

CLINICAL QUESTION

What safety and efficacy data exist for metformin use in pediatric patients with Type 2 Diabetes Mellitus?

BACKGROUND INFORMATION

American Diabetes Association Guideline (2015) Recommendations Regarding Children and Adolescents with (or at risk of) Type 2 Diabetes							
<p>Screening to detect Type 2 Diabetes or Pre-diabetes in Asymptomatic Children (Age ≤18yo)¹</p> <p>(Table 2.4, p. S13 in guidelines)</p>	<p>Overweight** or obese + ≥2 additional risk factors</p> <p>Risk Factors:</p> <ul style="list-style-type: none"> • First- or second-degree relative with Type 2 Diabetes • High-risk race/ethnicity: <ul style="list-style-type: none"> -African American -Latino -Native American -Asian American -Pacific Islander • Signs of (or conditions associated with) insulin resistance: <ul style="list-style-type: none"> -Acanthosis nigricans -HTN -Dyslipidemia -Polycystic ovarian syndrome -Small-for-gestational-age birth weight • Maternal h/o diabetes or gestational diabetes during the child's gestation <p>**Overweight =</p> <ul style="list-style-type: none"> • BMI >85th percentile for age and sex, OR • Weight for height >85th percentile, OR • Weight >120% of ideal for height 						
	<p>Begin screening for those at risk at 10yo or at onset of puberty (whichever occurs first)</p>						
	<p>Screen q3yrs for those at risk</p>						
<p>Preferred Diagnostic Test in Children¹</p>	<p>A1c</p> <p>("The ADA acknowledges the limited data supporting A1c for diagnosing diabetes in children and adolescents... Recent studies suggest OGTT or FPG as more suitable...however, validations are not currently available in the pediatric population, so...the ADA continues to recommend A1c in this cohort," p. S12).</p>						
<p>Pre-diabetes¹</p>	<p>A1c 5.7-6.4% (assuming it is the same as it is for adults because delineation btw children and adults not made)</p>						
<p>Diabetes¹</p>	<p>A1c ≥6.5% (assuming it is the same as it is for adults because delineation btw children and adults not made)</p>						
<p>Treatment Goals (across all pediatric age groups)²</p> <p>(Table 11.1, p. S71 in guidelines)</p>	<table border="1"> <tr> <td>A1c</td> <td><7.5% (Lower goals are reasonable if it can be achieved w/o excessive hypoglycemia)</td> </tr> <tr> <td>BG Before Meals</td> <td>90-130 mg/dL</td> </tr> <tr> <td>BG at Bedtime / Overnight</td> <td>90-150 mg/dL</td> </tr> </table> <p><i>Note: These goals are listed as pertaining to Pediatric Patients with Type 1 Diabetes, but separate goals are not provided for Pediatric Patients with Type 2. Therefore, it is hereby assumed that the Type 2 goals would be the same as the Type 1 goals.</i></p>	A1c	<7.5% (Lower goals are reasonable if it can be achieved w/o excessive hypoglycemia)	BG Before Meals	90-130 mg/dL	BG at Bedtime / Overnight	90-150 mg/dL
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<p>Exercise and Children with Diabetes or Pre-diabetes³</p>	<p>Engage in at least 60 mins of physical activity / day</p> <ul style="list-style-type: none"> • 3 of those days should include vigorous-intensity aerobic activity, muscle-strengthening activities, and bone-strengthening activities 						
<p>Treatment of Type 2 DM^{2,4}</p>	<p>The current guidelines do not provide a step-wise approach to managing T2DM in the pediatric patient like they do for the adult patient. They refer clinicians to an ADA consensus report published in 2000, which at the time of its publication, insulin was the only drug approved by the FDA for treatment of diabetes in children (metformin had not yet been approved for use in children).</p>						



Highlights from the 2000 ADA Consensus Statement regarding treatment of children with T2DM:

- Since the pathophysiology of T2DM in children and adolescents appears to be similar to adults, it is assumed that oral agents approved for adults will also be effective in children
- Lifestyle (diet, exercise, self-monitoring of BG)
- Metformin (1st-line oral agent)
-“Because most pediatric patients with T2DM are at or near adult weight, it is reasonable to use the doses recommended for adults.”⁴
- Insulin → add on to metformin if metformin tx does not achieve goals
- Insulin secretagogues (Sulfonylureas, Meglitinides) → add on to metformin if metformin tx does not achieve goals

Metformin and insulin are the only FDA-approved drugs for management of Type 2 Diabetes Mellitus in the pediatric population. Metformin is labeled for use in patients aged 10 years and up.

