

Lipid and Inflammatory Cardiovascular Risk Worsens Over 3 Years in Youth With Type 2 Diabetes

The TODAY clinical trial

TODAY STUDY GROUP*

OBJECTIVE—Type 2 diabetes increases cardiovascular risk. We examined lipid profiles and inflammatory markers in 699 youth with recent-onset type 2 diabetes in the TODAY clinical trial and compared changes across treatment groups: metformin alone (M), metformin plus rosiglitazone (M+R), and metformin plus intensive lifestyle program (M+L).

RESEARCH DESIGN AND METHODS—Multiethnic youth with type 2 diabetes received M, M+R, or M+L. Statin drugs were begun for LDL cholesterol (LDL) ≥ 130 mg/dL or triglycerides ≥ 300 mg/dL. Lipids, apolipoprotein B (apoB), LDL particle size, high-sensitivity c-reactive protein (hsCRP), homocysteine, plasminogen activator inhibitor-1 (PAI-1), and HbA_{1c} were measured over 36 months or until loss of glycemic control.

RESULTS—LDL, apoB, triglycerides, and non-HDL cholesterol (HDL) rose over 12 months and then stabilized over the next 24 months. Participants with LDL ≥ 130 mg/dL or using LDL-lowering therapy increased from 4.5 to 10.7% over 36 months, while 55.9% remained at LDL goal (< 100 mg/dL) over that time. Treatment group did not impact LDL, apoB, or non-HDL. Small dense LDL (particle size, ≤ 0.263 relative flotation rate) was most common in M. Triglycerides were lower in M+L than M, and M+L attenuated the negative effect of hyperglycemia on triglycerides and HDL in females. hsCRP, PAI-1, and homocysteine increased over time. However, hsCRP was lower in M+R compared with M or M+L.

CONCLUSIONS—Dyslipidemia and chronic inflammation were common in youth with type 2 diabetes and worsened over time. Diabetes treatment, despite some treatment group differences in lipid and inflammatory marker change over time, is generally inadequate to control this worsening risk.

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The marked increase in type 2 diabetes in adolescents and youth has raised the specter of early cardiovascular disease (CVD) in affected individuals. In adults with type 2 diabetes, the risks of diabetes-specific microvascular complications are largely related to the level of glycemia and duration of disease (1–3). Indicators of atherosclerosis, or macrovascular disease, are already present in youth with type 2 diabetes and dyslipidemia (4,5). Youth with type 2 diabetes are known

to have higher levels of LDL cholesterol (LDL), triglycerides, and non-HDL cholesterol (HDL) and lower levels of HDL than youth without diabetes or youth with type 1 diabetes (6). Elevated inflammatory markers have also been reported in adolescents with type 2 diabetes (7). However, the true prevalence of dyslipidemia and the proinflammatory state in youth and adolescents with type 2 diabetes, the evolution of risk over time, and whether glucose-lowering interventions ameliorate the atherogenic

profile are unknown. The TODAY study provides the opportunity to address these critical questions and determine whether three diabetes treatments differentially affected cardiovascular risk factors.

TODAY was a multiethnic, multicenter clinical trial of newly diagnosed children and adolescents with type 2 diabetes randomized to one of three interventions: metformin alone (M; $n = 232$), metformin plus rosiglitazone (M+R; $n = 233$), or metformin plus an intensive lifestyle program (M+L; $n = 234$) (8–10). The primary results have recently been published in detail (10). Briefly, of the 699 TODAY participants, 319 (45.6%) reached the primary outcome (loss of glycemic control defined as HbA_{1c} $\geq 8\%$ [64 mmol/mol] for 6 months or inability to wean from temporary insulin therapy within 3 months after metabolic decompensation) over an average follow-up of 3.86 years (10). Regarding glycemic control, M+R was superior to M ($P = 0.006$); M+L was intermediate but not different from M (10).

We hypothesized that 1) lipid profiles (LDL, non-HDL, apolipoprotein B [apoB], LDL particle density, triglycerides, and HDL) and inflammatory markers (high-sensitivity c-reactive protein [hsCRP], homocysteine, plasminogen activator inhibitor-1 [PAI-1], and nonesterified fatty acids [NEFA]) would indicate increased CVD risk in youth with recent-onset type 2 diabetes; 2) in the setting of standardized protocol-driven clinical management of hyperlipidemia in a randomized clinical trial for 36 months (or until attainment of primary outcome, loss of glycemic control), cardiovascular risk change would improve more with M+R and M+L than with M. Associations of race-ethnicity and sex with differences in dyslipidemia and inflammatory markers were also assessed.

