Is Metformin still a Gold Standard Drug in Managing Obese Type 2 Diabetes Mellitus – A Short Study

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ABSTRACT

Introduction: Metformin is most commonly prescribed drug in the management of diabetes. There is a global increase in the obesity prevalence in children, adolescents and it is accompanied by the appearance and there is increased prevalence of insulin resistance, prediabetes and type 2 diabetes mellitus. Metformin acts by inhibiting production of hepatic glucose and increased uptake of glucose in peripheral tissues. In obese patients apart from glycemic control the Metformin have shown additive effects in controlling the lipids and it has been document to also have a Cardio- protective action. Present study aimed to assess the cost-effectiveness of metformin-based therapies in patients with Type 2 Diabetes mellitus with hyperlipidemia in obese individuals.

Material and Methods: The study population consisted of 30 patients enrolled. All had BMIs exceeding 28- 30 kg/m2), fasting plasma glucose concentrations >126mg/dl and <180 mg/dl and hemoglobin A1c concentrations </=8.0%.

Results: Metformin caused a progressive decline in fasting blood glucose (from a mean of 135 to 97.1 mg/dl) and In contrast, fasting glucose levels in the placebo group rose slightly from 81.5 to 89.3 mg. Metformin reduced BMI by a mean of 1.42 kg/m2 compared with placebo. Metformin reduced mean HbA1c level by 0.8 %.HDL level increased after treatment from 26.69±9.5 to 31.26± 9.1, and Triglyceride level decreased after treatment from 208.16 ± 58.3 to 191.51 ± 55.9; whereas there was no change in LDL and cholesterol levels in both groups.

Conclusion: Patients treated with metformin had weight reduction in severely obese children and adolescents. Apart from reduction of BMI, metformin also helps in reduction of resistance to insulin in hyperinsulinemia children and adolescents who are obese. Longer-term studies in different populations are required to establish metformin role in the treatment of overweight children.

Keywords: Diabetes, Obesity, Metformin, Prediabetes, Hyperinsulinemia, Fasting Blood Glucose, Glycemic Index

INTRODUCTION

In 1922 Metformin was discovered.[1] In 1950 Jean Sterne a French physician studied the significance and importance of metformin in humans and it was used in France for first time in the year 1957, but it got FDA approval in 1995 as an oral hypoglycemic agent.[2] Metformin is grouped in the most essential drugs category by World Health Organization's, and it is termed as most essential drug for the Diabetic Patient.

European Association of the Study of Diabetes and American Diabetes Association guidelines has recommended Metformin in Type 2 Diabetes Mellitus patient as a first line drug. Metformin acts by inhibiting production of hepatic glucose and increased uptake of glucose in peripheral tissues. In obese patients apart from glycemic control the Metformin have shown additive effects in controlling the lipids and it has been document to also have a Cardio- protective action. Apart from usage of metformin in treating diabetes it can also be used in other conditions like prediabetes, obesity, PCOD (polycystic ovary disease), NASH-non-alcoholic fatty liver disease. In many Epidemiological studies it has been shown that when treated with metformin had lower incidence of cancer than those of Non- Metformin-treated patients, hence it was concluded that it has an anti-cancer activity.[3]

Aim of the study was to assess the cost-effectiveness of metformin-based therapies in patients with Type 2 Diabetes mellitus with hyperlipidemia in obese individuals.

MATERIAL AND METHODS

There were 170 patients enrolled randomly for the study, out of which only 30 patients were fitting the criteria of the study and these were considered as cases and 30 patients were taken in Placebo group. The study populations of 30 patients were aged nearly 15 to 26 years. All had BMIs exceeding 28- 30 kg/m^2, at least 1 first- or second-degree relative with type 2 diabetes, fasting plasma glucose concentrations >126mg/dl and <180 mg/dl and hemoglobin A1c concentrations </=8.0%. All had normal linear growth and sexual development for age, with no marked hirsutism, severe acne, or menstrual irregularities characteristic of polycystic ovary syndrome. 3 participants had acanthosis nigricans. Patients were randomized to receive metformin (500 mg twice daily to maximum 1 gm/day) or a placebo for a total of 6 months. The effects of metformin on BMI, glucose tolerance, and serum lipids were analyzed. Before the start of the study ethical clearance was obtained from the institutional ethical board and informed consent was taken from the patients.

Inclusion criteria

- Age: 15 to 28years
- BMI: >26 kg/m2 upto 30 kg/m2
- FBS: more than 126mg/dl
- HB1C: 6.5 – 8%
- Triglycerides upto 250mg/dl

Exclusion criteria

- Age: more than 28 years
- BMI more than 30
- Associated co-morbid condition
- Type 1 diabetic patients

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- TG >250 mg/dl
- Smokers
- Alcoholic
- Renal OR Hepatic Insufficiency
- Patients on Drugs Like Steroid's
- Hypothyroidism

STATISTICAL ANALYSIS

Statistical analysis was done by using SPSS version 17.0. Chi square test was used for the comparison. Descriptive statistics were used for categorical variables.

