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OPEN ACCESS

Archives of Pediatrics

Sunil B, et al. Arch Pediatr 4: JPED-172.

DOI: 10.29011/2575-825X.100172

Research Article

Postprandial Hyperglycemia in Insulin-Treated Adolescents with Type 2 Diabetes

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Citation: Sunil B, Barr MM, Kuo HC, Aban I, Ashraf A (2019) Postprandial Hyperglycemia in Insulin-Treated Adolescents with Type 2 Diabetes. Arch Pediatr 4: 172. DOI: 10.29011/2575-825X.100172

Received Date: November 06, 2019; **Accepted Date:** November 13, 2019; **Published Date:** November 18, 2019

Abstract

Treatment of Type 2 Diabetes (T2DM) in adolescents is challenging due to limited pharmacological options and inadequate therapy adherence.

Objective: This study aimed to evaluate differences in glucose handling and endogenous insulin secretion during a Mixed Meal Tolerance Test (MMTT) in adolescents with T2DM who were treated with metformin alone versus insulin + metformin.

Design/Methods: Cross-sectional study of 15 adolescents with T2DM who were on treatment with metformin alone or insulin + metformin.

Results: There were 10 participants on metformin alone and 5 participants on insulin + metformin. The mean hemoglobin A1C (HbA1C) was higher in the insulin-treated group (7.7 ± 0.85 % for insulin + metformin-treated versus 6.3 ± 1.03 % for metformin-treated groups, p=0.02). The first phase and the overall Area Under the Curve (AUC) glycemic response was significantly higher in the insulin + metformin-treated versus metformin-treated group (6179.50 ± 1394.17 mg/dl/30 min versus 4578.25 ± 689.44 mg/dl/30 min, p=0.028 and 43432.50 ± 11441.51 mg/dl/240 min versus 28256.75 ± 5901.16 mg/dl/240 min, p=0.028). These differences persisted after adjusting for HbA1C (p=0.05) and Body Mass Index (BMI, p=0.01). The corresponding endogenous insulin response measured by AUC C-peptide was lower in the insulin + metformin-treated versus metformin-treated group for both the first phase and overall MMTT (192.59 ± 67.13 pmol/L/30 min versus 300.29 ± 120.94 pmol/L/30 min, p=0.09 and 1599.08 ±708.77 pmol/L/240 min versus 2169.46 ± 798.62 pmol/L/240 min, p=0.12). The mean whole body insulin was lower in insulin + metformin-treated versus metformin-treated group (1.99 ± 0.58 versus 2.77 ± 0.99, p= 0.09).

Conclusions: Glycemic excursion during MMTT in adolescents with T2DM was worse in the basal insulin + metformin-treated group compared to metformin only treated participants, even after adjusting for BMI and HbA1C, indicating the inadequacy of basal insulin and metformin in maintaining glycemic control in adolescents with T2DM.

Keywords: Area Under the Curve Glucose; Endogenous Insulin Production; Insulin Resistance**;** Mixed Meal Tolerance Test, Pediatric Type 2 Diabetes

Abbreviations

AUC	:	Area Under the Curve
BMI	:	Body Mass Index
BP	:	Blood Pressure
HbA1C	:	Hemoglobin A1c
MMTT	:	Mixed Meal Tolerance Test
SD	:	Standard Deviation

T2DM : Type 2 Diabetes

WBISI : Whole Body Insulin Sensitivity Index

Introduction

Type 2 diabetes (T2DM) has become increasingly common in the pediatric age groups, paralleling the worldwide obesity epidemic [1]. Impaired glucose tolerance, prediabetes, and diabetes are considered a continuum in disease progression [2]. It is well established that diminution of first-phase insulin release is an early marker of the decline of β-cell function in individuals destined to develop T2DM. In children with genetic and environmental susceptibility, with the progressive imbalance between the ability of the β-cell to compensate and the degree of Insulin Resistance (IR), further β-cell failure manifests as T2DM [3,4]. Currently, the only medications approved for use in T2DM in children <18 years include metformin, liraglutide and insulin [5,6]. Insulin is hypothesized to provide "rest" to the β-cell when exogenously administered in addition to its effect to achieve euglycemia [7]. According to the 2018 American Diabetes Association (ADA) position statement, insulin treatment is recommended for patients with higher HbA1C ≥ 8.5% [5]. However, insulin, when used at higher doses as required to combat the IR in these children can be associated with weight gain, possibly worsening the underlying IR [8]. It may supplant the role of the β-cell, and while providing rest, may itself suppress - endogenous insulin response [9]. Recent studies have suggested that short term use of long acting basal insulin did not result in improvement in insulin sensitivity or β-cell function during follow up [10].

