The role of pharmacogenomics in response to metformin therapy in diabetes mellitus: Review Article

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Abstract

Background: Diabetes mellitus is a very well known metabolic disorder in daily clinical practice affecting males and females equally and no age is immune against its occurrence. The metformin therapy is the first line therapy and the response to it shows significant individual variation. The role of pharmacogenomics in predicting response to treatment is recently widely accepted by medical professionals.

Aim of the study: The current review was aiming at identifying the main genes enrolled in response to metformin treatment in type 2 diabetes mellitus.

Materials and methods: The current review was done in College of Medicine/ University of Al-Qadisiyah and involved the search in the Google search engine about the following key words: pharmacogenomics, type 2 diabetes mellitus, metformin. The studies that were published with this respect during the last 20 years were enrolled. Any article dealing with use of metformin for other indications other than diabetes mellitus of type 2.

Results: The metformin pharmacogenetics field has coalesced to form the MetGen Consortium. In a meta-analysis of 10,557 participants with a harmonised measure of metformin response, a genome-wide statistically significant association was observed at the SNP rs8192675, in an intron of the GLUT2 glucose transporter, encoded by *SLC2A2* and expressed in hepatocytes. The only member of biguanide class remains in clinical practice is metformin. However, it is regarded as the first line pharmacological agent to be used in control of hyperglycemia in type 1 DM.

Conclusion: The response to metformin showed significant variation in response based on HbA1c% results in diabetic patients treated with it as a first line anti-diabetic medication and tailoring dose with respect to gene polymorphism may provide better therapeutic results.

Key words: pharmacogenomics, metformin, diabetes mellitus

Introduction

The metabolic derangements in association with raised plasma glucose on chronic bases is due to a variety of pathologic processes but the shared common characteristic of hyperglycemia is often referred to diabetes mellitus (1). The disease process can affect people at any age and of either gender (2). Previously clinicians used to name the disease happening in children as insulin dependent diabetes mellitus because it often reflects absolute insulin deficiency and profound beta cells dysfunction (3). The disease occurring in adults was named as adult onset or insulin independent diabetes mellitus because the disease is mainly characterized at least early in its course by hyperinsulinemia and resistance to insulin action (4). However, these terms were later on changed into type 1 and type 2 diabetes mellitus respectively because several cases of insulin resistance have been documented in children and on the other hand the diagnosis of profound insulin deficiency in patients older than 40 has been seen often in daily clinical practice in addition to the fact that a number of patients with type

2 diabetes may develop late in the disease profound insulin deficiency and became insulin dependent (5).

In addition to type 1 and type 2 diabetes, other forms are also present. Gestational diabetes often affects women during pregnancy and it has been shown the probability of those women to develop type 2 diabetes in the future is higher than the general population (6). Endocrine abnormalities such as acromegaly, Cushing syndrome and polycystic ovary syndrome may be associated with hyperglycemia (7-9). Monogenetic forms of diabetes mellitus have been also described in the literatures in which a single gene defect is usually inherited based on well known basis of heredity (10).

Treatment of diabetes mellitus usually involve weight reduction, exercise and dietary measures in addition to the use of a number of pharmacological agents such as sulfonylureas and meglitinides and metformin (11). Metformin is cheap, effective and safe drug and usually referred to as the first line therapy when no contraindication exists (12).

More than 48 million prescriptions wer e filled for the medication in the USAin 2010 a lone, making it one of the most widely used tre atments for type 2 diabetes in the world. There is optimism that its use will extend to further i ndications, such as the treatment and/or preven tion of cancer. It is also used for the prevention of diabetes and the treatment of polycystic ov arian syndrome (13-15).

Overall, metformin is very effective and one of the few oral treatments for type 2 diabetes that encourage weight loss rather than weight gain (16, 17). In fact, metformin therapy is highly tolerated, with just 5% of users discontinuing their medicine due to severe intolerance and only 30% of patients reporting minor gastrointestinal side effects (18, 19). In addition, because it does not lower resting energy expenditure, this weight loss is highly advantageous and comparable to exercise-induced weight loss (20).

Some of the individual variations that cause the range in metformin response are probably genetic in origin. For instance, epidemiological studies indicate that there are ethnic differences in metformin response (21), and it is likely that some of these differences have genetic roots. Researchers may now evaluate the degree of genetic relatedness with sufficient precision and estimate its contribution to the variance in the trait of interest thanks to the availability of dense genome-wide genotyping in cohorts where metformin response has been quantified more recently (22).

The current review was aiming at identifying the main genes enrolled in response to metformin treatment in type 2 diabetes mellitus.

Materials and methods

The current review was done in College of Medicine/ University of Al-Qadisiyah and involved the search in the Google search engine about the following key words: pharmacogenomics, type 2 diabetes mellitus, metformin. The studies that were published with this respect during the last 20 years were enrolled. Any article dealing with use of metformin for other indications other than diabetes mellitus of type 2.

Results and discussion

The metformin pharmacogenetics field has coalesced to form the MetGen Consortium (23). In a meta-analysis of 10,557 participants with a harmonised measure of metformin response, a genome-wide statistically significant association was observed at the SNP rs8192675, in an intron of the GLUT2 glucose transporter, encoded by *SLC2A2* and expressed in hepatocytes (24, 25).

The only member of biguanide class remains in clinical practice is metformin. However, it is regarded as the first line pharmacological agent to be used in control of hyperglycemia in type 1 DM (13, 14). The mechanism by which the drug regulated plasma glucose level has been extensively

studies; however, it is incompletely understood till the time being (15).

But some effects of metformin are undeniable (such as the suppression of increased basal endogenous glucose production in T2D patients through a 25–40% reduction in the rate of hepatic gluconeogenesis, which is thought to be brought on by activation of AMPK and direct inhibitory effects on mitochondrial function) (26). Metformin can increase skeletal muscle's insulin sensitivity and insulin-stimulated glucose uptake. Through active tubular secretion in the kidney, metformin is eliminated unaltered from the body without being digested (27). Metformin's efficacy to reduce blood sugar was proven to have significant interindividual variation (28). Furthermore, compared to most other oral antidiabetic medications, metformin therapy is linked to higher gastrointestinal symptoms (range 2–63% in various clinical trials). In about 4% of cases, this may lead to the early end of therapy (29, 30). It is reasonable to expect that the polymorphisms of genes involved in the different metabolic pathways of metformin would lead to a variety of reactions as well as the emergence of adverse effects in patients receiving medication therapy. The development of more individualized and accurate T2D treatments may be possible with a better knowledge of the action mechanisms of metformin.

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