Original Article

A Pilot Study to Assess Effect of Metformin Therapy on Prevention of Double Diabetes in Indian Adolescents with Type-1 Diabetes

Chirantap Oza[1], Shruti Mondkar[1], Nikhil Shah[1,2], Chidvilas More[1], Vaman Khadilkar[3,4], Anuradha Khadilkar[1,4]

[1]Department of Growth and Pediatric Endocrinology, Cowasji Jehangir Medical Research Institute, Pune, Maharashtra, [2]Department of Paediatrics, Cloudnine Hospital, Mumbai, Maharashtra, [3]Department of Health Sciences, Savitribai Phule Pune University, Pune, Maharashtra, [4]Department of Growth and Pediatric Endocrinology, Senior Paediatric Jehangir Hospital, Pune, Maharashtra, India

Abstract

Introduction: Increased prevalence of metabolic syndrome in Indian adolescents owing to the obesity epidemic leads to double diabetes (DD), which is associated with an increased risk of complications in type-1 diabetes (T1D). Metformin may be a useful intervention for the prevention and treatment of insulin resistance in T1D. We conducted this pilot randomized controlled trial with the objective of investigating the effect of metformin on insulin sensitivity in Indian adolescents with T1D. **Method:** This pilot randomized controlled trial was performed on 59 participants with T1D aged 10–19 years distributed uniformly by gender and puberty across two groups with a 3-month intervention period. The intervention group received metformin (weight less than 60 kg received 500 mg twice daily and more than 60 kg received 1 gm twice daily) and non-metformin group received standard of care for diabetes. Anthropometric, clinical details, biochemistry and insulin sensitivity indices (ISI) were evaluated using standard protocols at baseline and endline. **Result:** 22.2% of subjects from non-metformin group and 12.5% from metformin group were at the risk of the development of DD. The odds ratio and relative risk for the development of DD in non-metformin subjects were 2.0 and 1.4, respectively, as compared to participants in metformin group. The mean improvement in ISI ranged from 1.4% to 4.6% in participants on metformin as opposed to deterioration of -2% to -14.1% in non-metformin group. On performing the paired sample t-test, the reduction in ISI in non-metformin group was significant. **Conclusion:** Metformin may prevent deterioration in insulin sensitivity in Indian adolescents with T1D.

Keywords: Adolescents, double diabetes, insulin sensitivity, metabolic syndrome, metformin, type-1 diabetes

Introduction

India has the largest number of cases of new cases per annum and existing cases of type-1 diabetes (T1D) by country in the 0- to 19-year age group.[1] When features of metabolic syndrome (MS) due to insulin resistance (IR) are present in T1D, the phrase double diabetes (DD) has been coined.[2] Given the mechanistic relevance of IR in MS, various studies have assessed the utility of various definitions of MS in predicting risk in T1D. In a prospective analysis of the Pittsburgh EDC cohort, the prevalence of MS was 8% by International Diabetes Federation (IDF) definition.[3] In a comparable examination of the FinnDiane study, a 36% prevalence of MS was reported.[4] A study from North India labelled 7% subjects as having double diabetes, whereas a study from South India reported 22.2% prevalence of MS in their T1D population.[5,6]

Microvascular and macrovascular complications are associated with IR in subjects with T1D. For example, the DCCT/EDIC study reported that higher estimated insulin sensitivity using

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Address for correspondence: Dr. Anuradha Khadilkar, Hirabai Cowasji Jehangir Medical Research Institute, Block V Lower Basement Jehangir Hospital, 32 Sassoon Road, Pune - 411 001, Maharashtra, India.
E-mail: anuradhavkhadilkar@gmail.com

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the Pittsburgh eGDR equation was associated with a reduced risk of retinopathy.[2] Besides, higher estimated insulin sensitivity in adolescents with T1D is inversely associated with the risk of cardiovascular disease.[7] The author's group has also demonstrated low insulin sensitivity as a predictor of the development of MS and nephropathy in Indian children and youth with T1D.[8,9]

