

In the name of God

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**Benefits of Metformin Combined with Insulin in Children with Type
1 Diabetes Mellitus.**

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Abstract:

Background: Some patients with type 1 diabetes mellitus have not good glycaemic control with ordinary doses of insulin. So applying other treatment modality in addition to insulin and diet therapy could improve glycaemic control.

Objective: To evaluate whether, in patients with type 1 diabetes mellitus, the addition of Metformin to insulin and standard diabetes management result in better glycaemic control and lower insulin dosage .

Methods: In a clinical trial study 16 children and adolescents with type 1 diabetes with had high insulin intake and HbA1c >8% were participated. HbA1c, FBS, 2hpp BG, insulin dosage and BMI were measured and compared at the onset and end of the treatment.

Results: There were significant differences in HbA1c and insulin dosage between the time of 0 of the study and after 4 months of Metformin addition therapy. But there were no significant differences between BMI, FBG and 2 h pp BG at the onset of the study and end of it.

Conclusion: Metformin treatment lowered HbA1c and decreased insulin dosage in patients with type 1 diabetes in poor metabolic control. Long term studies will determine if these improvements are sustained.

Keywords: Type 1 diabetes mellitus, Metformin, HbA1c, Fasting, Blood Sugar

Introduction:

Diabetes mellitus is the most common metabolic disorders worldwide. Ten percent of diabetic populations are those with type 1 diabetes mellitus.⁽¹⁾

Ninety percent of diabetic patients will develop complication in the kidneys, eyes, nervous system and or cardio vascular system.⁽²⁾

Improvement of glycaemic control can prevent or diminish the development and progression of these complications and provide a normal life for patients with type 1 diabetes mellitus.

Patients with type 1 diabetes have absolute insulin deficiency so they require insulin therapy for even short time survival.⁽³⁾ Until now treatment with insulin and diet therapy has been the only management modality that could lead to better glycaemic control in type 1 diabetic patients.^(2, 4)

However some patients on ordinary doses of insulin could not have good glycaemic control.

Insulin is an appetite stimulant particularly in large doses. So large doses of insulin is associated with weight gain and obesity is associated with insulin resistance⁽⁵⁾ followed by increase of the insulin doses necessary to improve blood glucose control.

Metformin is a biguanide that has been used in treatment of patients with type 2 diabetes for more than forty years. It acts by diminishing basal hepatic glucose production and increasing glucose uptake in muscles.⁽⁶⁾

Only few studies have investigated the effect of treatment with metformin combined with insulin in patients with type 1 diabetes. These studies have suggested a

positive effect of metformin in these patients too.^(7, 8, and 9)

On the convenient feature, until now this approach is not a common modality in the management of type 1 diabetic children.

In our community many patients may have fear of hypoglycaemia and it is seemed that they have poor adherence to this method of management.

So the purpose of this study was first to determine if the addition of metformin to regular diabetes care in type 1 diabetic patients would improve glycaemic control as assess by clinical outcomes of lowered HbA1C and insulin dosage and lack of weight gain and secondly how is the coping of our patients to this modality.

Methods and subjects:

Study design:

This was a clinical trial of 4 months duration that was conducted in a group of children and adolescents with type 1 diabetes mellitus. They were attending a pediatric clinic of diabetes in Endocrine and Metabolism Research center affiliated to Isfahan University of Medical Sciences. All patients or their parents provided written informed permission before entry to the study.

Subjects & Sample size:

The sample size was determined based on the below Equation:

16 diabetic patients who had inclusion criteria were enrolled in simple convenient method.

inclusion and exclusion criteria:

age 10-24 years, receiving two or three injection of insulin NPH plus insulin Regular daily and total daily insulin doses greater than 1 IU/kg.

Further inclusion criteria included poor Glycaemic control (mean of HbA1C 8% or higher) in the previous year, fasting serum C Peptide <0.18 nmol/lit after injection of Glucagons, History of diagnosis of T1DM following hyperglycemia and ketoacidosis, and duration of diabetes for at least 2 years.

Exclusion criteria were: history of unawareness hypoglycaemia, clinical or biochemical indication of renal or hepatic dysfunction, and any chronic disease other than diabetes that could make the interpretation of the results difficult.

Study protocol and treatment:

First, patients had been taught to estimate capillary blood glucose using own's glucometers or if they had not glucometer, at laboratory of the Clinic. They were asked to check blood glucose at fasting, 2hpp and before evening insulin injection at least twice per week.

Subjects were instructed to treat hypoglycemia and to call the doctor, if needed. Insulin regimen were adjusted by the patients/parents or the doctor via phone contact according to the blood glucose level. Patients were asked to continue meals and physical activity during the period of the study as before it.

Metformin was taken with starting dose 500 mg/day with breakfast and was increased each week 500 mg/day up to 1000mg/day (twice daily) for those weighing less than 50 kg and 1500mg/day (three times daily) for patients with weight more than 50 kg.

