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Brief Report: Metabolic Syndrome is Common and Persistent in Youth-Onset Type 2 Diabetes: Results from the TODAY Clinical Trial

Ruth S. Weinstock, MD PhD,
Dept of Medicine, SUNY Upstate Medical University, Syracuse NY

Kimberly L. Drews, PhD,
Biostatistics Center, George Washington University, Rockville, MD

Sonia Caprio, MD,
Dept of Pediatrics, Yale University, New Haven, CT

Natasha I. Leibel, MD,
Naomi Berrie Diabetes Center, Columbia University Medical Center, New York, NY

Siripoom Vudhipoom McKay, MD,
Dept of Pediatrics, Baylor College of Medicine, Houston, TX

Philip S. Zeitler, MD PhD, and
Dept of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, CO

for the TODAY Study Group

Abstract

Objective—To examine the prevalence of metabolic syndrome (MetS) in youth-onset type 2 diabetes in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study.

Methods—Prevalence of MetS (ATP III definition) was compared at baseline (n=679), 6 (n=625) and 24 months (n=545) using chi-square tests. Laboratory data were examined between MetS classifications at each time point using ANOVA.

Results—Baseline prevalence of MetS was 75.8% and did not differ by treatment group or change over time. MetS was more common in females (83.1%) than males (62.3%; p<0.0001) at baseline; this difference persisted over 24 months. Prevalence of MetS was similar between ethnic groups at baseline, but greater in Hispanics (82.7%) vs non-Hispanic Whites (67.5%; p=0.0017) and non-Hispanic Blacks (72.7%;p=0.0164) at 24 months. Although MetS was common in participants with A1c <7.0% (74.4% at baseline; no significant change over 24 months), it was more common in those who did not maintain glycemic control at 6 months (80.3%; p=0.0081). Elevated c-reactive protein, ALT, IL6 and PAI-1 levels were more frequent with MetS.

Conclusions—Persistent high prevalence of MetS in youth-onset diabetes, even with excellent glycemic control, is of concern given the associated increased cardiovascular risk.

Corresponding Author: Kimberly L. Drews, PhD, 6110 Executive Blvd, Suite 750, Rockville, MD 20882, Phone: 301-881-9260, Fax: 301-881-6737, kdrews@bsc.gwu.edu.

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Keywords

metabolic syndrome; type 2 diabetes; pediatrics

Introduction

With increasing abdominal obesity, the prevalence of the metabolic syndrome (MetS) has reached alarming levels in youth. In 2008, the prevalence of MetS in eighth grade students was 9.5% (1). It is estimated that 19–35% of youth with obesity have MetS compared with <2% of those with normal BMI (2). In youth with type 2 diabetes in the SEARCH for diabetes in youth study, the prevalence of MetS was 92% (3). This is similar to the prevalence of MetS in adults with type 2 diabetes (94%) in the LOOK Ahead study (4–5). The course of MetS over time in youth-onset type 2 diabetes has not been well-studied.

Since the cluster of risk factors that define MetS is associated with developing vascular disease in adulthood, a better understanding of MetS in the growing population of adolescents with type 2 diabetes is important. This can help direct development of new prevention and treatment strategies to reduce cardiovascular risk. Although lifestyle intervention did not reduce cardiovascular events in adults (4–5), it is possible that a longer period of time may be needed to observe an effect. Intervening in childhood may be of benefit (6).

The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study is the first large intervention study in youth-onset type 2 diabetes. This multicenter multiethnic trial randomized youth (n=699, ages 10–17 years) with recent onset of diabetes to receive metformin, metformin + intensive lifestyle intervention or metformin + rosiglitazone (7–9). The intensive lifestyle approach did not result in superior glycemic control or weight loss compared to metformin alone (8). Hypertension and dyslipidemia were common (10–11). The diagnosis and treatment of co-morbidities was previously described (10–11). In this report we describe the overall prevalence of MetS at baseline and over time, and examine effects of treatment approach, sex, race/ethnicity and glycemic control on MetS.

Methods and Procedures

The TODAY study design has been previously described (7–9). Presence of MetS was determined using adult ATP III criteria without modification (12) since many youth during the study became ≥18 years of age. Since all youth had diabetes, 2 of the following 4 criteria were needed: abdominal obesity [>102 cm (males); >88 cm (females)], triglycerides >150 mg/dl fasting or lipid-lowering drug treatment, low HDL-cholesterol [<40 mg/dl (males); <50 mg/dl (females)] and blood pressure ≥130/85 mm Hg or anti-hypertensive drug treatment.