Metformin (MOA)⁵

- Therapeutic Class: Biguanide
- Decreases glucose output from liver
- Enhances sensitivity to insulin (at liver and muscle cells) → encourages glucose uptake and utilization
- Approved on 12/15/2000 for use in pediatric patients age 10-16⁶

SEARCH STRATEGY

The following resources were utilized to prepare an answer to this clinical question:

- PubMed database (using search terms [metformin AND children], [metformin AND pediatric], and [metformin AND children AND type 2 diabetes])
- Drugs@FDA (U.S. Food and Drug Administration) → gave approval history of metformin for use in pediatrics
- American Diabetes Association clinical practice guidelines and consensus statements
- Lexi-Comp® online database → Metformin’s mechanism of action and approved labeled indications

CRITICAL APPRAISAL	
Title of Article	A clinical trial to maintain glycemic control in youth with type 2 diabetes: TODAY study group (TODAY = Treatment Options for Type 2 Diabetes in Adolescents and Youth)
Authors	Zeitler P, Hirst K, Pyle L, et al.
Journal / Citation	<i>N Eng J Med.</i> 2012; 366: 2247-56
Justification of the research	<p>Type 2 diabetes in youth is increasing in prevalence. However, there is little data that guides treatment options in this cohort.</p> <p>No large-scale randomized intervention trials with T2DM in children had been conducted prior to this study⁹</p> <p>Youth with T2DM will likely have a long duration of disease (and hence, comorbidities that come with it)</p> <p>Insulin resistance is often a characteristic of puberty (albeit transient), but makes treating this patient population even more difficult</p>
Purpose / Objective	<p>To compare the efficacy and durability of three treatment regimens for glycemic control in children and adolescents with recent-onset Type 2 diabetes mellitus</p> <p>Stated Hypothesis: "combination therapy initiated early in the course of youth-onset type 2 diabetes would maintain acceptable glycemic control better than metformin alone" (p. 2248).</p> <p>Does more aggressive therapy for adolescents with T2DM improve their health outcomes?⁹</p>
Funding	<p>National Institute of Diabetes and Digestive and Kidney Diseases (National Institutes Health)</p> <p>Study drugs donated by GlaxoSmithKline, but they had no role in the design, data collection, or analysis of the study</p>
METHODS	
Trial Design	Multi-center, randomized, double-blind, efficacy trial
Study Dates	July 2004 – February 2011 (ensured a minimum of 2yr f/u for each participant)
Interventions	<p>Metformin 1000mg BID Metformin 1000mg BID + Rosiglitazone 4mg BID Metformin 1000mg BID + Intensive lifestyle intervention program</p> <p>All study medication was encapsulated to ensure blinding All participants received 2 capsules BID (metformin, rosiglitazone, and / or placebo)</p> <p>Intensive lifestyle intervention program:</p> <ul style="list-style-type: none"> • Personal activity and nutrition leader provided to each child in this tx group • In-person contact provided weekly for 1st 6 months; then bimonthly x6months, then monthly for remainder of pt's participation in the study • Each visit lasted 45-60 mins • Dietary, physical activity, and behavior modifications • "Traffic-light eating plan" (Foods divided into Red, Yellow, and Green categories; limit foods in red category, eat more foods in green category, etc.) • Calorie intake recommendations were individualized to facilitate weight loss (1200-1500 cal/day) • Exercise 200-300 min/week (moderate-intensity) (=3hr, 20mins – 5 hrs) • Parent / guardian also played an active role in helping their child (critical component) <p>Run-in phase of 2-6 months for all study participants:</p> <ul style="list-style-type: none"> • wean study participants from non-study diabetes meds • initiate metformin and titrate up to 500-1000mg BID • attain glycemic control with metformin alone for at least 2months (defined as A1c <8%, measured monthly) • provide standard diabetes education and ensure mastery of material • confirm adherence to study meds, attendance at scheduled visits
Inclusion Criteria	<p>Age 10-17 yo Type 2 Diabetes diagnosis for < 2 years (diagnosis defined by American Diabetes Association 2006 criteria):⁸</p> <ul style="list-style-type: none"> • FPG ≥ 126 mg/dL