Behavioural modification and lifestyle recommendations are keys to prevent and treat IR caused by sedentary lifestyle and obesity.[10] Besides lifestyle modifications, drugs like metformin can improve insulin sensitivity. Some studies have shown that adding metformin to insulin therapy significantly improved IR in patients with DD similar profiles.[11] IR is frequently noted in South Asian populations and is associated with typical body composition of upper body adiposity, increased body fat and low muscle mass. An Indian study had noted a higher prevalence of IR in urban Asian adolescents aged 14–25 years.[12,13] No trial of metformin administration in Indian adolescents with T1D to reduce IR or risk of developing DD has been conducted; thus, we conducted this pilot trial with the objective to evaluate the effect of adding metformin as an adjunct to standard insulin therapy for 3 months in Indian adolescents with T1D on insulin sensitivity and prevention of DD.

Material and Method

Trial design, subjects and inclusion/exclusion criteria

The data presented here are a subset of a larger trial to assess an impact of metformin therapy on cardiometabolic risk of subjects with T1D (Manuscript in submission). This is single-centre, double-blind parallel-group, randomized and placebo-controlled pilot trial conducted in children with diabetes attending the outpatient clinic for T1D at a tertiary care hospital in Pune, Western Maharashtra, India, for a period of 3 months. The main trial was registered with The Clinical Trials Registry-India (CTRI) (CTRI/2019/11/022126). The study was approved by the institutional ethics committee. Around 550 children regularly attend the diabetes clinic (Sweetlings) at our facility, and diabetes care for these children is provided by the centre. Children who are enrolled at the clinic are provided with insulin, glucometers and strips as well as social, psychological and dietary counselling without charge. Inclusion criteria were patients aged 10 to 19 years with T1D duration greater than 1 year. Those with complications or comorbidities, on medications, lack of treatment adherence and severe illness in the past 6 months before recruitment, or those with a known hypersensitivity to metformin were excluded from this study. Based on these criteria, 82 participants were included in this study. A total of 23 subjects who had even one criterion as per the IDF definition of MS (except elevated fasting blood sugar) were excluded from the study. We used the IDF definition (Consensus 2017) for classifying study participants with MS: MS in children age 10 years or older, adolescents and adults was defined by IDF as follows. MS may be diagnosed with abdominal obesity and the presence of two or more of the following features: elevated triglycerides, low high-density lipoprotein cholesterol (HDL-c), high BP and increased fasting plasma glucose. Abdominal obesity was defined as WC >90th centile for age and gender or adult cut-off of >80 cm in females or >90 cm in males as per ethnicity-specific values. Other parameters were defined as follows: raised triglycerides: ≥150 mg/dL, reduced HDL-cholesterol: <40 mg/dL in males and <50 mg/dL in females, raised blood pressure: systolic ≥130 mmHg or diastolic ≥85 mmHg and impaired fasting glycaemia ≥100 mg/dL.[14] All our patients with diabetes had elevated fasting blood sugar (FBS); thus, patients who had one or more criteria as per the definition of MS (except elevated FBS) were termed to have risk of the development of double diabetes. Parents provided written informed consent and children gave assent for the study before any study procedures were performed. Participants of age more than 18 years gave consent for participation in the study. The study was conducted in accordance with the International Council on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. The duration of the intervention was 3 months, and the study was conducted between November 2019 and February 2022. A consort diagram of the study design is shown in Figure 1.