Prevalence of MetS was determined at baseline, 6 and 24 months overall, and by treatment, sex, race/ethnicity, hemoglobin A1c (A1c) and primary outcome status by frequency and percent. Comparisons were performed using chi-square tests. Pairwise comparisons were conducted when the overall test for >2 categories was statistically significant. Frequencies

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and percents were calculated for each of the four criteria used in determining MetS status in the youth classified as having MetS at each time point. Mean A1c, liver function and inflammatory markers were compared between the groups with and without MetS at baseline, 6 and 24 months using ANOVA methods. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

MetS was common (75.8% of participants) and persistent, with no overall change in prevalence or incidence over 24 months (p=0.8902; Table 1). The prevalence of MetS and its components (except for waist circumference at baseline) did not differ significantly between treatment groups at baseline, 6 months and 24 months. MetS was more common in females than males and this difference continued over 24 months. The factors primarily responsible for this difference were the increased prevalence of abdominal obesity and low HDL-cholesterol concentration in females (Table 2). The prevalence of MetS did not differ by race or ethnicity at baseline or 6 months, but at 24 months was highest in Hispanics (82.7%), lowest in non-Hispanic Whites (67.5%) and intermediate in non-Hispanic Blacks (72.7%); no statistical difference was found between non-Hispanic Blacks and non-Hispanic Whites. As previously described in the TODAY study and in a study of MetS in youth with and without diabetes, non-Hispanic Blacks had lower triglyceride levels (11,13). Hispanic participants had the greatest prevalence of low HDL-cholesterol levels (Table 2).

From baseline to 6 months, 39 participants developed MetS, with changes in obesity, triglycerides and HDL-cholesterol contributing similarly (the onset of elevated blood pressure occurred in only 4 subjects). For those who developed MetS from 6 to 24 months (n=41), all 4 risk factors contributed equally. For the 33 and 34 participants who had resolution of MetS from baseline to 6 months and 6 to 24 months respectively, changes in HDL-cholesterol followed by reduction in abdominal obesity were the major contributors, with little or no change in those developing elevated blood pressure and triglycerides.

The prevalence of MetS is high in these youth with type 2 diabetes regardless of glycemic status (Table 1). MetS was common (74.6%) in youth with type 2 diabetes in excellent glycemic control (A1c <6.0%) at baseline, with no significant change over 24 months (72.1% at 6 months; 70.7% at 24 months, p=0.6403). However, for youth who reached primary outcome (persistent A1c >8%) by the end of the study, MetS was more common at 6 months (80.3%; Table 1) and these youth had approximately 1.5 times the prevalence of elevated triglyceride and elevated blood pressure levels (Table 2). At 24 months, the prevalence of MetS was still high (70.7%) for those with A1c <6.0%, but even higher (83.5%) for youth with A1c 6.0–7.9% (p=0.0174). At baseline, 6 months and 24 months, mean A1c was not different in those with and without MetS, but those with MetS at each time point had higher levels of high sensitivity C-reactive protein (hsCRP), alanine aminotransferase (ALT), interleukin-6 (IL-6) and plasminogen activator inhibitor-1 (PAI-1), the clinical meaning of which is unknown (Table 3).

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Discussion

MetS is common in youth in the TODAY study with type 2 diabetes, and remains highly prevalent over time regardless of glycemic status. For adults who were overweight or obese with type 2 diabetes in the LOOK Ahead study, the prevalence of Met S was higher than in the TODAY youth (overall 94.0%, male 92.9%, female 94.8%) (5). In youth with type 2 diabetes in the SEARCH for diabetes in youth study (3), which examined subjects at one point in time, and used age-adjusted ATP III criteria, there was a higher prevalence of MetS compared to participants in the TODAY study. TODAY used the unmodified ATP III criteria since many youth during the study became ≥18 years of age. Examination of both individual and combinations of cardiovascular risk factors (as described for the MetS regardless of definition used) is important to further our understanding of likelihood of developing cardiovascular disease in the future. Whether type 2 diabetes itself confers greater cardiovascular risk than MetS is unclear. This report is unique in that MetS was examined over time in youth-onset type 2 diabetes.