	<ul style="list-style-type: none"> • 2h PG during OGTT \geq 200 mg/dL • Classic symptoms of hyperglycemia + random PG \geq200 mg/dL (polydipsia, polyuria, unexplained weight loss) • (Note: At that time, A1c was not recommended for use in diagnosis) <p>BMI \geq 85th percentile for age and sex Negative test for diabetes-related autoantibodies (if present, would have indicated a Type 1 picture) Availability of an adult caregiver willing to actively support study participation</p>
Exclusion Criteria ⁹	<p>CrCl <70mL/min LFTs >2.5 ULN DKA at any time after initial diagnosis (exception: could have 1 episode related to a significant medical illness) Use of any of the following medications:</p> <ul style="list-style-type: none"> • Inhaled glucocorticoids >1000 micrograms of fluticasone equivalent / day • Oral glucocorticoids w/in last 60 days OR been on for >20 days during the past year • Anabolic steroids w/in the past 60 days • Those known to affect insulin sensitivity or secretion w/in the last 30 days • Those known to cause weight gain w/in the last 30 days • Weight loss medications w/in the past 30 days • Those known to affect the metabolism of study drug <p>Participation in a formal weight loss program Abnormal reticulocyte count or abnormal hemoglobin variants (can skew A1c results) Genetic syndrome or disorder known to affect glucose Inability of either participant or family member to comprehend the lowest grade level at which lifestyle intervention materials were written Pregnant girls or planning to become pregnant w/in 2years of enrollment or girls who admit to sexual activity w/o appropriate contraception Psychiatric or development disorders that would prevent full participation Physical limitations preventing patient from being randomized to lifestyle intervention program</p>
Primary Outcome	<p>Time to treatment failure (=time to loss of glycemic control)</p> <ul style="list-style-type: none"> • A1c \geq8% for 6 consecutive months OR • Inability to wean participant from insulin within 3 months of starting insulin for an acute metabolic decompensation episode, illness, hospitalization, etc. <p>Note: All patients will have been at A1c goal of <8% during Run-In phase with metformin</p> <p>Authors state that the primary outcome of treatment failure was chosen as opposed to differences in A1c levels among treatment groups because it is more representative of clinical practice (i.e., when a patient's A1c remains elevated on one particular regimen, you either add on an additional agent or try new agents, not continue the current regimen).</p>
Other Outcome Measures	<p>Serious adverse events:</p> <ul style="list-style-type: none"> • Severe hypoglycemia • DKA • Lactic acidosis
Statistical Analyses	<p>Time to primary outcome (=treatment failure) analyzed using time-to-event survival methods</p> <ul style="list-style-type: none"> • Time of failure entered as an interval during which failure was known to have occurred, rather than the exact date of failure (unknown) • For patients w/o tx failure, total amount of time spent in the study was entered (=time to last visit) <p>Intention-to-treat utilized (=all randomized patients were included in analysis)</p> <p>1^o Outcome:</p> <ul style="list-style-type: none"> • Alpha = 0.05; Corrected Alpha = 0.0167 (to account for pair-wise comparisons btw the 3 tx groups) • Power = 90% <p>2^o Outcomes:</p> <ul style="list-style-type: none"> • Alpha = 0.05 (but no correction / adjustments made for multiple subgroup analyses – stated by author; results should be considered exploratory)