Study groups and intervention

The subjects with T1D were randomized to one of two 3-month intervention groups. The subjects belonging to group A (metformin group) weighing less than 60 kg received 500 mg metformin twice daily, whereas those weighing more than 60 kg received 1 gm twice daily and the subjects in group B did not receive any additional intervention besides

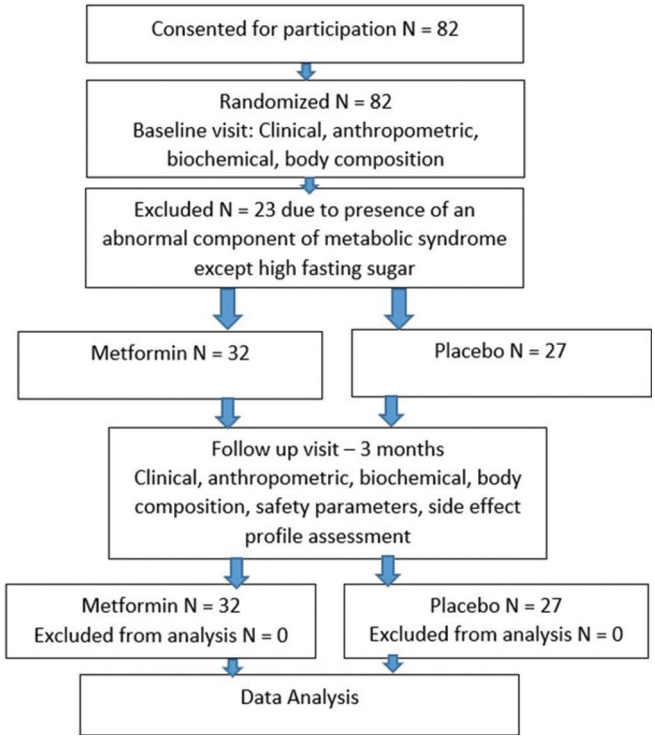

Figure 1: Consort diagram of study design

standard of care for diabetes (non-metformin group).[15] Diabetes management with insulin, regular blood sugar level monitoring, diet advice and lifestyle changes was administered to all participants of both groups. No other supplements were permitted during the study period, and subjects were instructed to continue their routine diabetes treatment including insulin, etc.

Compliance and adverse events

During the intervention period, subjects/parents in intervention groups reported to the centre monthly to pick up the metformin tablets. Compliance was measured by pill count on returned packs. The participants of group B visited the centre monthly for evaluation by a paediatric endocrinologist for T1D management and insulin supply. Intermittent illnesses were recorded for children in all groups. History of hospital admissions was also recorded. Safety parameters (SGOT, SGPT and number of hypoglycaemic episodes) and compliance were assessed at 3 months. The overall compliance was similar across the two groups (metformin: 92.5 ± 8.1%, non-metformin: 93.6 ± 10.1%; $P = 0.6$). Among those on metformin, four developed nausea/vomiting and one developed diarrhoea during the initial 3 months of intervention, whereas from the non-metformin group, one developed vomiting and one developed abdominal pain.

Outcome measures

The primary efficacy endpoints were the change in insulin sensitivity that indices at the end of 3 months of the intervention period. The assessment of clinical, anthropometric and biochemical parameters was performed at the beginning and end of the study intervention period (3 months) in all participants. Additionally, data on the duration of diabetes and insulin requirements were collected from participants in both groups.

Clinical history and examination

Data on the age of the subjects, age at onset of diabetes, duration of diabetes and total dose of insulin per day were collected using standardized questionnaires by physicians and were verified from hospital medical records. Tanner staging for sexual maturity was performed by a trained paediatric endocrinologist.[16]

Anthropometry

Standing height using a portable stadiometer (Leicester Height Meter, Child Growth Foundation, UK) was measured to the nearest millimetre, and weight was measured using an electronic scale to the nearest 100 grams. Body mass index (BMI) was computed by dividing weight in kilograms by height in meter squares. Subsequently, the height, weight and BMI were converted to Z scores using Indian references.[17] Waist circumference (WC) and hip circumference were measured using World Health Organization (WHO) guide to physical measurements. Waist circumference was converted to Z scores using Indian reference data, and waist-hip ratio (WHR) was calculated as waist circumference divided by the hip circumference.[18]

Blood pressure (BP)

BP was measured on the right arm with the child lying down quietly. The cuff was leak tested before commencement of the study. All air was removed from the cuff, and the cuff was wrapped snuggly and neatly around the limb to allow one finger under the cuff. The cuff was placed 2–5 cm above the elbow crease. All BP measurements were recorded manually with the same oscillometric non-invasive BP (NIBP) device (Goldway™ Multipara Monitor – Model Number GS20).