This study aimed to evaluate if there were differences in glucose response, insulin secretion, insulin sensitivity, and insulinogenic index in response to a Mixed Meal Tolerance Test (MMTT) in adolescent African American (AA) females with T2DM treated with insulin + metformin or metformin alone.

We sought to assess differences in baseline IR profiles between adolescents with T2DM on metformin therapy versus insulin + metformin by using a modified Whole Body Insulin Sensitivity Index (WBISI) adjusted for C-peptide (modified WBISI/ Matsuda Index) [11] Additionally, we evaluated differences in β-cell function by using MMTT–induced insulin secretion (modified insulinogenic index) in adolescents with T2DM on insulin versus metformin therapy by using Δ C-peptide/ Δ Glucose for the first thirty minutes of the MMTT.

Materials and Methods

Participants were 15 adolescents with T2DM identified from a clinical trial conducted at the University of Alabama at Birmingham (UAB) (clinical trial number NCT01325987). Inclusion criteria included AA female participants with known T2DM, body mass index (BMI) ≥85th percentile, Tanner stage ≥ 4, ages between 12-18Y. Exclusion criteria included those on vitamin D, other types of diabetes, use of medication(s) influencing glucose metabolism other than anti diabetic agents, and pregnancy. The protocol for the original study (NCT01325987) involved treatment of vitamin D deficiency in patients with T2DM with 50,000 IU weekly ergocalciferol vs. placebo. Only the baseline characteristics of the participants from the parent study were used for this manuscript.

All the study participants were on a dose of 2 g of metformin daily. The participants on insulin therapy were on a basal insulin dose of up to 0.5 units/kg daily as prescribed by their endocrinologist. Some patients (n=3) were also on a correction factor with short acting insulin. The participants were instructed to continue their current dose of metformin as well as long acting insulin. They were instructed to fast for 12 hours overnight, not to use short-acting insulin for at least 6 hours before the MMTT test. The participants underwent a 4-hr MMTT after a 12 hour fast while continuing the oral hypoglycemic agent and/or the long acting insulin. The MMTT was performed only if the finger-stick blood glucose level was above 70 mg/dL and no higher than 200 mg/dL. If the glucose was outside this range, the MMTT was rescheduled. A Mixed Meal Tolerance Test (MMTT) is considered a surrogate method to evaluate insulin sensitivity and β cell function [12]. Although a hyperinsulinemic euglycemic clamp is the gold standard to study the dynamics of insulin secretion, the MMTT is considered to be reflective of the physiology of food intake including glucose and other nutrients and subsequent metabolic responses.

Fasting blood samples were taken at 15 and 5 minutes before the patient started drinking the liquid meal. At time "zero", the patient consumed the entire liquid meal within 5 minutes of administration. Subsequent post-meal blood draws occurred every 5 minutes for the first thirty minutes, every ten minutes for the next 2.5 hours and every thirty minutes for the next hour. (time points in minutes -15, -5, 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90 100, 110, 120, 130, 140, 150, 160, 170, 180, 210, and 240). All collected blood was processed at the Core Processing Laboratory, and sera subsequently stored at –85° until analysis for glucose and C-peptide. Glucose was assayed using the glucose oxidase method on a Sirrus analyzer (Stanbio, Boerne, TX)

This protocol was approved by the UAB Institutional Review Board for Human Use, and written informed consent was obtained from all the participants before testing.

Analysis of Glucose Homeostasis Measures

The Whole Body Insulin Sensitivity Index (WBISI) was calculated using the formula:

$WBISI_{C\text{-}peptide}$ = 500,000/√ (fasting glucose*fasting C-peptide)*(mean glucose* mean C-peptide) [11]. The area under the curve (AUC) was calculated using trapezoidal estimation. Oral glucose–induced insulin secretion (referred as ΔC-Pep/ΔG) was

calculated as incremental plasma C-peptide (pmol/L) during the first 30 min of the MMTT divided by incremental plasma glucose (mmol/L) during the first 30 min of the MMTT [13,14].

Statistical Analysis

Statistical Analysis was performed using SAS software (version 9.4; SAS Institute, Cary, NC). Descriptive characteristics were reported as means ± SD. Wilcoxon exact tests were performed to compare outcomes between the groups. Linear regression models were used to see if the difference persisted after adjusting for covariates like HbA1C and BMI. A p value of ≤ 0.05 was considered statistically significant for all testing.

