Journal of Pharmaceutical Research International

33(41B): 187-192, 2021; Article no.JPRI.71890
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

The Impact of Metformin in Pediatric Type-1 Diabetes Mellitus in Addition to Insulin Therapy; Literature Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i41B32357
Editor(s):
(1) Dr. Begum Rokeya, Bangladesh University of Health Sciences, Bangladesh.
Reviewers:
(1) Prashant Yadav, UP University of Medical Sciences, India.
(2) Bhanu Rekha Bokam, Dr. NTR University of Health Sciences (NTRUHS), India.
(3) Mirela Grigoras, Victor Babeş University of Medicine and Pharmacy, Romania.
(4) Supriya Prashant Satpute, SAIMS, India.
Complete Peer review History: https://www.sdiarticle4.com/review-history/71890

Review Article

Received 12 June 2021
Accepted 17 August 2021
Published 23 August 2021

ABSTRACT

Background: Type 1 diabetes mellitus leads to significant cardiovascular risk through various mechanisms. Intensified insulin therapy is commonly required to achieve adequate glycemic control and reduce HbA1c. However, when insulin dose increases, it might increase insulin resistance and body weight, which directly affecting the cardiovascular profile.
Objective: We aim in this literature review to address the role of adding metformin to insulin therapy to limit the cardiovascular effect, insulin resistance and improve glycemic control in pediatric age.
Methods: We searched in the PubMed database for relevant articles using the following Mesh words: Metformin - Type 1 diabetes mellitus, pediatrics - Cardiovascular risk.
Conclusion: Metformin was found to has promising cardiovascular protection when adding to insulin therapy. However, the impact of metformin in type 1 diabetes mellitus glycemic control is controversial, and further multi-systemic randomized clinical trials are recommended to address this issue.

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Keywords: Metformin; type 1 diabetes mellitus; pediatrics; cardiovascular risk; HbA1c; glycemic control.

1. INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a systemic autoimmune disease manifested by pancreatic beta-cells immune-mediated destruction resulting in severely reduced or completely absent insulin secretion [1-2]. In the absence of appropriate insulin secretion, glucagon levels might be elevated in the fasting and postprandial state [1], resulting in hypoglycemia [1-2]. T1DM is the most common chronic childhood metabolic disease that affects all body organs and is caused by a combination of genetic susceptibility and environmental determinants [2-3]. The prevalence of T1DM has increased across the last decade [2]. Most T1DM patients have suboptimal glycemic control [2], and subsequently, intensive glycemic control might be warranted to reduce the risk of late diabetic complications; nevertheless, intensified insulin treatment also increases the risk of hypoglycemia and weight gain [1]. The latest might negatively alter the cardiovascular risk profile and may reduce adherence to treatment [1]. Therefore, the use of non-insulin additional pharmacotherapy has been recently an area of importance [2].

Moreover, targeting glycemic control in T1DM patients might increase the risk of hypoglycemia, especially when HbA1c approached target levels [4-5]. Furthermore, while insulin requirements might be increased to achieve optimal glycemic control, this might increase insulin resistance by weight gain, consequently escalating insulin dose requirements, elevating blood pressure and LDL-cholesterol levels [4-5]. Severe hypoglycemia has been reported in 13.9 and 12.5%, respectively, with a reported hypoglycemia-induced seizure or loss of consciousness in 11.8% among patients with HbA1c levels below 6.5% and 7% [5]. Importantly, glycemic variability itself is considered a hypoglycemia predictor, leading to poor glycemic control, poor patient satisfaction, diabetes burden, and poor compliance to treatment [5].

Based on the aforementioned above, the concept of adjunct non-insulin pharmacotherapy has been increasingly emerged to overcome these challenges and based on the nation that: 1) the addition of oral preparation to insulin might improve glycemic control; 2) the adjunct therapeutic agents might independently reduce diabetic complications [4]. Hence, the principle of adjunct therapy is to reduce insulin requirement, lower HbA1c without the risk of hypoglycemia, avoid weight gain, and directly reduce the risk of cardiovascular complications in order to improve life expectancy [4].