RESEARCH DESIGN AND METHODS

TODAY study design

The study design has been reported in detail (8,9,11). Briefly, the collaborative

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The opinions expressed in this article are those of the authors and do not necessarily reflect the views of the respective Tribal and Indian Health Service Institution Review Boards or their members.

*A complete list of the members of the TODAY Study Group can be found in the Supplementary Data online. The members of the writing group are listed in the APPENDIX.

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See accompanying articles, pp. 1732, 1735, 1742, 1749, 1765, 1772, 1775, and 1777.

study group included 15 clinical centers, a data-coordinating center, and a central laboratory (see Supplementary Data). At baseline (July 2004–February 2009), eligible individuals were 10–17 years of age with type 2 diabetes diagnosed <2 years at time of randomization and with a BMI \geq 85th percentile. During a prerandomization 2–6-month run-in period, all participants received standard diabetes education. After randomization, participants attended clinic visits for purposes of medical management every 2 months in the first year and quarterly thereafter; outcome data were collected at baseline, 6 months, and annually.

The lifestyle program was designed to work with pharmacotherapy to improve diabetes control in youth through sustained, moderate weight loss (7–10% of initial body weight or the equivalent for youth still growing in height). The program, as previously described in detail (9), consisted of family-based behavioral change delivered in a series of in-person visits during the first 2 years, followed by continued contact at quarterly medical visits. Primary behavior-change targets included energy-balance behaviors (dietary and physical activity) and family involvement/support. A trained interventionist delivered the program one-on-one to the youth and family using materials specifically developed for TODAY (e.g., manuals, booklets, logs, and fact sheets).

Lipid goals were defined in the study protocol as LDL <100 mg/dL and triglycerides <150 mg/dL. If lipid levels were outside the target range, initial therapy involved dietary counseling. If LDL levels remained \geq 130 mg/dL or if triglyceride levels remained 300–599 mg/dL after 6 months of nutrition and diabetes management, pharmacological treatment with atorvastatin was initiated and adjusted to achieve target goals according to an algorithm based on lipid levels (8). If triglycerides were \geq 600 mg/dL, fibrate therapy could be initiated at the discretion of the physician. Additional cardiovascular risk factors, including LDL particle density, apoB, NEFA, hsCRP, PAI-1, and homocysteine levels, were measured throughout the TODAY trial.

The protocol was approved by an External Evaluation Committee convened by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health and by the Institutional Review Boards for the Protection

of Human Subjects of each participating institution. All participants provided informed consent, and minor children confirmed assent according to local guidelines. A Data and Safety Monitoring Board convened by the National Institute of Diabetes and Digestive and Kidney Diseases reviewed progress, safety, and interim analyses throughout the study.

Laboratory methods

Lipids. Measurements of fasting total plasma cholesterol, cholesterol in the lipoprotein fractions, and triglycerides were performed enzymatically on a Roche Modular P autoanalyzer (Roche Diagnostics, Indianapolis, IN), standardized to the Centers for Disease Control and Prevention Reference Methods. HDL was measured after precipitation of apoB-containing particles by dextran sulfate Mg^{2+} . LDL was calculated by the Friedewald equation (12), except if triglyceride levels were >400 mg/dL, in which case ultracentrifugation was performed using the Lipid Research Clinic Beta Quantification procedure. Non-HDL was defined as the difference between total cholesterol and HDL. The interassay coefficients of variation (CVs) were <1.5% for triglycerides and <2% for HDL. LDL physical properties and the flotation distribution of other lipoprotein fractions were determined by a single ultracentrifugation procedure (13). LDL buoyancy (relative flotation rate [Rf]) was calculated as the LDL peak fraction divided by the total number of fractions collected. The Rf of each plasma sample calculated by this procedure is highly reproducible with CV <1.8%. Small dense LDL was defined as an Rf of \leq 0.263. Immunochemical determination of apoB concentration in plasma was performed on the Siemens Nephelometer BN II (Siemens Healthcare Diagnostics Inc., Newark, DE) using Siemens reagents and in-house-prepared calibrator and quality-control materials.

Inflammatory factors. Levels of hsCRP in plasma were measured immunochemically using Siemens reagents (Siemens Healthcare Diagnostics Inc.) on a Siemens nephelometer autoanalyzer (BNII). Homocysteine levels were measured in plasma samples by enzymatic assay with reagents from Axis Shield Inc. (Bothell, WA) on a Roche Modular P analyzer (Roche Diagnostics). Measurement of plasma PAI-1 levels was performed using a quantikine ELISA kit from R&D Systems (Minneapolis, MN). The assay

sensitivity was 0.15 ng/mL, and it was linear up to 20 ng/mL. The interassay CVs for the high, medium, and low PAI-1 controls were 6.1, 6.4, and 9.5%, respectively. Analysis of NEFA was performed using reagents from Wako Diagnostics (Richmond, VA) on a Roche Hitachi Modular P analyzer (Roche Diagnostics).