Biochemical evaluation

Glycaemic control was evaluated by measuring glycosylated haemoglobin (HbA1C). A fasting blood sample (5 ml) was collected between 7 and 9 am by a phlebotomist. HbA1C was measured by high-performance liquid chromatography (HPLC, BIO-RAD, Germany). Fasting blood samples were then assessed for lipid profile (total cholesterol, high-density lipoprotein-cholesterol (HDL-C) and triglycerides) using the enzymatic method, and low-density lipoprotein-cholesterol (LDL-C) concentrations were calculated by the Friedewald formula.[19] SGOT and SGPT were tested by International Federation of Clinical Chemistry (IFCC) method without pyridoxal phosphate (fully automated analyser Selectra Pro S, Germany).

Body composition

Fat mass, fat-free mass and total body water were assessed using Bioelectrical Impedance Analyzer (BIA) (Tanita Model BC420MA) in standing position after a minimum of 3 hours of fasting, and voiding before measurements. Z scores for fat percentage and muscle mass percentage were calculated using Indian reference data.[20]

Estimated insulin sensitivity indices

Insulin sensitivity was calculated using the formulae as follows:

A) Estimated GDR (EGDR in mg/kg/min) = 24.31 – 12.22(WHR) – 3.29(HTN) – 0.57(HbA1C).[2,21]

B) SEARCH study: log eIS = 4.64725 – 0.02032 (waist; cm) – 0.09779 (HbA1c; %) – 0.00235 (Triglyceride; mg/dl).[22]

C) CACTI excluding adiponectin (CACTI exa) = exp (4.1075 - 0.01299 [waist, cm] - 1.05819 [insulin dose, daily units per kg] - 0.00354 [triglycerides, mg/dL] - 0.00802 [DBP, mm Hg]).[23]

Statistical analysis

All statistical analyses were carried out using the SPSS for Windows software programme, version 26 (SPSS, Chicago, IL, USA). All outcome variables were tested for normality before performing statistical analyses. Differences in means were tested using Student's t-test for parametric data, Mann–Whitney U-test for non-parametric data and Chi-squared test for categorical variables. Paired sample t-test was used to compare parameters at baseline and 3 months in the metformin group and the non-metformin group. P value <0.05 was considered as statistically significant.

Ethical clearance statement

The study was approved by the institutional ethics committee named as 'Ethics Committee, Jehangir Clinical Development Center Pvt Ltd.' vide letter no NA (our ethics committee does not provide an approval number) on 1st November 2019. Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The procedures follow the guidelines laid down in Declaration of Helsinki 2008.

Results

A total of 59 subjects were studied at baseline and endline, of which 32 (54.2%) were males and 27 (45.8%) were females. The subjects were uniformly distributed across both groups by pubertal status. The mean age of participants in the study group at baseline was 13.7 ± 2.3 years with a mean duration of diabetes of 5.0 ± 2.2 years. The subjects' mean HbA1c was 9.9 ± 1.7%, and mean insulin requirement was 1.0 ± 0.3 IU/kg/day at baseline. Only 1.7% (n = 1) participants met ISPAD glycaemic control target guidelines (HbA1c<7%). Six (10.2%) subjects were prepubertal, 31 (52.5%) were pubertal, and 22 (37.3%) were post-pubertal. Only three (5.1%) subjects were overweight or obese according to BMI for age criteria, whereas none were adipose (fat percentage above >85th percentile for age and gender). The demographic, anthropometric, body composition and laboratory parameters of participants in the study group at baseline are compared in Table 1.