RESULTS

<p>Enrollment / Assignment</p>	<p>699 children underwent randomization (from 13 different clinical centers)</p> <ul style="list-style-type: none"> • Metformin alone: 232 • Metformin + rosiglitazone: 233 • Metformin + lifestyle intervention program: 234 • Note: A minimum of 684 patients (228 / treatment arm) was needed to provide 90% power to detect a 40-50% reduction in failure rates between metformin alone group and one of the combination groups; investigators set out to get 250 / tx arm to account for a 10% dropout rate⁹ 1.1(x) = 250; x=227.3; 228(3) = 684 Thus, the trial was powered with the appropriate number of patients <p>July 2004 – February 2009</p> <p>Mean duration of Type 2 diabetes in the cohort = 7.8 months</p> <p>Block randomization utilized: Patients randomly assigned to treatment group on a 1:1:1 basis, with a block size of 9</p>																																																					
<p>Monitoring</p>	<p>Length of time participants were followed:</p> <ul style="list-style-type: none"> • Mean 3.8 yrs • Max 6.5 yrs <p>Medical visit q2months in the 1st year, then q3 months thereafter to obtain:⁹</p> <ul style="list-style-type: none"> • A1c • Adherence to medication regimens: pill counts (target = 80% adherence) • Ht, Wt, BMI, % Body Fat • BP • Safety / documentation of all adverse events (severe hypoglycemia episodes, GI complaints, edema, weight gain) • 7-day diet recall • Physical activity (obtained from patient’s accelerometer) • Lab work (Hbg, Hct, LFTs, CrCl, Lipids) • Avg BG over past 14 and 30 days (BG meters downloaded; patients instructed to self monitor blood glucose 2x/day – when wake up in morning and one additional time) <p>Microalbumin/creatinine ratio from spot urine: at randomization and then annually</p>																																																					
<p>Baseline Characteristics¹⁰</p>	<p>No statistical difference in baseline characteristics between tx groups</p> <table border="1" data-bbox="365 1249 1502 1816"> <thead> <tr> <th><i>Baseline characteristic</i></th> <th><i>Mean Value Overall</i></th> <th><i>Our Patient</i></th> </tr> </thead> <tbody> <tr> <td>Age at randomization</td> <td>14 yo</td> <td>11 yo</td> </tr> <tr> <td>% Female</td> <td>65%</td> <td>Male</td> </tr> <tr> <td>Hispanic</td> <td>40%</td> <td rowspan="3">White</td> </tr> <tr> <td>African American</td> <td>30%</td> </tr> <tr> <td>White</td> <td>20%</td> </tr> <tr> <td>Household Income <\$25,000</td> <td>42%</td> <td rowspan="2">Unknown</td> </tr> <tr> <td>Household Income \$25,000-49,999</td> <td>34%</td> </tr> <tr> <td>FH of diabetes</td> <td>60%</td> <td>Mother has</td> </tr> <tr> <td>Duration of diagnosis</td> <td>7.8 months</td> <td>Since 8/2014 = 5 months</td> </tr> <tr> <td>BMI</td> <td>34.9</td> <td>31.3</td> </tr> <tr> <td>BMI Z-score</td> <td>2.15 (2.23 +/- 0.47)</td> <td>2.35</td> </tr> <tr> <td>A1C</td> <td>5.9 (7.1 +/- 2.2)</td> <td>6.2 (down from 6.8)</td> </tr> <tr> <td>LDL</td> <td>83</td> <td>93</td> </tr> <tr> <td>HDL</td> <td>38</td> <td>43</td> </tr> <tr> <td>TG</td> <td>94</td> <td>206</td> </tr> <tr> <td>CrCl (estimated) mL/min</td> <td>147</td> <td>226</td> </tr> <tr> <td>BP ≥90th percentile</td> <td>26%</td> <td rowspan="2">Diastolic was 95th percentile</td> </tr> <tr> <td>BP ≥95th percentile</td> <td>14%</td> </tr> </tbody> </table>	<i>Baseline characteristic</i>	<i>Mean Value Overall</i>	<i>Our Patient</i>	Age at randomization	14 yo	11 yo	% Female	65%	Male	Hispanic	40%	White	African American	30%	White	20%	Household Income <\$25,000	42%	Unknown	Household Income \$25,000-49,999	34%	FH of diabetes	60%	Mother has	Duration of diagnosis	7.8 months	Since 8/2014 = 5 months	BMI	34.9	31.3	BMI Z-score	2.15 (2.23 +/- 0.47)	2.35	A1C	5.9 (7.1 +/- 2.2)	6.2 (down from 6.8)	LDL	83	93	HDL	38	43	TG	94	206	CrCl (estimated) mL/min	147	226	BP ≥90 th percentile	26%	Diastolic was 95 th percentile	BP ≥95 th percentile	14%
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<p>Withdrawal or lost to f/u</p>	<p>Metformin alone: 15 Metformin + rosiglitazone: 20 Metformin + lifestyle intervention program: 15 Note: Since ITT analysis was utilized, these patients were still included in final analysis</p>																																																					