MetS was more common in females and Hispanics at 24 months. MetS was also seen with increased prevalence in Hispanics in the SEARCH for diabetes in youth study (MetS in 35% Hispanic, 32% African American, 16% non-Hispanic Whites) and in females (23%) compared to males (19%), but only <8% of their study population were youth with type 2 diabetes (3). MetS in childhood has been shown to be associated with elevated levels of the inflammatory markers hsCRP and PAI-1 (14–16), findings confirmed in the TODAY population. The TODAY study excluded youth with any hepatic transaminase concentration >2.5 times the upper limit of normal, but transaminase levels were higher in participants with MetS compared to those without MetS. Elevated alanine aminotransferase, associated with pediatric nonalcoholic fatty liver disease has been reported in other studies of pediatric MetS (17–19). In TODAY, hypertension was common after 3.9 years (33.8%), as was dyslipidemia (23.3% had elevated triglyceride levels and 10.7% had LDL-cholesterol >130 mg/dl or using lipid-lowering drugs at 3 years) (10–11). These are major contributors to MetS. Poor glycemic control is known to be associated with higher triglyceride concentrations.

The prevalence of MetS did not change in the youth in the TODAY study with an intensive lifestyle intervention. Whether greater duration or intensity of physical activity and/or better weight loss can reduce this high prevalence of MetS will require further study. The complex clustering of cardiometabolic risk factors in youth with obesity and type 2 diabetes is difficult to mitigate. For adults in the LOOK Ahead study, disappointingly, there has been no reduction in cardiovascular events with intensive lifestyle to date (5).

These results have important and disturbing implications. There is evidence that the presence of MetS predicts cardiovascular disease later in life, and that resolution of MetS before adulthood may be able to significantly reduce cardiometabolic risk (6, 20). It is unfortunate that resolution of MetS in youth with type 2 diabetes is so difficult. Better approaches for the prevention and management of co-morbidities in youth need to be investigated in efforts to improve morbidity and mortality in adulthood. Clearly the

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prevention of the cardiovascular risk factors that define MetS should be a major public health focus, and new approaches for treating these risk factors should be explored.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RSW researched data and wrote manuscript, KLD performed data analysis and interpretation, helped write, edited and approved manuscript, and SC, NIL, SVM and PSZ helped research data, edited and approved the manuscript.

Conflicts of Interest

RSW: Trials sponsored by Medtronic, Sanofi, NovoNordisk, Intarcia and Eli Lilly; PSZ: Consulting Daichii-Sankyo, Takeda Pharmaceuticals, Janssen Pharmaceuticals, BristolMyer Squibb, AstraZeneca;.

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What is already known about this subject?

1. Metabolic syndrome (MetS) is common in type 2 diabetes
2. Adults with MetS and type 2 diabetes are at high risk for cardiovascular disease
3. Resolution of MetS before adulthood may be able to reduce cardiometabolic risk

What does this study add?

1. There is a high prevalence of MetS in youth with recent onset type 2 diabetes, which persists over 2 years of treatment in the TODAY trial, including during an intensive lifestyle intervention
2. Although MetS is common regardless of glycemic status in the TODAY trial, the highest prevalence was observed in those with poor glycemic control at 6 months
3. In TODAY, MetS was most common in females and Hispanics at 2 years, and was associated with elevated hsCRP, ALT, IL6 and PAI-1 concentrations

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Table 1

Prevalence of Metabolic Syndrome (MetS) by Sex, Race/Ethnicity, and Glycemic Status

	Baseline (N=679)			6 Months (N=625)			24 Months (N=545)		
	N and (%)		p-value	N and (%)		p-value	N and (%)		p-value
Overall	515	(75.8%)		472	(75.5%)		418	(76.7%)	
Sex			<.0001			<.0001			<.0001
Female	368	(83.1%)		331	(81.5%)		293	(81.8%)	
Male	147	(62.3%)		141	(64.4%)		125	(66.8%)	
Race/Ethnicity			0.7036			0.4198			0.0038[#]
Non-Hispanic Black	172	(76.4%)		153	(75.7%)		125	(72.7%)	
Hispanic	205	(76.8%)		190	(77.2%)		187	(82.7%)	
Non-Hispanic White	101	(73.2%)		91	(71.1%)		77	(67.5%)	
Glycemic Status[##]									
For those not reaching primary outcome by end of trial[*]									
A1c<6.0%	188	(74.6%)		173	(72.1%)		130	(70.7%)	
A1c< 7%	264	(74.4%)		228	(70.8%)		204	(74.2%)	
A1c 6.0% – 7.9%	89	(75.4%)		59	(68.6%)		86	(83.5%)	
Reached primary outcome at or before reported visit[*]	N/A[**]	N/A[**]		56	(83.6%)		136	(79.5%)	
Reached primary outcome by end of trial[*]	238	(77.0%)		237	(80.3%)		195	(78.3%)	