HbA_{1c}. HbA_{1c} concentration was measured with a dedicated high-performance liquid chromatography method (TOSOH Biosciences Inc., South San Francisco, CA), certified by the National Glycohemoglobin Standardization Program.

Statistical methods

Longitudinal data were analyzed using generalized linear mixed models to account for the multiple observations per participant (SAS PROC MIXED and PROC GENMOD, version 9.2; SAS Institute Inc., Cary, NC). Standard cutoffs for risk categories were applied to six of the outcomes (LDL, triglycerides, HDL by sex, hsCRP, apoB, and LDL particle size). Analyses included all data available at each of the four annual visit time points (baseline and 12, 24, and 36 months), as long as prior to attainment of the primary outcome. Variables not normally distributed were log-transformed for testing; descriptive summary statistics and plots are presented using the original scale. HDL was analyzed separately for males and females due to the known differential in levels. Effects of treatment group, visit (time), sex, and race-ethnicity (American Indian and Asian combined into "other" category due to sample size) and their interactions were tested.

Each lipid outcome was regressed on HbA_{1c} with treatment group and the treatment-by-HbA_{1c} interaction in the model; the effect of BMI was determined by adding BMI as a covariate adjustment. This analysis included follow-up data only (i.e., months 12, 24, and 36) and removed values collected while the participant was taking a lipid-lowering medication.

The *P* values <0.05 are identified as statistically significant with no adjustment for multiple testing. The TODAY study was powered for the primary time-to-failure outcome only, although secondary analyses were predefined.

RESULTS

Participant characteristics

At baseline, participants were 14.0 (\pm SD 2.0) years of age, obese (BMI 34.9 \pm 7.6

kg/m²), with a mean duration of type 2 diabetes of 7.8 (± 5.9) months. Participants were all pubertal, and 88.7% were Tanner stage 4 or 5. The majority (64.7%) were female, 32.5% were non-Hispanic black (NHB), 39.7% Hispanic (H), 20.3% non-Hispanic white (NHW), 5.9% American Indian, and 1.6% Asian. Patient flow through the study is presented in the CONSORT diagram (10) (Supplementary Fig. 1).

Elevated LDL

Prevalence of high-risk LDL (i.e., LDL ≥130 mg/dL or taking LDL-lowering medications) increased from 4.5 to 10.7% over 36 months, while the proportion of subjects at target (LDL <100 mg/dL) declined (Table 1). At baseline, 6 participants used lipid-lowering drugs (4 in M, 2 in M+L); by 36 months, an additional 47 participants were using lipid-lowering drugs (46 on statin, 1 on sequestrant). Treatment-group assignment was not statistically different between those who did and did not use lipid-lowering drugs. Demographics of those treated were not different from the cohort as a whole. Of the 46 treated with statin, 32 had at least one follow-up lipid panel prior to reaching primary outcome, of whom only 10 achieved LDL goal.

Longitudinal trends in lipid and inflammatory factors

For all variables described below, Table 1 shows longitudinal trends in mean values from baseline to 36 months; Table 2 shows trends for percent of the cohort with risk factor values above the threshold for high risk. Longitudinal descriptive statistics for all variables discussed, with stratification by treatment group, sex, and race/ethnicity, are provided in more detail in the Supplementary Material (Supplementary Tables 1 and 2).

Lipids. LDL levels rose from baseline to month 12 and remained at this higher level at months 24 and 36 ($P < 0.0001$) (Fig. 1A). Of the 517 participants who attended any of the three annual follow-up visits, 74 (14.3%) had at least one high-risk classification (LDL ≥130 mg/dL or taking lipid-lowering medication), and only 289 (55.9%) were always at goal (LDL <100 mg/dL). A similar pattern was observed for apoB and non-HDL ($P < 0.0001$; Table 1).