Results

A total of 15 adolescents were included in the analysis, 5 in the insulin + metformin-treated and 10 in the metformin only treated group (see Table 1). The two groups did not show significant difference in the variables such as age, BMI, systolic and diastolic blood pressure. The average time since diagnosis was not significantly different between the groups, mean of 22.4 months in the insulin-treated and 19.9 months in the metformin-treated groups. The group treated with insulin + metformin had significantly higher mean HbA1C (7.7 ± 0.85%) compared to metformin-treated groups (6.3 ± 1.03%), p=0.02. 3 patients in the insulin-treated group had HbA1C >8.5% and they were on prandial insulin. Glucose response during the first phase (0 – 30 mins) of the MMTT, represented by mean AUC glucose 0 – 30 min was higher in the insulin-treated compared to metformin-treated group (6179.50 ± 1394.17 mg/dl/30 min versus 4578.25 ± 689.44 mg/dl/30 min, p=0.028). These differences persisted after adjusting for HbA1C (p=0.05) and BMI (p=0.01). Glucose response during the entire duration of the MMTT, represented by mean total AUC glucose 0 – 240 min was higher in insulin-treated compared to metformin-treated groups (43432.50 ± 11441.51 mg/dl/240 min versus 28256.75 ± 5901.16 mg/dl/240 min, p=0.028). Figure 1 illustrates the higher mean glucose response in the insulin + metformin-treated group compared to the metformin-treated group during the MMTT.

	Insulin + metformin group (N=5)	Metformin group (N=10)	p-value
Age (years)	15.20 ± 1.1	14.40 ± 1.71	0.4699
BMI (kg/m²)	40.66 ± 3.76	38.98 ± 6.91	0.3710
BMI Z score	2.52 ± 0.15	2.42 ± 0.33	0.4562
Systolic BP (mm Hg)	121.20 ± 10.4	123.50 ± 6.88	0.9800
Diastolic BP (mm Hg)	65.60 ± 5.6	70.70 ± 9.03	0.3097
HbA1c (%)	**7.70 ± 0.85**	**6.38 ± 1.03**	**0.0250**
Time since diagnosis (months)	22.4 ± 3.2	19.9 ± 2.7	0.76
(BMI- Body Mass Index, BP- Blood Pressure, HbA1C – Hemoglobin A1C) Values are expressed as Mean ± Standard deviation			

Table 1: Descriptive and metabolic characteristics.

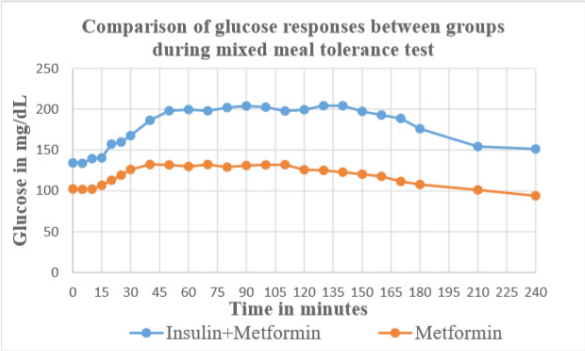

Figure 1: Mean glucose response during the Mixed Meal Tolerance test**.**

Figure 1 depicts higher glycemic response in insulin+ metformin treated group versus metformin only group during standard MMTT (Mixed Meal Tolerance Test).

Table 2 portrays the glucose- C-peptide responses to MMTT. Endogenous first phase insulin release response, represented by AUC C-peptide 0 – 30 min was lower but not statistically different in insulin-treated compared to metformin-treated groups (192.59 ± 67.13 pmol/L/30 min versus 300.29 ± 120.94 pmol/L/30 min, p=0.09). Endogenous overall insulin release, represented by total AUC C-peptide 0- 240 min was lower but not statistically significant in insulin-treated versus metformin-treated group in the first phase (1599.08 ± 708.77 pmol/L/240 min versus 2169.46 ± 798.62 pmol/L/240 min, p=0.12) Figure 2 shows a relatively lower C-peptide secretion (i.e., a lower endogenous insulin response) to the MMTT in the basal insulin-treated group.

	Insulin + metformin group (N=5)		**Metformin group (N=10)**		
	Mean	SD	Mean	SD	**p-value**
First phase AUC $_{\text{glucose 0 - 30}}$	6179.5	1394.1	4578.3	689.4	**0.028**
First phase AUC $_{\text{C peptide 0 - 30}}$	192.59	67.13	300.29	120.9	0.099
Total AUC $_{\text{glucose 0 – 240 min}}$	43432	11441	28256.8	5901.1	**0.028**
Total AUC $_{\text{C peptide 0 – 240 min}}$	1599.1	708.7	2169.5	798.7	0.129
ΔC-peptide $_{\text{0 – 30 min}}$ / Δ Glucose $_{\text{0 – 30 min}}$	690.1	690.4	1467.7	977.2	0.28
WBISI $_{\text{C-peptide}}$	1.99	0.58	2.77	0.99	0.09
AUC: Area Under The Curve; WBISI: Whole Body Insulin Sensitivity Index; SD Standard Deviation					

Table 2: Outcome variables related to glucose homeostasis.