RESULTS

Metformin caused a progressive decline in fasting blood glucose (from a mean of 135 to 97.1 mg/dl) and In contrast, fasting glucose levels in the placebo group rose slightly from 81.5 to 89.3 mg. Transient abdominal discomfort or diarrhea occurred in 33% of treated participants; there were no episodes of vomiting or lactic acidosis. Metformin reduced BMI by a mean of 1.42 kg/m2 compared with placebo. Metformin reduced mean HbA1c level by 0.8 %.HDL level increased after treatment from 26.69±9.5 to 31.26± 9.1 P-value was 0.0001, and Triglyceride level decreased after treatment from 208.16 ± 58.3 to 191.51 ± 55.9 P value was 0.0002; whereas there was no change in LDL and cholesterol levels in both groups.

DISCUSSION

European Association of the Study of Diabetes and American Diabetes Association guidelines have recommend Metformin as a first line drug to be used in Type 2 Diabetes Mellitus patient. Metformin Mechanism of action: It acts by counteracting the resistance of insulin, particularly in liver and skeletal muscle. It suppresses hepatic gluconeogenesis, increases peripheral sensitivity of insulin in tissues like adipose tissue and muscle, and results in peripheral utilization of glucose.[4-6] The most common side effect are diarrhea, Nausea, vomiting, abdominal pain, drowsiness, and, rarely, hypoglycemia. The Gastrointestinal effect of metformin was believed due to inhibition of serotonin reuptake transporter (SERT) -mediated intestinal reuptake of serotonin which resulted in increased motility of intestinal and water retention. Most cases of Metformin-associated lactic acidosis was documented in patient suffering with the tissue hypoxia especially in conditions like myocardial infarction, acute left ventricular failure or septicemia.[7]

It has been in multiple studies that Long-term usage of metformin can lead to vitamin B12 malabsorption and increased levels of homocysteine. DeJager J et.al. 2010 has shown that 30 % of Diabetic patient who were on metformin for long term developed vitamin B12 Malabsorption.[7-9] Early signs and symptoms were in feet (numbness and Paresthesia), if during this period of signs and symptoms the patent is not treated for the Vit B12, it would progress and eventually leading to weakness, ataxia, sphincter disturbance, and changes in mental status. Proceeding to development of neuropathy, the patient hematological pattern can help in picking up the deficiency i.e. (B12 deficiency –associated macrocytic anemia).

Metformin in Type 2 Diabetes Mellitus (T2DM): Metformin is still preferred first line drug in the treatment of T2DM in adolescents. Patient whose HbA1c < 9% at Diagnosis and Blood Glucose levels < 250mg/dl should be initiated with first line OHA i.e. Metformin as per guidelines. Apart from metformin patient should be initiated on lifestyle modification which includes Diet, nutrition, exercise and physical activity.

In Canada, Metformin was approved in the year 1972, but metformin did not receive any approval for type 2 diabetes mellitus from U.S. Food and Drug Administration (FDA) until 1994. In 1995 the US- FDA approved metformin for children with T2DM aged 10 years and older. In United States the first formulation of Metformin was branded as Glucophage.[10]

In Children with Type 2 Diabetes Mellitus Metformin is recommended as first line drug by The International Society of Pediatric Diabetes (ISPAD). The complication and Side effect are less than compared to other OHA'S. Incidence of Hypoglycemia is also less when patient is on Metformin. Other added benefits of metformin is to decreases or stabilizes the weight and decreases LDL-C and triglyceride level.[10]

In 2012 Zeitler P. et.al had done a study i.e. TODAY study (Treatment Options for T2DM in Adolescents and Youth) which has shown that nearly 51.7% of adolescents who had recent onset of Diabetes were treated with metformin alone, over a few years after the diagnosis these metformin group patients were non-responder's to metformin alone but require multiple drugs or insulin later on.[11]

Obesity, insulin resistance and Prediabetes: Over the past three decades the incidence and the rate of overweight and obesity in childhood have been tripled in United States of America and western countries. McGovern L et.al 2008 has shown that as there was rise in childhood obesity coexisting there was increase in incidence of prediabetes or impaired glucose tolerance, cardiovascular risk factors, insulin resistance, Childhood Type 2 Diabetes mellitus, Non-alcoholic fatty liver disease (NAFLD), Hypertension, and Dyslipidemia.[12] Knowler WC et.al 2002 has shown the benefits of Lifestyle modification and its importance. Hence it was recommended as a primary treatment for childhood obesity. Excessive weight gain reduction will have has positive effect on blood pressure and good glycemic control. However, outcome of the long-term lifestyle interventions for childhood obesity had been carried out in a clinical-practice setting which have varied widely. Low rate of success in long term was shown in many trials, which promoted an interest in addition of pharmacological interventions and bariatric surgery to prevent diabetes among adolescents and obese children.[13-14] Many studies have shown the other major effect of Metformin could be through inhibition of appetite probably by GLP-1 levels increasing and by interacting with signaling of other hormones or cytokines (such as ghrelin, leptin and insulin).