Triglyceride values rose significantly from baseline to month 12 ($P = 0.0038$) and remained at the higher level over months 24 and 36. In males, HDL rose

Table 1—Lipid profiles and CVD risk markers over 36 months in youth with type 2 diabetes

	Baseline (n = 699)	Month 12 (n = 512)	Month 24 (n = 404)	Month 36 (n = 264)
LDL (mg/dL)	85.0 (24.8)	89.1 (26.3)	88.1 (27.7)	87.6 (27.2)
<100	71.9	63.7	66.4	65.3
≥130 or LLM	4.5	8.6	9.9	10.7
Triglycerides (mg/dL)	114.0 (75.2)	117.0 (70.9)	115.1 (74.9)	113.2 (70.7)
<150	79.0	77.3	77.6	76.7
≥150 or LLM	21.0	22.7	22.4	23.3
HDL female* (mg/dL)	39.6 (8.8)	43.7 (10.7)	42.7 (9.7)	43.8 (11.1)
HDL male* (mg/dL)	37.0 (7.9)	39.6 (8.8)	39.0 (8.7)	38.7(9.0)
Non-HDL (mg/dL)	107.4 (29.0)	112.3 (31.2)	110.8 (32.4)	110.5 (32.4)
apoB (mg/dL)	76.6 (20.9)	80.3 (23.3)	78.9 (23.0)	80.1 (23.3)
Small dense LDL**	58.6	52.3	48.7	48.8
hsCRP (mg/dL)	0.41 (0.64)	0.36 (0.56)	0.39 (0.58)	0.50 (0.70)
>0.3	41.2	33.9	36.2	46.3
Homocysteine (μmol/L)	6.23 (1.94)	6.80 (2.09)	6.94 (2.36)	7.54 (2.69)
PAI-1 (ng/mL)	20.6 (15.8)	22.6 (17.5)	22.6 (17.9)	23.3 (17.8)
NEFA (mEq/L)	0.59 (0.20)	0.49 (0.19)	0.55 (0.20)	0.56 (0.20)

Data are mean (SD) or percent. LLM, lipid-lowering medication (statin or sequestrant for LDL, fibrate for triglycerides). *HDL was analyzed separately by sex due to the known difference in normative values. **Particle size ≤0.263 Rf.

from baseline to month 12 and then maintained this higher level ($P < 0.0001$). Females also followed this trend but also showed more variability over follow-up (month 12 > 24, $P = 0.0075$; month 24 < 36, $P = 0.0437$). The percentage of small dense LDL was significantly higher at baseline than at months 12, 24, and 36 ($P = 0.0043$); as small dense LDL percentage usually increases as triglycerides increase, this trend was unexpected.

Inflammatory factors. A greater percentage of participants had high-risk hsCRP (>0.3 mg/dL) at baseline in the M

compared with the M+R group ($P = 0.0136$; Table 2). Overall, in the entire cohort, there was a slight increase over time in percent of participants with high-risk hsCRP levels (41.2% at baseline and 46.3% at month 36; $P = 0.0217$). Homocysteine increased significantly over time ($P < 0.0001$), jumping from baseline to month 12, leveling off to month 24, and jumping again to month 36, while PAI-1 values rose significantly ($P = 0.0059$) from baseline to month 12 and remained at the higher level thereafter (Table 1). There were significant differences in mean NEFA over time ($P <$

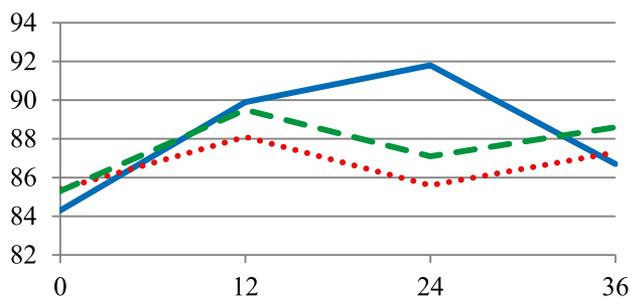
Table 2—Percent in high-risk categories by treatment* and visit

Visit	LDL ≥130 mg/dL or statin or sequestrant			HDL (females <50, males <40 mg/dL)			Triglycerides ≥150 mg/dL or fibrate		
	M	M+R	M+L	M	M+R	M+L	M	M+R	M+L
Base	4.8	4.8	3.9	80.9	79.7	79.0	24.4	20.7	18.0
Month 12	9.4	7.6	9.0	72.3	69.0	67.7	25.8	24.5	18.0
Month 24	11.0	8.8	9.8	72.4	70.8	69.9	22.1	24.8	20.3
Month 36	11.4	12.1	8.7	76.0	69.2	70.7	29.1	22.0	19.6
Visit	hsCRP >0.3 mg/dL			apoB ≥110 mg/dL or statin or sequestrant			Small dense LDL ≤0.263 Rf		
	M	M+R	M+L	M	M+R	M+L	M	M+R	M+L
Base	44.1	37.2	42.2	8.3	4.3	4.3	64.2	57.3	54.3
Month 12	41.5	29.0	31.9	12.6	10.9	11.5	60.4	47.0	50.3
Month 24	41.7	32.1	35.1	15.8	9.5	10.6	57.5	38.5	50.8
Month 36	53.2	44.8	41.8	15.2	14.4	12.1	64.6	34.8	48.9

*Significant treatment differences are: hsCRP, M vs. M+R, $P = 0.0136$; small dense LDL, M vs. M+R, $P = 0.0001$ and M vs. M+L, $P = 0.0121$.

