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Opinion Article

The Use of Metformin in Non-Diabetic Obesity: An Educational Article and Expert Opinion

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Abstract

The synthesis of biguanides was reported as early as 1879 by Rathke. Metformin (dimethylbiguanide hydrochloride) is a biguanide that was first reported to have anti-hyperglycemic effect in 1922 by Emil Werner and James Bell. The use of Guanidine derivatives, including metformin to treat diabetes was suggested during the 1920s and 1930s, but was disregarded later because of the risk of lactic acidosis which is less likely with metformin than other biguanides such as phenformin.

Thereafter, the use of metformin derived from a guanidine-based anti-malarial medication, proguanil by Eusebio Garcia in experimental studies during the 1940s was associated with blood glucose lowering in animals. During that time, Eusebio Garcia also suggested that metformin (Flumamine) can to be useful in treating influenza.

Jean Sterne reintroduced metformin as an anti-hyperglycemic medication in France in 1957. He suggested using the name "Glucophage" which means glucose eater for marketing purpose. The aim of this paper is to provide and education review and expert opinion regarding the use the metformin in non-diabetic obesity.

Conclusion and expert opinion: The use of metformin in non-diabetic obesity is can be useful and is safe in the absence of renal impairment.

Keywords: metformin; non-diabetic obesity

Introduction

The synthesis of biguanides was reported as early as 1879 by Rathke. Metformin (dimethylbiguanide hydrochloride) is a biguanide that was first reported to have anti-hyperglycemic effect in 1922 by Emil Werner and James Bell [1-3]. The use of Guanidine derivatives, including metformin to treat diabetes was suggested during the 1920s and 1930s, but was disregarded later because of the risk of lactic acidosis which is less likely with metformin than other biguanides such as phenformin [3-6].

Thereafter, the use of metformin derived from a guanidine-based anti-malarial medication, proguanil by Eusebio Garcia in experimental studies during the 1940s was associated with blood glucose lowering in animals. During that time, Eusebio Garcia also suggested that metformin (Flumamine) can to be useful in treating influenza [6].

Summary

Jean Sterne (Figure-1) reintroduced metformin as an anti-hyperglycemic medication in France in 1957. He suggested using the name "Glucophage" which means glucose eater for marketing purpose.

Figure 1: Jean Sterne, a French physician (1909-1997)

As early as 1969, Munro et al reported a double-blind study which included females with refractory obesity who had normal oral glucose tolerance. The study showed that treatment with metformin was associated with important weight-losing effect that continued for about three months [8].

In 1986, a study reported by Rizkalla et al showed that metformin has a blood glucose lowering effect chiefly in diabetes type II, but not in non diabetics (whether obese or not). They thought that this could possibly because metformin has a direct effect on the cell membrane [9].

In 1998, Carlsen and colleagues from France reported a 12-week study which included sixty non-diabetic men who were treated before with coronary artery bypass surgery or angioplasty. The patients were treated with lovastatin 40 mg a day. The patients were randomized to receive metformin up to 2000 mg daily. The study showed that fasting glucose levels and oral glucose tolerance test was not affected by the addition of metformin. Insulin resistance was lowered by 24% ($P = 0.028$) in all patients, while it was lowered by 30% in obese patients ($P = 0.049$). The decrease in body weight by metformin was not correlated with improvement in insulin resistance nor with changes in lipids profile. However, the improvement in insulin resistance was correlated with changes in lipid levels [10].

Also, in 1998, Paolisso et al from Italy reported a placebo-controlled study which included 30 non-diabetic obese patients. 15 patients received metformin and 15 patients received placebo for 15 days. Metformin was associated with more reduction in body weight ($P < 0.01$), body fat ($P < 0.01$), plasma leptin level ($P < 0.05$), and in food intake ($P < 0.01$).

In patients who received metformin, the decrease in food intake was markedly correlated with the reduction in weight ($P < 0.007$) and body fat ($P < 0.001$). The decreases in body fat, the reduction in food intake and in fasting leptin levels were correlated. Therefore, Paolisso et al suggested that metformin can be useful to decrease food intake, weight, and body fat in non-diabetic obese patients [11].

In 1999, Stang and colleagues from Canada that during the period from 1980 to 1995, the incidence rate of lactic acidosis in metformin users was 9 per 100,000 person-years (95% CI 0-21) [12]. In 2014, Willemijn L Eppenga from the Netherland and her research group reported a study which emphasized the higher risk of lactic acidosis in metformin users in patients with renal impairment [13].

In 2008, Alessandra Zulian from Italy and her research group reported a study which showed that metformin can up-regulate adiponectin gene expression in vivo and in vitro, and can increase adiponectin protein secretion from human SAT in vitro [14].

In 2015, Cátia Jesus from Czech Republic and her colleagues reviewed the evidence in 12 papers published during the period from 2006 to 2013, and suggested that metformin can effectively counteract atypical antipsychotic-induced increase in body weight and can contribute a moderate decrease in body weight loss in non-diabetic subjects. Metformin is generally more useful in young adults especially when used early with antipsychotic medications [15].

In 2019, Armen Yerevanian and Alexander Soukas reviewed the literature and emphasized that several cohort reported that metformin can reduce body weight through decreasing hepatic gluconeogenesis, decreasing insulin production, and also reducing appetite by modulating hypothalamic appetite centers and changing gut microbiome [16].

In 2021, Reem Masarwa from Canada and her research group conducted a systematic review of randomized controlled trials which showed the use of metformin in obesity is safe despite the possibly of the occurrence of gastrointestinal side effects, and it can be used in children and adolescents with obesity [17].

Conclusion and expert opinion

The use of metformin in non-diabetic obesity is can be useful and is safe in the absence of renal impairment.

Acknowledgment

The author has the copyright of the figure included in this paper.

Conflict of interest

None.

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