To minimize GI side effects, the drug was taken with meals.

Patients were requested to visit the doctor every month. At each visit they were evaluated for metabolic control, protocol compliance, daily insulin injection, hypoglycaemic episodes and GI side effects of metformin. Hepatic and renal function tests, also complete blood count were measured to monitor adverse effects of metformin after 3 months of the beginning of study. SPSS version 11 was used for data analyses. Data were expressed as mean±SD, paired t test assessed differences in the subjects before and after treatment. P value<0.05 was considered significant.

Results:

1) patients characteristics:

From all 16 subjects who enrolled the study, 3 patients withdrew after first month because of their unwillingness to continue the protocol and thirteen patients continued the study period.

The mean age of participants was 15.23±3.7 years, 69.2% of them were female (n=9) and 30.7% of them were male (n=4). Duration of diabetes was 2-16 years with mean of 4.92±3.62 years. All subjects received conventional regimen of insulin therapy as previously (as a mixture of NPH and Regular 2 times a day in 12 patients and 3 times a day in one patient).

2) adverse events:

During the study, there were no episodes of vomiting, loose stools or abdominal discomfort. 3 patients unsatisfied with metformin because of unpleasant taste of it but no patients were withdrawn because of this problem.

3) Blood glucose control:

Mean of HbA1C, at the time of 0 of study was 9.6 ± 2 , as the study progressed HbA1C gradually decreased and at the end of study it was 8.3 ± 1.2 . Paired t test showed this difference is significant ($p=0.021$). Fasting blood glucose was 195 ± 43 mg/dl at the beginning the study and it was 164 ± 36 mg/dl at the end. The difference was not significant ($p=0.06$). (table1)

At the beginning of study mean of 2 hpp BS was 203 ± 44 mg/dl and at the end it was 181 ± 41 mg/dl. This difference was not significant ($p=0.17$). (table1)

Also there was not significant difference between mean of evening blood glucose

(before evening insulin injection) at the onset of the study and at the end of it (221 ± 89 mg/dl and 186 ± 59 mg/dl retrospectively), however this indicator was decreased during the study. (table1)

4) Daily insulin doses:

At the time of 0 of study mean of daily insulin doses was 1.34 ± 0.4 Iu/kg, it gradually was reduced with the study progression, and at the end of the study it was significantly less than the time of 0 (1.2 ± 0.4 Iu/kg, $p < 0.001$) (table1)

BMI:

There was no significant difference between BMI at the time of 0 and at the end of study (20.39 ± 2.7 , and 20.42 ± 2.7 retrospectively). (table1)

Table 1, Comparison of glycaemic control and metabolic indicators before and after the intervention

| | At the time of 0 of study | At the end of study | P |
|-----------------------------|---------------------------|---------------------|--------|
| HbA1C(%) | 9.6 ± 2 | 8.3 ± 1.2 | 0.021* |
| FBS(mg/dl) | 195 ± 40 | 164 ± 36 | 0.06 |
| BS 2hpp(mg/dl) | 203 ± 44 | 181 ± 41 | 0.176 |
| Pre meal BS(evening, mg/dl) | 221 ± 89 | 186 ± 59 | 0.134 |
| BMI(kg/m ²) | 20.39 ± 2.7 | 20.42 ± 2.7 | 0.87 |
| daily insulin doses (Iu/kg) | 1.34 ± 0.4 | 1.2 ± 0.4 | 0.013 |

Discussion:

In this trial we have determined the effects of metformin combine with insulin in diabetic children with badly glycaemic control.

Findings showed that such regimen can result in significant improvement of glycaemic control as shown by reduction of HbA1C.

This favourable effect of metformin was accompanied with reduction of total daily insulin doses.

Our findings were consistent with findings of previous studies.^(2, 3, and 7) Tatsu-

hiko Urakomi et al' study showed reduction of weight in patients with type 1 diabetes receiving metformin adjunct to insulin.⁽⁷⁾ Our results were inconsistent with their study; explanation is probably due to short period of the present study. Study of khan et al showed adding up of metformin to insulin regimen leads to significant decrease in fasting plasma glucose.⁽³⁾ Inconsistently our data showed FBS, BS 2hpp and late afternoon BS were lower following 4 months of protocol however these decreases were not statistically significant. It may be be-

cause of reduction of insulin dosage in our patients as their blood glucoses were decreased. Our data are consistent with Meyer et al' study.

In the present study we had some limitations. In our community patients have poor coping with adding new drugs to their previous drug regimen, this causes some limitation for the present study e.g. minute sample sizes, short duration of study and lack of control group getting placebo.

In conclusion, Metformin has beneficial effect on patients with type 1 diabetes who are treating with conventional insulin regimen. It must be used under closed clinical supervision.

However we suggest further randomized clinical trials with larger sample sizes and longer duration before we can say our patients can tolerated this regimen and will copy with this modality of treatment.

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