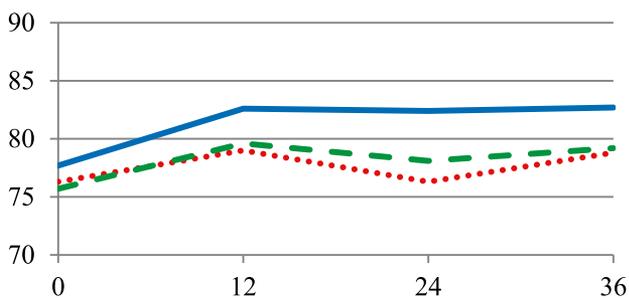
Means Across Visit Month by Treatment (M —, M+R ·····, M+L - - -)

A LDL (mg/dL)



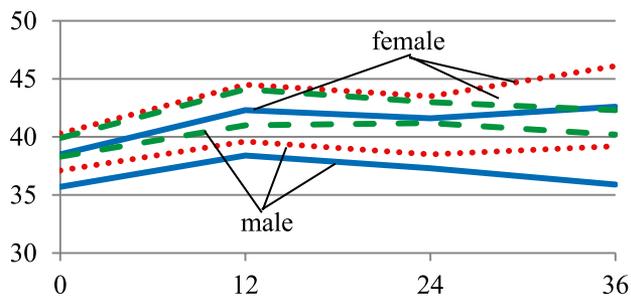
A. For LDL no significant treatment group differences were found at any point in time, but over time LDL rose from baseline to 12 months and leveled off ($p < 0.0001$).

B ApoB (mg/dL)



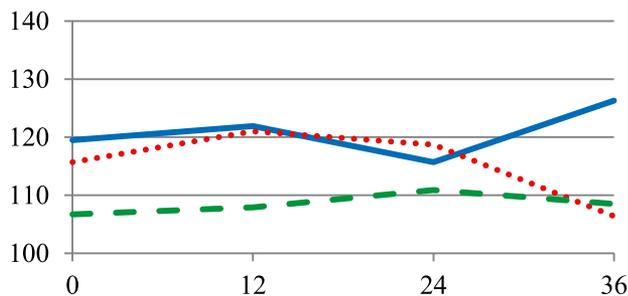
B. ApoB also was not significantly different across treatments but was across visits ($p < 0.0001$); baseline was different from the other 3 time points and 24 months was different from 36 months (note the dip at 24 months for both M+R and M+L).

C HDL (mg/dL)



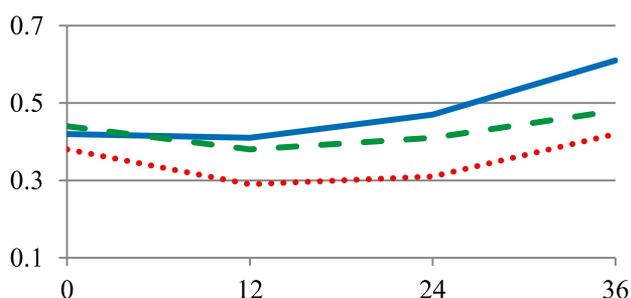
C. HDL in both females and males was significantly different across visits ($p < 0.0001$). Females rose from baseline to 12 months, dipped at 24 months, and increased again to 36 months; males rose from baseline to 12 months and then leveled off.

D Triglycerides (mg/dL)



D. Triglycerides were significantly different between M and M+L ($p = 0.0035$) and a significant rise from baseline to 12 months was detected across treatments ($p = 0.0037$).

E hsCRP (mg/dL)



E. For hsCRP treatment groups were significantly different across visits ($p = 0.0261$); only M+R dropped from baseline to 12 months ($p < 0.0001$), but increases between 12 and 36 months were significant in all treatments (M $p = 0.0006$, M+R $p = 0.0266$, M+L $p = 0.0309$) and at 12, 24, and 36 months M+R was significantly different from both M and M+L.

Figure 1—Means (mg/dL) by treatment group and annual visit from baseline to 36 months for treatment groups M, M+R, and M+L. Vertical axes are scaled to show differences. Tests were performed using the log transform to normalize the distributions of triglycerides and hsCRP, but means were calculated for the original scale.

0.0001), with a drop from baseline to 12 months, followed by an increase at 24 months and then a leveling off from month 24 to 36 (Table 1).