Results: Primary Endpoint

Tx Group	# that reached 1 ^o Outcome (= # that failed)	% that reached 1 ^o Outcome (% of total participants) ABSOLUTE RISK	% that reached 1 ^o Outcome (% of all failures)	% that reached 1 ^o Outcome (% of that treatment group)
Overall	319	319/699 → 45.6%	---	---
Met alone	120	120/699 → 17.2%	120/319 → 37.6%	120/232 → 51.7%
Met + Rosi	90	90/699 → 12.8%	90/319 → 28.2%	90/233 → 38.6%
Met + Lifestyle	109	109/699 → 15.6%	109/319 → 34.2%	109/234 → 46.6%

Difference in 1^o outcome was statistically significant between Met alone and Met+Rosi groups (P=0.006)

Absolute Risk Reduction btw Met alone and Met + Rosi groups = 17.2-12.8 = 4.4%

NNT = 1/0.044 = 23 → Need to treat 23 patients with Met + Rosi for approx. 3.8 years to prevent 1 treatment failure, compared to metformin alone

Relative Risk = 0.128/0.172 → 74.4% → Patients treated with Met + Rosi were 74% as likely (or 26% LESS likely) to experience treatment failure, compared to metformin alone

Met + Rosi group had greatest # of patients w/o glycemic failure (=lowest failure rates)

Metformin alone had least # of patients w/o glycemic failure (=highest failure rate)

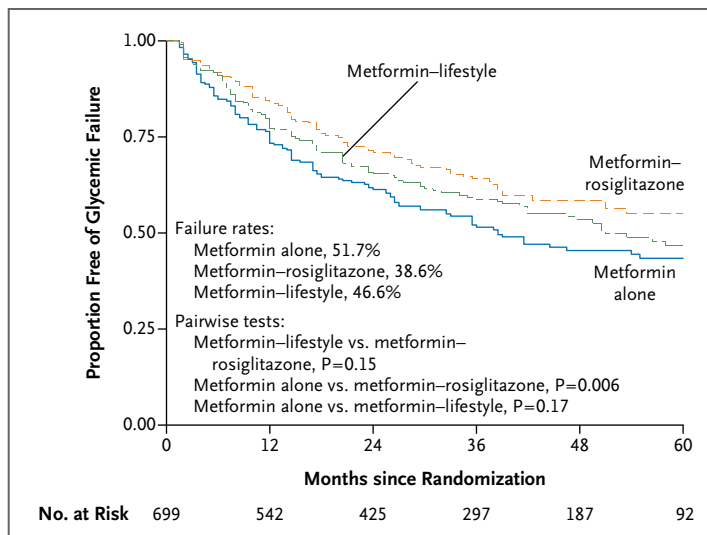


Figure 2. Overall Primary Outcome Results.

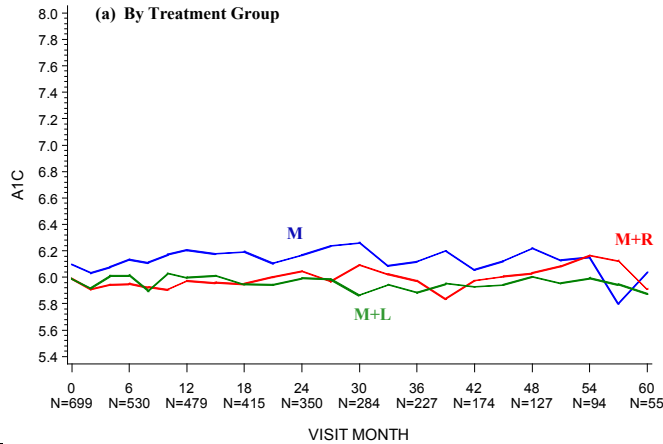
Survival curves for freedom from glycemic failure are shown. Data are shown for up to 60 months of follow-up (accounting for 98.4% of cases of glycemic failure), although the rates and analysis are based on the complete data set.