1.1 Diagnosis and Types of Diabetes Mellitus in Adulthood

The diagnostic criteria for diabetes mellitus in adulthood are similar to adult; mentioned in Table 1 [6]. However, the laboratory findings should be repeated if unequivocal hyperglycemia is absent [6]. The American Diabetes Association (ADA) recommended the use of blood glucose levels rather than HbA1c in T1DM diagnosis [6].

Overall, diabetes is classified into [6]:

- T1DM
- T2DM
- Gestational diabetes mellitus
- Specific types of diabetes mellitus secondary to other causes

In this article, T1DM management will be discussed, and other classes are beyond the scope of this literature review.

The target glycemic control in adulthood are summarized into the following [6]:

- HbA1c <7.5%
- Pre-meal blood glucose level 90 to 130 mg/dL
- Bedtime or overnight blood glucose level 90 to 150mg/dL

The goal of glycemic control must be individualized based on the risk of hypoglycemia, and higher targets might be needed if frequent or severe hypoglycemia were reported [6].

2. DISCUSSION

Metformin is an antihyperglycemic agent that belongs to biguanide that reduces hepatic glucose output from the liver and enhances insulin sensitivity [7], as concentrated in the hepatic circulation [8]. Metformin works by inhibiting the complex-1 effect of the mitochondrial respiratory chain, resulted in

Table 1. Diagnostic criteria of diabetes mellitus

- HbA1c of at least 6.5% approved by the National Glycohemoglobin Standardization Program (NGSP) laboratory standardized to the Diabetes Control and Complication Trial (DCCT) assay
- Two-hour plasma glucose of at least 200mg/dL following an oral glucose tolerance test using a glucose load containing 75 g
- An 8 hours fasting plasma glucose level of at least 126mg/dL
- Presence of typical symptoms of hyperglycemia or hyperglycemic crisis with a random plasma glucose of at least 200mg/dL

regulating AMP-activated protein kinase (AMPK), particularly in muscle and liver [7-8]. Subsequently, this increased insulin-stimulated glucose uptake in skeletal muscles and adipocytes and reduced glucose output from the liver [7], leading to indirectly lowers circulatory insulin and glucose levels [8].

Additionally, metformin activates AMPK in the endothelium and smooth muscle; this likely explains the dependent and independent endothelium vascular response following metformin administration in adults with T1DM and polycystic ovarian syndrome [7]. Also, it may explain the beneficial outcome of metformin on cardiovascular risk independently of its glucose lowering effect [7]. Besides, in T1DM, Gao-Fei ran et al. have found that metformin improves insulin resistance and inflammatory response through P53/RAP2A pathway [9]. Consequently, the P53/RAP pathway regulation was associated with improving the efficacy of metformin in the treatment of insulin-resistant [9].

2.1 The Effect of Metformin in Type-1 Diabetes Mellitus

Recent interest has emerged in using metformin in T1DM to improve glycemic control and control weight gain in overweight teens [8]. Metformin use in T1DM patients was associated with decreased insulin dose, improve BMI and waist circumference in female participants [8]. While insulin is the mainstay therapy for T1DM patients, many other pharmacotherapies have been used or under investigation [10]. In a retrospective study conducted by Selvihan Beysel et al., the addition of metformin to insulin therapy in T1DM patients was associated with lower glucose concentrations, metabolic syndrome prevalence, and insulin requirement compared to insulin therapy alone after one year of treatment [11]. In addition, weight control was better in the metformin with insulin group than the insulin therapy alone [11].