Impact of treatment-group assignment

In Fig. 1, vertical axes are scaled to distinguish lipid values, apoB, and hsCRP by

treatment group. Longitudinal analysis of triglycerides found a significant difference between M and M+L ($P = 0.0035$), with lower values associated with intensive lifestyle (Fig. 1D and Supplementary Table 1B). For LDL (Fig. 1A), apoB (Fig. 1B), HDL (Fig. 1C), and non-HDL (not shown), there were no statistically significant differences among treatment groups

over the 36 months. Small dense LDL was less common at all time points in M+R ($P = 0.0001$) and M+L ($P = 0.0121$) in comparison with M alone.

Levels of hsCRP over time were significantly different ($P = 0.0261$) among treatment groups (Fig. 1E); M+R dropped from baseline to month 12 ($P < 0.0001$) and remained lower than M and M+L, but

values rose from month 12 to 36 in all treatment groups (M, $P = 0.0006$; M+R, $P = 0.0266$; M+L, $P = 0.0309$). Mean homocysteine levels were higher in the M+R group compared with the M group ($P = 0.0002$) or M+L group ($P = 0.0002$) (Supplementary Table 1H), but rose significantly from baseline to month 36 ($P < 0.0001$; Table 1). For PAI-1 and NEFA, no treatment group differences were detected (Supplementary Table 1I and J).

Sex and racial-ethnic effects

For LDL, non-HDL, and apoB, there was no effect of sex or race-ethnicity across time or treatment group (Supplementary Tables 1A, E, F, 2A, and 2F). For triglycerides, females had significantly lower values than males overall ($P = 0.0351$), and NHB had lower than H or NHW (both $P < 0.0001$; Supplementary Table 1B). The percent of participants at high risk (triglycerides ≥ 150 mg/dL or on fibrate) was also different by race-ethnicity across treatment groups (interaction $P = 0.0368$; Supplementary Table 2B); in all three treatment arms, high-risk levels in NHB were significantly less prevalent than in both H and NHW, while among NHB, percent at high risk was significantly higher in M than in M+L ($P = 0.0133$).

Mean HDL levels in females were well below their high-risk cutoff of < 50 mg/dL (the majority were at high risk), while mean levels in males were quite close to their cutoff of < 40 mg/dL (Table 1 and Supplementary Table 1C and D). The percent in the higher-risk category for sex significantly decreased over time; in females, it fell from 87.6% at baseline to 80.3% at month 36, while males decreased from 65.6 to 57.7% (female vs. male, $P < 0.0001$; Table 2 and Supplementary Table 2C and D). Mean HDL values in males were significantly different across time by race-ethnicity (interaction, $P = 0.0269$); by month 36, values were 37.1 and 40.7 mg/dL for H and NHB, respectively ($P = 0.0194$; neither different from NHW, 40.2 mg/dL).

There were significant differences by sex within treatment group in LDL particle density (interaction, $P = 0.0455$). In M+R, the percentage with small dense LDL was significantly lower in females than in males ($P = 0.0003$); in females but not males, percentages in M were higher than in M+R ($P < 0.0001$) and M+L ($P = 0.0150$). The sexes were also different across time (interaction, $P = 0.0378$); females dropped from baseline to month

12 and then remained at the lower level, but males did not vary over time (Supplementary Table 2G). Across treatment arms, NHB had significantly lower percentages with small dense LDL than H ($P < 0.0001$) and NHW ($P < 0.0004$), even at baseline (NHB, 46.0%; H, 64.5%; and NHW, 63.1%).

For hsCRP, by month 36, levels in females had risen significantly from baseline (0.43 to 0.56 mg/dL; $P = 0.0059$) compared with males (0.37 to 0.40 mg/dL; not significant). Percentage of females in the high-risk category increased from baseline to month 36 (41.8 to 53.7%; $P = 0.0005$) and fell in males (39.9 to 33.7%; not significant). NHW had lower mean levels than H ($P = 0.0171$) or NHB ($P = 0.0059$), but there were no differences across racial-ethnic groups in percent at high risk. Males had significantly higher homocysteine values than females ($P < 0.0001$; Supplementary Table 1H). H had higher mean PAI-1 values than NHB ($P < 0.0001$) or NHW ($P = 0.0480$) (Supplementary Table 1I). For NEFA, levels in females were significantly higher than those of males ($P = 0.0114$) and in NHW were significantly higher than in NHB ($P = 0.0034$) and H ($P = 0.0150$; Supplementary Table 1J).