Although not statistically significant, could be clinically significant:

- Combining intensive lifestyle modifications with metformin had slightly less treatment failure than metformin alone

Metformin alone had highest mean A1c over the study duration

APPENDIX E. Figures of Mean A1c Over Time in Study (all values prior to failure)



Results: Other Endpoints

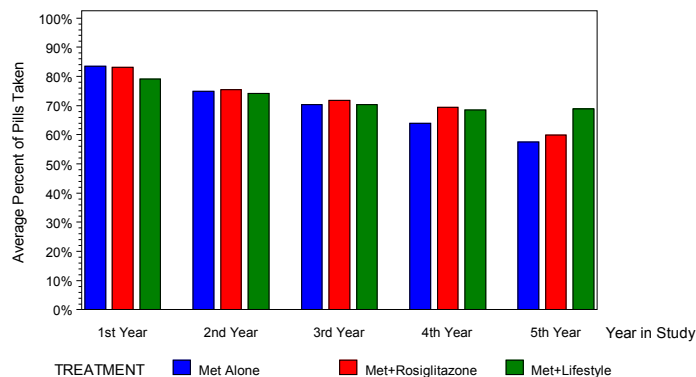
Adherence

- 84% at month 8, 57% at month 60
- No statistical significance found between tx groups for adherence
- When analysis of primary outcome included only adherent patients, the results remained the same

Although adherence waned over time, the decrease was fairly consistent across tx groups

Interestingly, there may have been better adherence in the lifestyle group by the end of the study

APPENDIX G. Medication Adherence Over Time in Study by Treatment Group



BMI

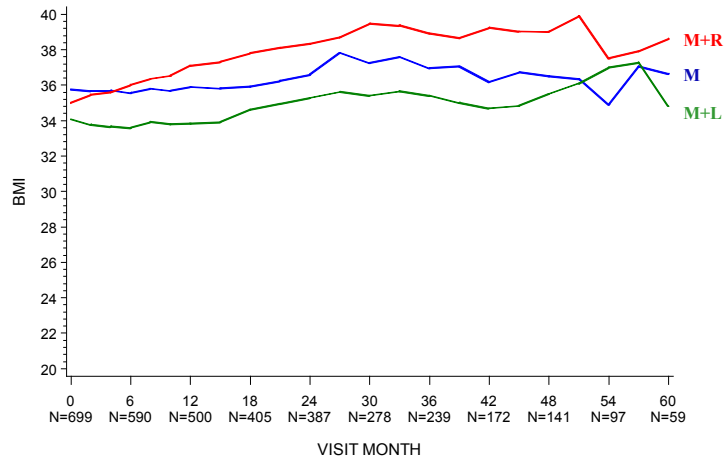
- Differences were significantly different among tx groups ($p < 0.001$; but remember, authors did not control for multiple comparisons)
- Met + Rosi group had greatest increase in BMI, % overweight, and increase in fat mass during tx duration

✓ TDZs like Rosiglitazone are known for causing weight gain

- Met + Lifestyle group had least increase in BMI and % overweight during tx duration
- Authors state: "Neither BMI at baseline or BMI over time was a determinant of treatment failure" (p. 2251).

Met + Rosi group had greatest BMI values over the study

APPENDIX F. Figure of Mean BMI Over Time in Study by Treatment Group (all values prior to failure)



Cardiovascular Risk Factors (HTN, Dyslipidemia, Microalbuminuria)

- Proportion of patients with these risk factors increased over time throughout the study amongst all treatment groups
- No significant differences across treatment groups found for identification of NEW risk factors during treatment
- However, slightly fewer cases of HTN, elevated LDL, and microalbuminuria developed in the Met + Lifestyle group could be clinically significant

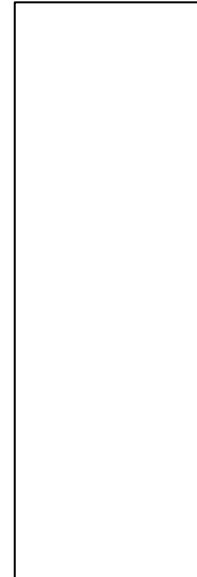


Table 1. Major Coexisting Conditions at Baseline and during the Study, According to Treatment Group.*

