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Effect of Metformin as adjunct therapy with insulin in adolescent Pakistani people with type 1 diabetes

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Abstract: Type 1 diabetes is a growing metabolic disorder, its ultimate therapy is the use of taking insulin regularly but, despite of that these patients cannot survive for longer durations due to poor glycaemic control, insulin resistance and development of complications. This clinical trial was designed to see if the addition of metformin can affect the dose of insulin and its complications and conducted for three months in Baqai Institute of Diabetology and Endocrinology. It included 80 patients of Type 1 Diabetes above 12 years of age between April 2019 to March 2020. Patients were divided into two groups. Group 1(n=30) was given Metformin with insulin and in Group 2 (n=50) patients were prescribed insulin only. Blood samples were collected at the beginning and end of trial to check Fasting and Random blood glucose and HbA1c levels. Paired sample t test and independent t test were applied, p value 0.05 was considered significant. A significant difference in HbA1c ($p<0.001$) and Random Blood Glucose ($p=0.006$) was noticed in group 1after three months. BMI increased in group 2, ($p=0.024$). The study concludes that Metformin might have a role in decreasing HbA1c and Random blood glucose levels in children above 12 years of age.

Keywords: Type 1 diabetes mellitus, metformin, insulin, glycaemic control.

INTRODUCTION

Type-1 Diabetes is a chronic autoimmune disease caused by an abnormal immune response to ill-defined environmental factors, leading to the formation of antibodies attacking and destroying the persons own beta cells of the pancreas that produce insulin. In these patients' insulin deficiency occurs when about 80% of beta cells are destroyed. This condition causes glucose to stay in the blood leading to hyperglycemia although most common age of presentation of type 1 diabetes is childhood and early adulthood, but it can appear at any age (Holt *et al*., 2021). It accounts for only 5-10% of all cases of diabetes but its occurrence is increasing; especially in children less than 5 years of age worldwide, it is estimated to be 15 per one lac people per year (Mobasseri *et al*., 2020). According to the International Diabetes Federation's Diabetes Atlas 9th Edition (2019), the occurrence of type 1 diabetes in Pakistan is evaluated to be around 5,200 cases among individuals aged 0-19 years. However, it is important to account that this estimate may not be accurate, as diabetes data in Pakistan is limited and there may be undiagnosed cases (Ogle *et al*., 2022).

Ultimate treatment of Type 1 Diabetes to date is by insulin preparations (Hirsch *et al*., 2020) but despite of its intensive and lifelong use, the haemoglobin (HbA1c) levels remain above 7.0 in many patients. Additionally, standard insulin therapy is associated with many side effects like hypoglycemia, weight gain and dyslipidaemia. Also, its continuous use leads to resistance to insulin and chronic complications Management of insulin resistance usually requires an increase in insulin dose which might lead to weight gain, hypoglycemia and ultimately poor glycaemic control. To deal with these problems, there is a great need for additional therapeutic strategies in Type-1 Diabetes which can improve insulin sensitivity (Snaith *et al*., 2020). Metformin is the best candidate for it. It is an inexpensive oral anti-hypoglycemic biguanide agent widely used in type 2 diabetes. It increases hepatic and peripheral insulin sensitivity and decreases hepatic gluconeogenesis, fatty acid oxidation and intestinal glucose absorption. Metformin has a safety profile and is generally well-tolerated (Liu *et al*., 2020). Metformin can be added with insulin of patients with Type 1 Diabetes 12 years or above and a BMI of 25kg/m^2 (23 kg/m^2 for people from South Asian and related minority ethnic groups) or above wants to improve their blood glucose control while minimizing their effective insulin dose (Chiang *et al*., 2014)

The aim of the present study was to investigate a possible beneficial effect of metformin in addition to insulin on glycaemic control of Type 1 diabetic patients aged 12 years or above.

MATERIALS AND METHODS

This open-label clinical trial was conducted in Baqai Medical University, Karachi in collaboration with Baqai

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Institute of Diabetes and Endocrinology, for three months in which patients were recruited between April 2019 to March 2020. Approval was taken from the ethical committee of Baqai Medical University, Karachi for conducting the research (Ref: BMU-ECL/04-2019-02).

In this study sample size was calculated using the website open epi. Assuming a Confidence interval of 95% and Power of 80% it was calculated to be 80. A reference study was used in which the HbA1c of patients treated with Metformin and insulin was 8.85±0.10 and HbA1c of patients treated with only insulin was 9.34±0.94 after 24 weeks [Jacobsen *et al*., 2009). Sampling was done using a purposive sampling method. 80 patients of age 12 years and above were recruited, major inclusion criteria were patients of type 1 diabetes taking insulin for the treatment above 12 years of age and of any gender, with no other comorbidities. Exclusion criteria was Patients of type 2 diabetes and gestational diabetes. These patients were divided into two groups. In group 1, 30 patients were enlisted, following clinicians' decision as to whether they needed metformin (250 mg-2000 mg) with insulin, keeping in mind the patient's BMI, insulin dose, and glucose profile. The rest of the subjects recruited for the study were included in group 2 and continued insulin therapy only for the treatment of type 1 diabetes. Also, it was an interventional study and clinicians had to give medicine very carefully with a limited time, so we could include a smaller number of patients in group 1 compared to group 2. The subjects were interviewed in detail about their medical and treatment history through a questionnaire. Written consent was taken from patients older than 18 years and from parents/guardians of patients less than 18 years.