Relationship between HbA_{1c} and lipid levels

Fig. 2 shows regression lines comparing the relationship among HbA_{1c} and LDL, triglycerides, and HDL (separately by sex) by treatment group. LDL levels rose with increasing HbA_{1c} levels ($P < 0.0001$), with no difference across treatment groups (Fig. 2A). The relationship between HbA_{1c} and triglyceride differed by treatment group ($P = 0.0250$; Fig. 2B); both M and M+R had significant positive slopes ($P = 0.0240$ and $P = 0.0105$, respectively), but M+L was flat, indicating that higher HbA_{1c} levels were not associated with higher triglyceride levels in this treatment group. HDL was examined separately by sex (Fig. 2C and D). In both females and males, differences by treatment group seen in the figures were not detected statistically ($P \approx 0.08$), perhaps due to diminished sample size, although the negative slope for M+R was significant (females, $P = 0.0314$; males, $P = 0.0419$), indicating that HDL decreased as HbA_{1c} increased in this treatment group. BMI was a significant covariate term in all models but did not affect the significance of the relationship between lipid levels and HbA_{1c}.

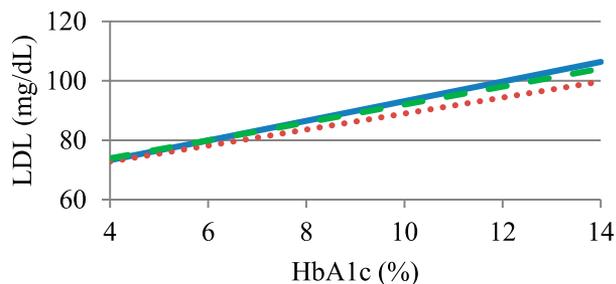
CONCLUSIONS—At baseline, the TODAY cohort had a remarkably high prevalence of dyslipidemia compared with age-matched nonobese youth and adolescents without diabetes (14,15). More importantly, over the average follow-up of 3.86 years, LDL, non-HDL, and apoB levels, which changed in parallel, triglycerides, and homocysteine levels all rose over time, and a majority of participants had high-risk (low) HDL levels. The percent of TODAY subjects requiring lipid-lowering drugs according to protocol tripled to 10.7%, with a minority achieving LDL goal. In the TODAY study, the only CVD risk factors that appeared to decline over time were the percentages with high-risk HDL and with small, dense, more atherogenic LDL, largely in the first year of follow-up.

Overall, none of the three diabetes interventions prevented the worsening of CVD risk factors over time; however, treatment differences were observed specifically in the proportion of small dense LDL particles and in hsCRP and homocysteine levels, all of which were more atherogenic in the M group. In general, the benefits of a lifestyle intervention, similar in design to that used in TODAY, on lipoprotein and other CVD risk factors in adult patients with prediabetes (16,17) and type 2 diabetes (18) were not seen in the TODAY cohort. The exception was that lifestyle intervention appeared to attenuate the relationship between HbA_{1c} and triglyceride levels in the entire cohort and between HbA_{1c} and HDL levels in females. Whether this effect was related to a greater decrease, albeit small and transient, in adiposity (lower BMI, percent fat mass, waist circumference, and abdominal height) in M+L is unknown. The adverse effects of rosiglitazone on conventional lipid levels demonstrated in adults (19) were not seen in TODAY.

Ethnicity and sex had an impact on atherogenic profiles. In all three treatment arms, triglyceride levels in NHB were significantly lower than those in both H and NHW. Among NHB, the percentage with high-risk triglycerides was significantly higher in M than in M+L. These results are consistent with ethnic differences in triglycerides in the general population and suggest triglyceride thresholds regarding metabolic risk may need to be ethnicity-specific (20). Mean HDL levels in females were well below their high-risk cutoff of < 50 mg/dL, while levels in males were quite close to their cutoff of 40 mg/dL. Males had

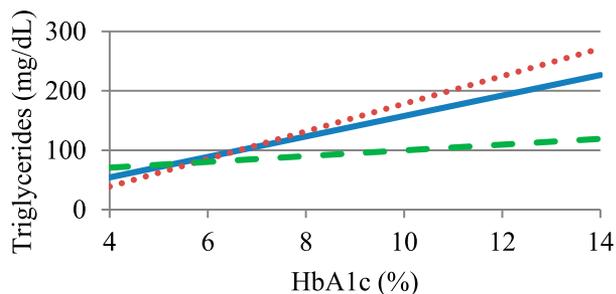
Regression of Lipid on HbA_{1c} adjusted for BMI, by Treatment Group (M —, M+R ·····, M+L - - -)

A LDL versus HbA_{1c}



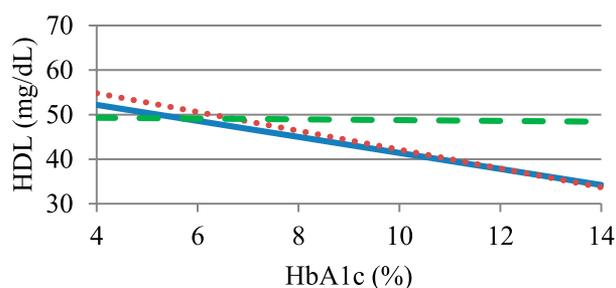
A. For LDL there was no difference across treatments but there was a significant positive slope (3.0%, $p < 0.0001$).