At endline, 16.9% (n = 10) subjects developed the risk of double diabetes. Eight (13.6%) subjects were overweight or obese according to BMI for age criteria, whereas three (5.1%) were adipose (fat percentage above >85th percentile for age and gender). The comparison of clinical, biochemical, anthropometric, body composition and insulin sensitivity indices at endline in both groups is illustrated in Table 2. Only mean HDL cholesterol concentrations were significantly different between the two groups.

Around 22.2% (n = 6) subjects of non-metformin group, whereas only 12.5% (n = 4) from metformin group were at risk of the development of double diabetes. The odds ratio and relative risk of the development of risk of double diabetes in non-metformin subjects were 2.0 and 1.4, respectively, as compared to participants receiving metformin therapy. The percentage change in various parameters of insulin sensitivity is shown in Table 3. The subjects of metformin group showed a significant difference in change in systolic blood pressure and HDL cholesterol as compared to non-metformin group. The mean improvement in insulin sensitivity indices by various equations ranged from 1.4% to 4.6% in participants receiving metformin therapy as opposed to deterioration of -2% to -14.1% in non-metformin group over a period of 3 months. On performing the paired sample t-test, the reduction in insulin sensitivity in non-metformin group by CACTI equation was significant as shown in Table 4.

Table 1: Comparison between study groups at baseline

Parameter	Metformin (*n*=32)		Non-metformin (*n*=27)	
	Mean	Std. Deviation	Mean	Std. Deviation
Clinical				
Age in years	13.8	2.5	13.8	2.4
Duration of illness in years	5	2.2	5.2	2.5
Systolic blood pressure in mmHg	110.3	6.3	108.9	8.6
Diastolic blood pressure in mmHg	72.8	6.1	72.5	6.5
Insulin requirement in U/kg/day	1.1	0.3	1.1	0.4
Anthropometry				
Height z score	-0.5	1	-0.7	1.1
Weight z score	-0.5	0.9	-0.8	0.8
BMI z score	-0.3	0.8	-0.6	0.7
Waist circumference in cm	65	7.7	63.5	8.7
Hip circumference in cm	79.3	8.6	77.8	9.2
Waist z score	-1.8	1.1	-2	1.2
Waist-hip ratio	0.9	0.1	0.9	0.1
Biochemistry				
HbA1C%	10.2	2	9.8	1.6
Lactate	10.4	3.5	10.8	3.4
Cholesterol in mg/dl	146.3	22.4	132.5	28
Triglyceride in mg/dl	65.5	18.5	59.1	28.5
HDL in mg/dl	54.5	5.7	52.5	6.5
LDL in mg/dl	78.7	21.2	68.3	27.6
VLDL in mg/dl	13.1	3.7	11.9	5.7
SGOT in IU/L	15.8	5.5	15.5	4.9
SGPT in IU/L	14.5	6.1	16.8	6
Body composition				
FAT percentage Z score	-0.3	1	-0.7	0.9
LBM percentage Z score	-3	0.7	-2.8	0.6
Insulin sensitivity indices				
CACTI excluding adiponectin	4	1.5	4.5	1.8
SEARCH	9.2	2.3	10	2.4
eGDR	8.6	1.5	8.8	1.2

BMI: Body mass index, HbA1c: glycated haemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, LBM: Lean body mass, eGDR: estimated glucose disposal rate, SGOT: Serum glutamate oxalate transaminase, SGPT: Serum glutamate pyruvate transaminase

Discussion

We report that higher proportion of subjects of non-metformin group developed risk of DD as compared to the metformin group. The odds ratio and relative risk of development of risk of DD in non-metformin subjects were 2.0 and 1.4, respectively, as compared to participants receiving metformin therapy. The subjects of metformin group showed a significant difference in change in systolic blood pressure and HDL cholesterol as compared to non-metformin group. The mean improvement in insulin sensitivity ranged from 1.4% to 4.6% in participants receiving metformin therapy as opposed to deterioration in