Non-alcoholic fatty liver disease (NAFLD): Commonly seen in children who are obese and adolescents. It is commonest cause of liver disease in obese patients. NAFLD includes hepatic steatosis, nonalcoholic steato-hepatitis (NASH), NASH progressing to cirrhosis, and finally end stage liver disease/ hepatocellular carcinoma. Treatment of NAFLD is modification of diet and lifestyle.

Schwimmer JB et. al 2005[15] have shown that with physical exercise regularly, life style modification, proper diet intake, has helped patients in 1) reduction of weight and it was seen there was 5 to 10 %reduction of weight, 2) it has also resulted in decreased

incidence of metabolic syndrome, 3) improvement in the liver enzyme, and 4) hepatic steatosis resolution. A pharmacological treatment is not universally accepted in patients with diagnosed with NAFLD. However, it know well known fact that in pathogenesis of NAFLD, insulin resistance plays an important role, many studies have postulated and shown the benefits of using insulin sensitizers (Metformin and Thiazolidinediones) as a possible treatment for NAFLD. Nadeau et al. 2009[16] randomized 50 patient who were obese and adolescents who were insulin-resistant, these subjects were placed on proper lifestyle modification and Metformin (a dose of 850 mg morning and evening in a day for nearly 6 months) or placebo. There was significant reduction in serum aminotransferases level, liver fat, and increased insulin sensitivity in patient treated with lifestyle modification and metformin group than compared to untreated or placebo-treated group.

Alkhouri N 2012[17] randomized multicenter placebo controlled trial called the TONIC trial. In this trial NAFLD diagnosed patient were enrolled i.e.173 children and adolescents. These enrolled groups of patients were treated with Metformin (1 gm per day) for 96 weeks. After 96 weeks the study has shown that Metformin was not superior to placebo in neither reducing in ALT levels nor significant improvements in histological features. Conclusion: no drug is currently available as specific treatment for NAFLD, the available evidences is controversial in relational to Metformin in improving metabolic alterations associated with NAFLD.

Polycystic Ovary Syndrome (PCOs): In adolescents PCOS is the most common cause of menstrual dysfunction and hyperandrogenism.

Metabolic dysfunction is manifested at the early age and it is an important risk associated with PCOs. One-third of adolescents with PCOs meet criteria for the metabolic syndrome including (obesity, dyslipidemia, hypertension, and glucose intolerance) when compared with 5% of adolescents from the general population.

Lewy VD et.al 2001[18] study had enrolled girls who were diagnosed with PCOS and they were grouped as group of obese, non-hyper-androgenic girls. It was shown that Girls with PCOs found to have nearly 50% reduction in peripheral tissue insulin sensitivity when compared to controls, and they also exhibited hepatic insulin resistance and compensatory hyperinsulinemia. Joshi B et.al 2014[19] has done a community-based cross-sectional study. The study has shown that obese girls with PCOS were having hirsutism, elevated blood pressures, and had mean insulin higher and the 2 h post 75 g glucose levels when compared with non- obese PCOS. Therefore, using Metformin for PCOS is attractive because this medication is known to improve these variables among adults with PCOS.

The anti-cancer effect of metformin: Metformin activates AMPK, which directly or indirectly helps in reduction of mammalian target of rapamycin (mTOR) complex 1 levels, this mTOR plays an important role in controlling cell growth, proliferation, and metabolism.[20] Many epidemiological data, observational data and laboratory data had suggest a potential anticancer effect of Metformin in various cancers like hepatocellular carcinoma, cancer breast and colorectal cancer and others. While others did not find significant anti-cancer effect of using Metformin.

CONCLUSION

Incidence of insulin resistance is higher in Adolescents during their pubertal growth spurt than compared to other periods in life. Metformin is a good sensitizer of insulin and its effectiveness and efficacy is proved in adolescent and adult patient with type 2 diabetes mellitus. However, long term controlled studies are further required to assess the degree and duration of safety and effectiveness of using Metformin in all other diseases apart from Type 2 Diabetes Mellitus and Polycystic ovarian disease. Metformin appears to be efficacious in reduction of BMI and resistance to insulin in hyperinsulinemia children and adolescents who are obese in the short term. Longer-term studies in different populations are required to establish metformin role in the treatment of overweight children. Metformin has been shown to reduce weight gain, hyperinsulinemia, and hyperglycemia in adults with type 2 diabetes and to reduce progression from impaired glucose tolerance to diabetes in those without diabetes.

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