B Triglycerides versus HbA_{1c}



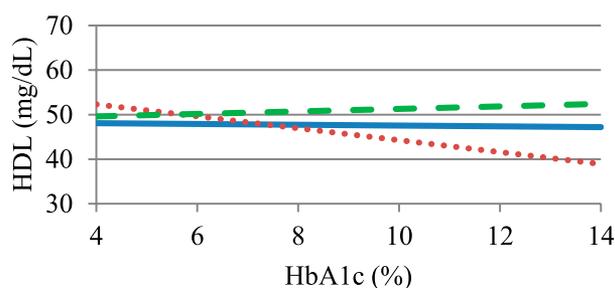
B. For triglycerides there was a significant difference across treatment groups ($p = 0.0250$); both M and M+R had significant positive slopes (17 mg/dL, $p = 0.0240$, and 23 mg/dL, $p = 0.0105$, respectively) but M+L was flat.

C HDL versus HbA_{1c} - Females



C. For HDL in females test of treatment differences was not significant ($p = 0.0887$) although M+R had a significantly negative slope (-2 mg/dL, $p = 0.0314$); the slope for M was not significant ($p = 0.0972$).

D HDL versus HbA_{1c} - Males



D. For HDL in males there was also no treatment difference ($p = 0.0871$) but M+R had a significantly negative slope (-1.6 mg/dL, $p = 0.0419$).

Figure 2—Regression of HbA_{1c} (%) on lipid outcomes (mg/dL) for treatment groups M, M+R, and M+L. Data were included at 12-, 24-, and 36-month visits prior to treatment failure. The analysis tested treatment group differences adjusted for BMI. Slopes indicate change in lipid value per unit increase in HbA_{1c}. Tests were performed using the log transform to normalize the distribution of triglycerides, but estimates of slope were calculated for the original scale.

significantly higher homocysteine values than females. The addition of either rosiglitazone or lifestyle increased LDL particle size in females.

Limitations of the TODAY study included the variable follow-up over time, although the majority of the cohort had assessments at 36 months. Only three racial-ethnic groups were large enough to provide reliable estimates of their effects. Moreover, the adherence to dietary and exercise management and subsequent statin therapy was likely less in our cohort than is generally seen in adults. Specific adherence data for statin therapy in TODAY are not available. It is possible that worsening lipid profiles were secondary to worsening compliance over time rather than to duration of diabetes. However, while adherence to glycemic control

medications waned over time in the TODAY trial, adherence remained $>70\%$; therefore, it is likely that adherence to lipid therapy also remained reasonable in this setting. In addition, hsCRP was higher at baseline in the M group, making it possible that the significantly higher levels of hsCRP after treatment were secondary to randomization effects.

The deteriorating atherogenic and inflammatory risk profile observed in the TODAY cohort over time, despite intensive intervention in the setting of a randomized clinical trial, suggests CVD will become prevalent in the third and fourth decades of life in adolescents with type 2 diabetes. Furthermore, the overall poor psychological health of affected individuals already reported in this cohort will likely further challenge the ability to deliver

effective interventions (21). Trials of more aggressive interventions, both pharmacologic and behavioral, to lower CVD risk are necessary in this vulnerable population.

APPENDIX—The members of the writing group are as follows: Ruth S. Weinstock (co-chair), MD PhD, SUNY Upstate Medical University; Sonia Caprio (co-chair), MD, Yale University School of Medicine; Kenneth C. Copeland, MD, University of Oklahoma Health Sciences Center; Samuel S. Gidding, MD, Nemours Cardiac Center; Kathryn Hirst, PhD, George Washington University; Lorraine L. Katz, MD, Children's Hospital of Philadelphia; Santica Marcovina, PhD, Northwest Lipid Research Laboratories;

Kristen J. Nadeau, MD, University of Colorado Denver; and David M. Nathan, MD, Massachusetts General Hospital.

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R.S.W., S.C., K.C.C., K.H., L.L.K., K.J.N., and D.M.N. researched data, contributed to the discussion, wrote the manuscript, and reviewed and edited the manuscript. S.S.G. contributed to the discussion, wrote the manuscript, and reviewed and edited the manuscript. S.M. contributed to the discussion and reviewed and edited the manuscript. K.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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