[*] Primary outcome: A1c > 8.0% over 6 months or inability to wean from temporary insulin therapy following acute metabolic decompensation

[**] A1c<8.0% during pre-randomization run-in period was an eligibility criteria so no possibility for having primary outcome at baseline

[#] Non-Hispanic Black vs. Hispanic p-value=0.0164, Hispanic vs. Non-Hispanic White p-value=0.0017, Non-Hispanic Black vs. Non-Hispanic White p-value=0.3514

[##] Only statistically significant difference is for the prevalence of MetS in those who did not reach the primary outcome with A1c values of 6.0% – 7.9% versus other A1c values at 24 months (p=0.0174)

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Table 2

Prevalence of Components of Metabolic Syndrome (MetS) for Sex, Race/Ethnicity and Glycemic Status

	Baseline (N=679) N and (%)		6 Months (N=625) N and (%)		24 Months (N=545) N and (%)	
Sex						
Female						
Abdominal Obesity	399	(90.1%)	367	(90.4%)	324	(90.5%)
Elevated Triglycerides	90	(20.3%)	113	(27.8%)	119	(33.2%)
Blood Pressure	75	(16.9%)	80	(19.7%)	111	(31.0%)
HDL-Cholesterol	388	(87.6%)	332	(81.8%)	291	(81.3%)
Male						
Abdominal Obesity	161	(68.2%)	149	(68.0%)	128	(68.4%)
Elevated Triglycerides	53	(22.5%)	69	(31.5%)	69	(36.9%)
Blood Pressure	66	(28.0%)	69	(31.5%)	89	(47.6%)
HDL-Cholesterol	155	(65.7%)	131	(59.8%)	107	(57.2%)
Race/Ethnicity						
Non-Hispanic Black						
Abdominal Obesity	198	(88.0%)	180	(89.1%)	149	(86.6%)
Elevated Triglycerides	14	(6.2%)	28	(13.9%)	26	(15.1%)
Blood Pressure	54	(24.0%)	55	(27.2%)	65	(37.8%)
HDL-Cholesterol	172	(76.4%)	146	(72.3%)	120	(69.8%)
Hispanic						
Abdominal Obesity	218	(81.6%)	202	(82.1%)	191	(84.5%)
Elevated Triglycerides	81	(30.3%)	91	(37.0%)	96	(42.5%)
Blood Pressure	47	(17.6%)	50	(20.3%)	84	(37.2%)
HDL-Cholesterol	215	(80.5%)	189	(76.8%)	173	(76.5%)
Non-Hispanic White						
Abdominal Obesity	107	(77.5%)	97	(75.8%)	85	(74.6%)
Elevated Triglycerides	34	(24.6%)	46	(35.9%)	52	(45.6%)
Blood Pressure	33	(23.9%)	32	(25.0%)	39	(34.2%)
HDL-Cholesterol	111	(80.4%)	90	(70.3%)	76	(66.7%)