Table 2: Comparison between study groups at endline (3 months)

Parameter	Metformin (*n*=32)		Non-metformin (*n*=27)	
	Mean	Std. Deviation	Mean	Std. Deviation
Clinical				
Age in years	14.1	2.5	14.1	2.4
Systolic blood pressure in mmHg	109.7	7.4	112.5	9.8
Diastolic blood pressure in mmHg	73.7	6.1	74	8.6
Insulin requirement in U/kg/day	1.1	0.5	1.1	0.4
Anthropometry				
Height z score	-0.6	1	-0.6	1.1
Weight z score	-0.4	0.9	-0.7	0.8
BMI z score	-0.2	0.9	-0.5	0.8
Waist circumference in cm	66.9	8.2	65.2	8.3
Hip circumference in cm	80.7	9	80.1	8.5
Waist z score	-1.6	1.1	-1.9	1.1
Waist-hip ratio	0.9	0.1	0.9	0.1
Laboratory				
HbA1C%	9.6	1.7	9.6	1.9
Lactate in	11.8	4.9	16.2	3.9
Cholesterol in mg/dl	147.9	28.5	139	26.7
Triglyceride in mg/dl	74.1	31	84	46
HDL in mg/dl*	52.9	6.7	47.3	5.3
LDL in mg/dl	80.1	27.3	75.1	25.4
VLDL in mg/dl	15.2	6	16.3	8.9
SGOT in IU/L	18.2	7.5	18.6	9.4
SGPT in IU/L	16.6	5.8	17.4	8.8
Body composition				
FAT percentage Z score	0.1	1	-0.4	0.9
LBM percentage Z score	-3.1	0.7	-2.8	0.6
Insulin sensitivity indices				
CACTI excluding adiponectin	4	2	3.9	1.7
SEARCH	9.2	2.4	9.4	2.8
eGDR	8.8	1.3	8.6	2

BMI: Body mass index, HbA1c: glycated haemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, LBM: Lean body mass, eGDR: estimated glucose disposal rate, SGOT: Serum glutamate oxalate transaminase, SGPT: Serum glutamate pyruvate transaminase, *Statistically significant difference at $P<0.05$

Table 3: Comparison of percentage change in parameters of insulin sensitivity in study groups at endline

Parameter difference in %	Metformin (*n*=32)		Non-metformin (*n*=27)	
	Mean	Std. Deviation	Mean	Std. Deviation
HbA1C	-5.1	12.5	-1.4	15.4
Waist circumference	3	4.7	3.2	8.5
Systolic blood pressure*	-0.5	5.9	3.5	7.7
Diastolic blood pressure	1.9	11.1	2.5	10.7
Triglycerides	15.9	39.9	61.8	98.9
HDL*	-1.9	16.6	-8.7	13.7
% Insulin requirement change	-0.7	3.4	7.3	1.6
eGDR	4.1	14.7	-2	21.9
CACTI	4.6	50.4	-14.1	20.5
SEARCH	1.4	16.7	-5.3	18.9

HDL: High-density lipoprotein, HbA1c: glycated haemoglobin.
*Statistically significant difference at $P<0.05$

non-metformin group. There was significant reduction in insulin sensitivity in non-metformin group.

A retrospective study on the effect of metformin in adults with T1D reported that the prevalence of MS was lower in the metformin–insulin group than in the insulin-alone group after treatment. They also report that increase in systolic blood pressure and diastolic blood pressure was higher in insulin group as compared to the insulin–metformin group.[24] We observed mean reduction in systolic blood pressure by 0.5% in metformin group as opposed to mean increase of 3.5% in non-metformin group. Similar results were obtained by a study on effects of low-dose metformin in adolescents with T1D; authors reported a significant increase in systolic blood pressure in the placebo group at 3 months compared to baseline.[25] However, unlike our study, they also reported a significant reduction in waist circumference at the end of 3 months in metformin group. Some studies have also reported no change in waist circumference between metformin–insulin and only insulin groups.[24] Särnblad *et al*.[26] did not observe any significant changes in waist circumference between metformin and placebo groups at the end of 3 months. They also reported insulin sensitivity as measured by hyperinsulinaemic–euglycaemic clamp to be significantly improved in the metformin group. Gin *et al*.[27] also reported that metformin improved insulin sensitivity by 18% as measured by a hyperinsulinaemic–euglycaemic clamp in adults with T1D.