For three months patients were asked for any adverse effects. Compliance to the medicine was assessed by asking them verbally. These patients were also asked to report self-monitoring blood glucose values in a book provided by the hospital. After 3 months patients were called for follow-up visit. All adverse events were reported.

The 12-week trial was completed by all 80 patients however two patients in metformin group stopped taking metformin in 2nd week, but these patients remained in the study to complete follow up.

At baseline and 12 weeks each participant Age (in years), weight (kg), height (cm) was measured. BMI was calculated by dividing weight by height meter (kg/m^2) (Peterson *et al*., 2016). Insulin doses (units) were noted, and blood was drawn for measurement of HbA1c, Fasting and Random plasma glucose levels. Fasting and Random Plasma Glucose levels were estimated by glucose oxidase method and HbA1c by HPLC method.

Ethical approval

This study was approved by the Ethical Committee of Baqai Medical University (Ref: BMU-ECL/04-2019-02).

STATISTICAL ANALYSIS

Data was analysed using SPSS (Version 22.0). Paired sample t-test was used to compare data within the group before and after 3 months of treatment, p value of less than 0.05 was considered significant.

RESULTS

A total of 80 type 1 diabetic patients were selected in this study. Patients in group 1 were given metformin with insulin (n=30) and in group 2, patients were given insulin (n=50) only. The demographic characteristics of both groups are shown in table 1. Table 2 shows the Biochemical parameters of both groups and depicts the significant difference in Random blood glucose (p=0.06) and HBA1c (<0.001) in group 1 and BMI in group 2 (p=0.024). Changes in FBS and insulin dose were not significant statistically.

DISCUSSION

The present study revealed the effects of metformin as an adjunct to insulin therapy on blood glucose control, BMI, and insulin dose in patients with Type 1 Diabetes mellitus. In this study, HbA1c levels decreased significantly after three months of treatment in the metformin-treated group while on another hand level of HbA1c level decreased non-significantly in the insulin-treated group. The same results were obtained in a study where HbA1c levels from baseline were decreased by 0.2% in the metformin group but increased by 0.1 % in the placebo group (Libman *et al*., 2015).

Another study found that metformin improves whole-body insulin resistance in adolescents who were overweight or obese (Cree-Green *et al*., 2019). Our study demonstrates that fasting plasma glucose levels decreased in the group that took metformin along with insulin but increased in the group that took only insulin which was in accordance with another study done for 12 months (Beysel *et al*., 2018). This might have occurred because biguanides increase sensitivity of the body to insulin. Hence, decreasing Fasting plasma glucose levels and glycated haemoglobin levels.

In the present study, Random Plasma Glucose levels decreased significantly in the group prescribed metformin along with insulin compared to the other group prescribed insulin only. These results were supported by another study done in Type 2 Diabetic patients when it was given with insulin (Abniaya *et al*., 2020).

Table 1: Comparison of demographic characters of two groups N = 80

Variables		Group 1 Patients Taking Metformin with Insulin. N (%)/ Mean ± SD N = 30	Group 2 Patients Taking insulin only. N (%)/ Mean ± SD N = 50	P Value
Age in Years		20.83±6.05	21.68±5.54	0.534
Gender	Male	17 (56.7)	31 (62.0)	0.637
	Female	13 (43.3)	19 (38.0)	
Marital Status	Single	24 (80)	38 (76.0)	0.678
	Married	6 (20)	12 (24)	
Duration of Disease (years)		8.70±6.27	10.08±5.77	0.319

Table 2: Comparison of biophysical and biochemical parameters of both groups

Variables	Group 1 Patients taking Metformin with Insulin. Mean ± SD. N = 30				Group 2 Patients taking Insulin only. Mean ± SD. N = 50			
	At the start of three months	At the end of three months	Mean Difference	P value	At the start of three months	At the end of three months	Mean Difference	P value
BMI ($kg/m^{2)}$	22.91±3.43	22.94±3.43	-0.03±1.097	0.869	21.55±2.82	21.89±3.01	-0.340±1.03	0.024*
FBS (mg/dl)	156.10±63.67	154.30±77.96	1.333±7.950	0.916	130.10±56.55	142.36±77.64	-9.10±89.45	0.400
Random Plasma Glucose (mg/dl)	230.67±84.72	188.70±65.30	41.97±77.56	0.006*	188.16±76.66	182.64±86.49	5.52±62.24	0.533
HbA1c (%)	10.70±2.94	9.06±2.33	1.65±1.57	<0.001*	9.23±1.94	8.71±1.59	0.52±1.87	0.06
Insulin Dose (units)	67.57±27.14	66.20±22.75	1.800±92.899	0.366	60.66±19.26	59.70±19.69	0.96±9.64	0.485

*p value ≤ 0.05 is significant

Metformin decreases the absorption of carbohydrates from the digestive tract which may be the reason of the decrease in Random Plasma glucose in the metformin group. Regarding dose of insulin required to keep blood glucose level within its range, a slight decrease in insulin requirement occurred in both groups, but more in the group which took metformin with insulin which was in favour of a retrospective study done for 10 years (Staels *et al*., 2017). This suggests that metformin decreases insulin resistance and hence the dose. A mechanism for it was suggested in a study that states that metformin increases the effect of insulin suppression on gluconeogenesis, increases insulin-stimulated glucose utilization in peripheral muscles, increases fasting plasma glucose clearance and inhibit the effect of glucagon (Apostolova *et al*., 2020).

CONCLUSION

Our study indicates that the combination of metformin with insulin controls plasma glucose concentration more effectively as compared to insulin alone for the treatment of type 1 diabetes mellitus in the Pakistani population aged 12 years and above.

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