic nephropathy, leading to a progressive decline in renal function, and ultimately a complete inability of the organ (5). Diabetic nephropathy is known to cause over 14% of mortality due to diabetes and 40% of kidney

failure (6). Diabetes leads to nephropathy by causing lesions in both the renal tubular and glomerular sections (7). Diabetic nephropathy (diabetic kidney disease) in the glomerular kidney leads to sclerosis, dissemination of mesenchymal matrix, papillary necrosis and fibrinous cap and thickening of the basement membrane (8). Some of symptoms have been defined for diabetic nephropathy include elevated albumin excretion in urine, proteinuria, polyuria, hypertension, edema, and progressive reduction of glomerular filtration (9). Several biochemical and molecular factors such as increased blood glucose, oxidative stress, increased concentrations of ultimate glycosylated products, inflammation can affect nephropathy. Studies have shown that oxidative stress is an important factor in the development of pathological complications associated with diabetes. There is also a direct correlation between injuries to the kidney and increased blood glucose levels. Chronic hyperglycemia is the most important factor in oxidative stress and is one of the most important sources of ROS (reactive oxygen species) production. As a result of increased ROS production, lipid peroxidation increases during diabetes, and this causes tissue damage

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in the kidney. Many strategies are used in order to prevention of diabetes-related kidney complications. For example, conventional treatments for improving diabetic nephropathy include control of blood sugar and blood pressure, and new methods emphasize the prevention of injuries. New treatments for controlling diabetic nephropathy include reducing the production of ROS and AGEs (Advanced glycosylation end products) (10). In order to control the level of glucose, these patients should be prescribed insulin. Insulin is a peptide hormone produced by pancreatic beta cells and plays a major role in regulating carbohydrate and fat metabolism in the body. Insulin uptakes blood glucose by liver, musculoskeletal, and adipose tissue. Insulin is considered as the main treatment for all types of diabetes mellitus. Due to the increasing prevalence of diabetes in the world, the use of insulin as the best method for treating diabetes is also increasing (11). Metformin (1, 1-Dimethylbiguanide) is another treatment for diabetes which mainly used as the first treatment in patients with type 2 diabetes (T2D). The main mechanism of action of metformin is the inhibition of gluconeogenesis and liver glycogenolysis and increased sensitivity of peripheral tissues to insulin. Moreover, weight loss effects and lipid lowering properties and consequently, a reduction in the risk of cardiovascular disease are other beneficial properties of metformin (12).

The recent published article by Driver et al showed beneficial effect of administration of metformin with insulin on amelioration of diabetic kidney disease. They reported that treatment with metformin and insulin affect blood glucose level. Moreover, renal damage markers such as urea and creatinine reduced after treatment. Antioxidant effects of combined treatment were also established by a significant increase in glutathione (GSH) and superoxide dismutase (SOD) activity and significant decreased level of malondialdehyde (MDA) after treatment. Histopathological assessments were also confirmed the decreased renal injuries caused by diabetes in addition to biochemical assays (13). Louro et al, similar to above study indicated that insulin and metformin play a beneficial role in prevention of renal injury caused by type 2 diabetes. The results of their study showed that combined treatment improved insulin resistance and reduced blood glucose level. Moreover, they evaluated anti-inflammatory effects of treatment which finally approved this property (14).

Conclusions

Taking together, insulin and metformin are recognized as potent anti-diabetic agents which combination of them

could ameliorate diabetes. Therefore, further studies are required for determination of signaling pathways involved in pathogenesis of this disease such as AMPK.

Acknowledgments

The authors wish to thank that the staff of Lorestan University of Medical Sciences.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

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

Funding/Support

None.

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