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	Baseline (N=679) N and (%)		6 Months (N=625) N and (%)		24 Months (N=545) N and (%)	
Glycemic Status						
For those not reaching primary outcome by end of trial[*]						
A1c<6.0%						
Abdominal Obesity	204	(81.0%)	191	(79.6%)	148	(80.4%)
Elevated Triglycerides	45	(17.9%)	56	(23.3%)	49	(26.6%)
Blood Pressure	41	(16.3%)	40	(16.7%)	51	(27.7%)
HDL-Cholesterol	208	(82.5%)	177	(73.8%)	128	(69.6%)
A1c< 7%						
Abdominal Obesity	290	(81.7%)	255	(79.2%)	227	(82.5%)
Elevated Triglycerides	63	(17.7%)	78	(24.2%)	80	(29.1%)
Blood Pressure	64	(18.0%)	59	(18.3%)	84	(30.5%)
HDL-Cholesterol	286	(80.6%)	230	(71.4%)	196	(71.3%)
A1c 6.0% – 7.9%						
Abdominal Obesity	99	(83.9%)	68	(79.1%)	91	(88.3%)
Elevated Triglycerides	24	(20.3%)	24	(27.9%)	40	(38.8%)
Blood Pressure	28	(23.7%)	21	(24.4%)	40	(38.8%)
HDL-Cholesterol	89	(75.4%)	57	(66.3%)	79	(76.7%)
Reached primary outcome at visit[*]						
Abdominal Obesity	N/A[**]	N/A[**]	57	(85.1%)	135	(78.9%)
Elevated Triglycerides	N/A[**]	N/A[**]	32	(47.8%)	73	(42.7%)
Blood Pressure	N/A[**]	N/A[**]	23	(34.3%)	70	(40.9%)
HDL-Cholesterol	N/A[**]	N/A[**]	53	(79.1%)	130	(76.0%)
Reached primary outcome by end of trial[*]						
Abdominal Obesity	257	(83.2%)	253	(85.8%)	205	(82.3%)
Elevated Triglycerides	74	(23.9%)	101	(34.2%)	95	(38.2%)
Blood Pressure	72	(23.3%)	87	(29.5%)	104	(41.8%)
HDL-Cholesterol	246	(79.6%)	226	(76.6%)	184	(73.9%)

[*] Primary outcome: A1c > 8.0% over 6 months or inability to wean from temporary insulin therapy following acute metabolic decompensation

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** A1c<8.0% during pre-randomization run-in period was an eligibility criteria so no possibility for having primary outcome at baseline

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Table 3

Prevalence of Metabolic Syndrome (MetS) by Hemoglobin A1c (A1c), Liver Function and Inflammatory Markers

	Baseline (N=679)			6 Months (N=625)			24 Months (N=545)		
	Mean (SD)		p-value	Mean (SD)		p-value	Mean (SD)		p-value
A1c (%)			0.1581			0.0328			0.3253
No Metabolic Syndrome	5.95	(0.68)		6.15	(1.34)		7.07	(2.45)	
Metabolic Syndrome	6.05	(0.79)		6.43	(1.45)		7.31	(2.30)	
HsCRP (mg/dL)			<.0001			0.0001			<.0001
No Metabolic Syndrome	0.23	(0.32)		0.20	(0.49)		0.22	(0.37)	
Metabolic Syndrome	0.47	(0.71)		0.41	(0.59)		0.49	(0.62)	
ALT (U/L)			0.0001			<.0001			<.0001
No Metabolic Syndrome	25.49	(19.54)		21.80	(18.03)		20.87	(16.26)	
Metabolic Syndrome	32.99	(22.28)		33.79	(31.66)		37.23	(40.39)	
AST (U/L)			0.0618			0.0028			0.0135
No Metabolic Syndrome	22.80	(10.31)		22.88	(14.29)		23.55	(16.74)	
Metabolic Syndrome	24.60	(10.81)		27.78	(18.47)		28.89	(22.44)	
FFA (mEq/L)			0.3686			0.8615			0.4567
No Metabolic Syndrome	0.60	(0.22)		0.56	(0.21)		0.55	(0.21)	
Metabolic Syndrome	0.59	(0.19)		0.55	(0.20)		0.57	(0.21)	
IL-6 (pg/mL)			<.0001			<.0001			<.0001
No Metabolic Syndrome	1.69	(1.33)		1.32	(0.88)		1.65	(1.57)	
Metabolic Syndrome	2.38	(1.74)		2.22	(1.41)		2.51	(1.72)	
Homocysteine (μmol/L)			0.7232			0.3546			0.2631
No Metabolic Syndrome	6.27	(1.78)		6.55	(2.05)		6.93	(2.31)	
Metabolic Syndrome	6.21	(1.98)		6.34	(2.50)		6.69	(2.05)	
PAI-1 (ng/mL)			<.0001			<.0001			<.0001
No Metabolic Syndrome	14.82	(11.77)		14.30	(12.84)		14.00	(11.14)	
Metabolic Syndrome	22.47	(16.56)		23.77	(17.41)		27.37	(20.45)	

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