Moreover, Melanie et al. have concluded in a double-blind, placebo-controlled clinical trial that adding metformin to insulin therapy in obese or overweight with T1DM improves whole-body and specifically muscle insulin resistance during a 13 weeks duration [12]. Nevertheless, the target hepatic insulin resistance needs alternative approaches in T1DM, obese or overweight youth [12]. Importantly, insulin resistance improvement secondary to metformin therapy was strongly linked to improved cardiovascular disease risk in adults and youth with T1DM [12]. Furthermore, Most US and UK guidelines recommended adding metformin to insulin therapy in overweight or obese adults with T1DM [13]. Similarly, these guidelines suggested that metformin not only improves insulin resistance but also provides potential or transit benefits on body weight and HbA1c [13].

On the other hand, metformin did not improve diabetic control among T1DM adults in a placebo-controlled randomized clinical trial and resulted in unfavorable gastrointestinal side effects [14]. However, metformin and insulin were associated with maintaining weight control and insulin requirement [14]. Likewise, James J et al. was concluded that adding metformin to insulin therapy does not lower HbA1c in poorly controlled T1DM [10]. Nonetheless, adding metformin led to decrease insulin requirement, body weight, and LDL-cholesterol [10].

2.2 The Effect of Metformin on Cardiovascular Risk

Although hyperglycemia is the most common finding of T1DM, a consensus has demonstrated that patients with T1DM are also affected by intense insulin resistance [15]. In addition, insulin resistance in T1DM is more significant than expected compared to metabolic syndrome-related factors, such as obesity, hypertension, and dyslipidemia [15]. Interestingly, in the Coronary Artery Calcification in T1DM (CACT1)

cohort study, adults with T1DM were found to have double insulin resistance compared to adults without T1DM who had various risk factors, including obesity and poor physical activity [15].

In T1DM, metformin improves the quality of life and reduces cardiovascular risk factors through weight loss and improving the lipid profile [16]. Bjornstad et al. found that metformin has promising cardiovascular protection in T1DM by reducing insulin sensitivity, BMI, and fat mass along with improving aortic and carotid vascular health over three months [17]. Moreover, reducing insulin resistance was not limited to obese patients [17]. This was supported by the REMOVAL double-blind, randomized, placebo-controlled trial [18]. The trial concluded that metformin might provide cardiovascular protection in the management of T1DM and possibly beneficial in reducing insulin dose requirements [18].

However, despite the previous promising metformin effect on CVD, the REMOVAL trial does not support the idea that metformin improves glycemic control in overweight/obese T1DM patients [18]. Furthermore, metformin was reported to improve vascular smooth muscle function over 12 months in overweight children with T1DM [19].

2.3 Safety Consideration

Regarding metformin safety profile, the most commonly reported side effect is gastrointestinal events, such as abdominal pain, anorexia, diarrhea, nausea, taste disturbance, and vomiting [14, 20-21]. Rare side effects, such as erythema, lactic acidosis, pruritis, and urticaria, were reported [20]. Kidney function should be assessed before and after starting treatment [20]. Metformin should be used cautiously in patients with renal insufficiency, and a lower maximum daily dose is recommended for people with a glomerular filtration rate (GFR) of 30-59mL/min [20].

The most severe adverse effect is lactic acidosis, which carries a mortality rate of approximately 50% between 1960 and 2000, but it has decreased to approximately 25% [21]. Metformin is contraindicated if GFR below 30mL/min and in acute kidney injury secondary to acute conditions, such as dehydration and severe infection [20]. Rarely, metformin use was associated with decreased vitamin-B12 absorption [20].

3. CONCLUSION

Type 1 diabetes mellitus is a chronic multi-systemic autoimmune disease that carries significant cardiovascular risk. Adequate management is mainly achieved by insulin therapy, but it adversely affects the total body weight and insulin resistance. Metformin has been shown to improve insulin resistance, decrease body weight, and improves lipid profile as well, particularly in overweight or obese patients, although no consensus yet about its efficacy in achieving glycemic control and reduce HbA1c. Further multi-systemic randomized clinical trial would be warranted to establish metformin efficacy on glycemic control and HbA1c.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/71890