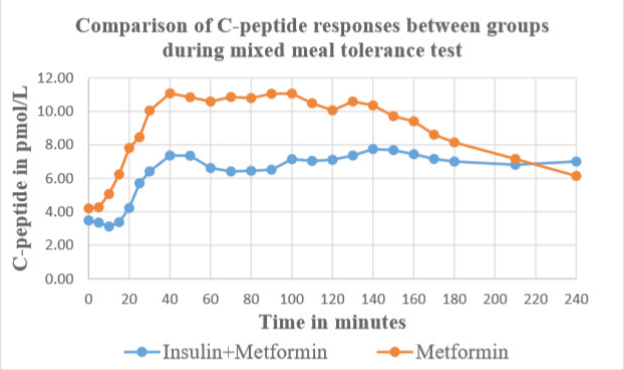

Figure 2: Outcome variables related to glucose homeostasis.

Figure 2 illustrates lower endogenous insulin secretion in insulin + metformin treated versus metformin only group during standard MMTT.Baseline insulin sensitivity profile, calculated by the mean WBISI C-peptide was lower but not statistically significant in insulin-treated versus metformin-treated groups (1.99 ± 0.58 versus 2.77 ± 0.99, p= 0.09)

Discussion

Our study found that glycemic excursion during the MMTT was worse for adolescents with T2DM treated with basal insulin + metformin compared to those treated with metformin alone. The basal insulin + metformin-treated adolescents had a higher AUC glucose in the first phase, in addition to having overall higher glycemic response throughout MMTT, even after adjusting for HbA1C and BMI. This reflects an inadequate first phase and overall endogenous insulin response to the glycemic challenge in the basal insulin-treated adolescents. ADA guidelines recommend that youth with marked hyperglycemia (A1C ≥ 8.5%) be treated initially with basal insulin and to initiate multiple daily injections of basal and pre-meal rapid-acting insulin when glycemic targets are

not achieved [5]. Our study illustrates that blood sugars in response to a meal are significantly higher even at lower HbA1C levels of < 8.5%, and it may be necessary to consider prandial insulin/other therapies to optimize postprandial blood sugar elevations. Moreover, even after insulin + metformin therapy for a mean duration of 22.4 months, glycemic response to a meal was still higher in this group of patients [15].

Metformin and insulin each have been shown to be beneficial in β-cell function in adults with early T2DM, however, the same generalization cannot be made in children [16,17]. It remains unclear if the dysregulation in glucose control in more severe cases of pediatric T2DM is caused purely by a more severe disease state – as indicated with a higher HbA1C – or whether insulin treatment contributes to glycemic dysregulation. There is a component of the dose response effect of insulin demonstrated in adults, where, when used at high basal levels, the side effects like weight gain may outweigh glycemic benefits [8] The lack of adequate pharmacotherapeutic options, combined with the well proven effect of adolescence on worsening IR and poor adherence to lifestyle modifications may contribute to the worse metabolic outcome seen in T2DM in children and adolescents [3,4]. Our data indicates that amendments to the current treatment practices are much needed in children with T2DM. Further research is necessary to evaluate optimal treatment options to achieve euglycemia and β-cell recovery in children with T2DM.

Our study has several limitations. Due to our small sample size we were not able to draw conclusions related to differences in WBISI or insulinogenic index between the groups. All the adolescents in the study were African American girls from a single center, so the results are not easily generalizable. The cross-sectional nature of the data makes it difficult to establish a causal explanation. The variability of duration of illness in our participants, combined with the known silent nature of T2DM makes it difficult to predict endogenous baseline β-cell function. Increased weight gains on insulin, worsening IR and underlying poorer control in the insulin-treated groups are all potential confounders, and although we found a difference in the glycemic response despite controlling for BMI and HbA1C, we recognize that adjusting for HbA1C levels could be inherently problematic, as HbA1C is influenced by glycemic control and resistance.

Conclusions

The adolescents with T2DM who were receiving insulin along with metformin treatment had higher glucose response to a MMTT, even after adjusting for HbA1C levels and BMI, reflecting inferior control of prandial glycemic excursion during meals. These results indicate inadequacy of basal insulin and metformin in maintaining glycemic control in adolescents with T2DM.

Funding Sources

This work was supported by the use of the Minority Health Research Center Grant, 2010-2011, University of Alabama at Birmingham, the Child Health Research Center Grant K12 HD043397 (T0909180013) and the Center for Clinical and Translational Science (5UL1 RR025777).

Ethical Approval

The clinical trial was approved by University of Alabama at Birmingham Institutional Review Board for Human Use.

Informed consent: Written consent was obtained from parents/guardians, and assent from the study participants

Declaration of Competing Interest: The authors declare that they have no conflicts of interest.

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