A study on effects of metformin on insulin resistance and risk factors for cardiovascular disease in type-2 diabetes mellitus subjects showed that metformin treatment was associated with significantly improved insulin sensitivity. The proposed mechanism was improvement in fasting glucose along with improved insulin sensitivity at hepatic and skeletal muscle level.[28] The major mechanism of metformin action in improving insulin sensitivity is attributable to events at the post-receptor level, that is by activating energy regulating AMP-activated protein kinase.[14,29] However, unlike our study they reported reduction in total cholesterol concentrations accompanied by significant fall in LDL cholesterol concentrations with no effect on HDL cholesterol concentrations.

We also report trend of better outcome in mean HbA1c (5.1% vs 1.4%), mean triglycerides and mean HDL levels in metformin group as compared to non-metformin group. A systematic analysis studying effect of metformin in adolescents with T1D reported mean reduction in HbA1c by 0.6-0.9% with no

Table 4: Comparison of paired *t*-test in study groups

Change in insulin sensitivity	Metformin ($n=32$)			Non-metformin ($n=27$)		
	Mean	Std. Deviation	Sig. (2-tailed)	Mean	Std. Deviation	Sig. (2-tailed)
CACTI*	0.04	1.82	0.91	-0.64	0.97	<0.01
SEARCH	0.02	1.40	0.93	-0.55	1.87	0.13
eGDR	0.22	1.02	0.22	-0.23	1.89	0.54

*Statistically significant difference in non-metformin group at $P<0.05$, eGDR: estimated glucose disposal rate

significant change in majority of studies.[30] A study has shown that HDL increased by 7 mmol/l (22%) with metformin in subjects with T1D.[31] Besides, total triglyceride concentrations have also shown a significant fall after metformin therapy, due to its effect on VLDL levels.[32,33] A review reported reduction in total cholesterol by 14.3 mg/dl in comparison with placebo in the study with larger sample size.[34] Another systematic review reports that metformin therapy may have no significant effect on lipid parameters, blood pressure or metabolic effects, whereas its effect on insulin sensitivity was controversial.[35] The cardiovascular and metabolic effects of metformin in patients with type-1 diabetes (REMOVAL) study reported that adding metformin to insulin therapy and standard of care for 3 years in adults with T1D and high cardiovascular risk did not have a sustained effect on glycaemic control; however, reductions in LDL cholesterol and insulin dose requirement per unit of bodyweight were observed.[36]

In a previous study, the author's group has reported similar prevalence of MS in Indian children and youth with T1D as in otherwise healthy Indian school children without T1D. Besides, low HDL was found to be the commonest abnormal component of MS in Indian children and youth with and without T1D.[8,37] We therefore believe metformin may have a role in the improvement of HDL levels besides improving insulin sensitivity in subjects with T1D and hence may be useful in the prevention of the development of double diabetes in Indian adolescents with T1D. Inability to perform clamp study to measure insulin sensitivity, small sample size, poor glycaemic control of the study group, lack of data on diet and physical activity, lack of data on adiponectin levels and insulin carbohydrate ratio, short period of follow-up and recruiting study participants from single centre are the limitations of the present study.

In conclusion, lifestyle modifications along with adding metformin as an adjunct to standard insulin therapy for 3 months in Indian adolescents with T1D improved insulin sensitivity and may be useful for the prevention of double diabetes.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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