Condition	Overall (N = 699)	Metformin Alone (N = 232)	Metformin plus Rosiglitazone (N = 233)	Metformin plus Lifestyle Intervention (N = 234)
<i>number of participants (percent)</i>				
Hypertension				
Cases at baseline	81 (11.6)	28 (12.1)	27 (11.6)	26 (11.1)
New cases during study	155 (22.2)	57 (24.6)	53 (22.7)	45 (19.2)
Dyslipidemia				
Elevated LDL cholesterol				
Cases at baseline	23 (3.3)	9 (3.9)	8 (3.4)	6 (2.6)
New cases during study	49 (7.0)	18 (7.8)	16 (6.9)	15 (6.4)
Triglyceridemia				
Cases at baseline	127 (18.2)	51 (22.0)	38 (16.3)	38 (16.2)
New cases during study	70 (10.0)	20 (8.6)	28 (12.0)	22 (9.4)
Microalbuminuria				
Cases at baseline	44 (6.3)	21 (9.1)	8 (3.4)	15 (6.4)
New cases during study	72 (10.3)	25 (10.8)	27 (11.6)	20 (8.5)

	<p>Serious Adverse Events (hypoglycemia, DKA, or lactic acidosis)</p> <ul style="list-style-type: none"> No significant differences found across treatment groups <p>Other Adverse Events:¹¹</p> <ul style="list-style-type: none"> Statistically significant: <ul style="list-style-type: none"> ✓ Met + Rosi group had fewer GI complaints ($p = 0.018$) ✓ Met + Rosi had fewer cases of elevated LFTs ($p=0.005$) (Some of the TZDs have been known to cause hepatotoxicity, so this was a promising finding) Met + Rosi group had very low rates of peripheral edema (1.7%) and was not significantly different than the other tx groups. Zero deaths 19 Serious Adverse Events (all similar across tx groups) <ul style="list-style-type: none"> ✓ Severe hypoglycemia (n=5) ✓ DKA (n=12) ✓ Lactic Acidosis (n=1) 	<p>HTN defined: $\geq 130/80$ mmHg</p> <p>Dyslipidemia defined: LDL ≥ 130 or TG ≥ 150</p> <p>Microalbuminuria defined: Alb/Cr ≥ 30</p>
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AUTHORS' CONCLUSIONS

Metformin monotherapy provided lasting glycemic control in only 50% of the patients randomized to this group; this is lower than what is seen in adults with T2DM. This may be due to biological or pathological differences between adults and children with T2DM (more studies needed).

Metformin + Lifestyle Intervention helped with weight loss, but was statistically no better than metformin alone for sustained glycemic control

Metformin + Rosiglitazone combination seems to provide more durable glycemic control than metformin alone in children, despite small increases in BMI and fat mass. More studies are needed to determine if this is a class effect of TZD's, specific to rosiglitazone, or a synergistic effect between the 2 agents.

The rates of peripheral edema in children treated with rosiglitazone were lower than in adult populations and hepatotoxicity may not be an issue with pediatric use of rosiglitazone.¹¹

Although no fractures or changes in bone mass were observed in this study with rosiglitazone, by no means should one assume that this risk does not exist in children (rosiglitazone carries a warning regarding fracture risk, among other things).

In terms of safety, all three treatment groups were safe and well-tolerated. The addition of rosiglitazone may help lower GI side effects associated with metformin.

The majority of children with T2DM may require dual therapy for glycemic control.

STRENGTHS / LIMITATIONS

Strengths:

- ITT analysis strengthens external validity of results (more representative of real-world setting); harder to find statistical differences in ITT, so since differences were found, conclusions are more trustworthy
- Large cohort, multi-center, relatively long duration
- Run-in phase allowed for leveling the playing field while still remaining ethical (metformin given as standard of care)
- ITT group met pre-specified statistical power requirement
- Controlled for pair-wise testing (alpha threshold re-set at 0.0167)
- Sample size met statistical power requirement (if there was a difference to be found, it was powered to be found)
- Large, multi-center, and relatively long duration

Limitations / Weaknesses:

- Could not ascertain how drop-outs were handled since ITT was utilized (was it Last Observation Carried Forward? Worst case scenario?)
 - ✓ If LOCF was utilized, this could have shown better outcomes (less failure rates) for one particular tx group because the goal of the trial was focused on durability of glycemic control
 - ✓ If Worst-case scenario was utilized (assumed drop-outs met the 1^o outcome of treatment failure), this could have shown worse outcomes for one particular tx group)
- Rosiglitazone carries a BBW for heart failure exacerbation and several other warnings / precautions which may make providers hesitant to use this agent in children until more studies are carried out
- Rosiglitazone, although helped achieve more durable glycemic control, was associated with weight gain, which may make efforts to help these children lose weight more difficult
- The intensive lifestyle therapy provided in this study may not be an affordable, easily implementable option in the real-world setting

OTHER NOTABLE STUDIES

Effects of metformin on energy intake and satiety in obese children (Adeyomo et al.)

- RCT, double-blind, placebo-controlled
- 6 months
- Metformin 1000mg BID
- N=84 obese children w/ hyperinsulinemia, aged 6-12 yo (n=45 metformin; n=39 placebo)
- Children were allowed to eat what they wanted from standardized food trays on 2 separate occasions before and then 6 months after being on metformin
- Energy intake (kcalories) were recorded, children rated their hunger, fullness, and desire to eat

	Metformin	Placebo	P value
Reduction in calorie intake (kcal)	-104.7	+144.2	0.034
Ratings of hunger	-1.5	18.6	0.013
Ratings of fullness	+10.1	-12.8	0.01

- Metformin significant decreased perception of hunger, resulting in less food intake in obese children. This is the likely mechanism by which it decreases body weight in overweight children and may help prevent progression to pre-diabetes / diabetes.

Review Article by Boland et al.

- Several small clinical trials exist that suggest metformin has the ability to lower BMI in obese pediatric and adolescent patients. (table below adapted from Boland review article)

Study	Design	Duration	Population	# of pts	Dose of Metformin	ΔBMI (kg/m ²) in Met group P<0.05	ΔWt (kg) in Met group P<0.05
Freemark and Bursey (2001)	R, DB, PC	6 months	12-19 yo	29	500mg BID	-0.5	(not reported)
Srinivasan et al (2006)	R, DB, PC, crossover	6 months	9-18 yo	22	1000 mg BID	-1.26	-4.35
Atabeck et al (2008)	R, DB, PC	6 months	9-17 yo	120	500 mg BID	-1.8	-3.4
Clarson et al (2009)	R, controlled, parallel grp	6 months	10-16 yo	25	1500 mg QD	-1.8	(not reported)
Wilson et al (2010)	R, DB, PC, MC	48 weeks	13-18 yo	77	?	-0.9	(not reported)
Rezvanian et al (2010)	R, triple-masked, PC	12 weeks	10-18 yo	135	1500 mg QD	-1.1	(not reported)
Yanovski et al (2011)	R, DB, PC	6 months	6-12 yo	100	1000 mg BID	-0.78	-1.47
Kendall et al (2013)	R, DB, PC	6 months	8-18 yo	151	1500 mg QD	-1.07	-2.6

BEST AVAILABLE ANSWER

The pediatric patient with Type 2 Diabetes represents a unique challenge. Due to early age of disease onset, these patients are exposed to risks for longer periods of time. Thus, it may behoove providers to pursue more aggressive treatment at the outset. Few trials exist which evaluate how to best treat these patients. Metformin and insulin are the only two drugs which carry FDA approval for use in children. All treatment groups in the TODAY study seemed to have a positive safety profile, but it also suggests that metformin monotherapy may not be sufficient to provide lasting glycemic control in the pediatric population and that the addition of a second agent may be necessary. Short of introducing insulin, a second agent would have to be used off-label. Although not statistically different from metformin monotherapy, adding an intensive lifestyle modification program to metformin did provide some benefit with glycemic control. Rosiglitazone may be a safe add-on agent to use in children and may even help to reduce some GI side effects that are associated with metformin.

NARRATIVE OF THE PROCESS

I set out on this project with the goal of finding data to support metformin use in children, and actually discovered that although it carries an FDA approval for use in children with T2DM, it may not provide sufficient glycemic control by itself. A second agent may need to be utilized to help achieve glycemic targets and prevent diabetes complications over the long-term.

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