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Improvement in Liver Histology is Associated with Reduction in Dyslipidemia in Children with Nonalcoholic Fatty Liver Disease

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Abstract

Objectives—Nonalcoholic fatty liver disease (NAFLD), the most common cause of liver disease among American children, may be associated with cardiovascular disease (CVD) risk. This study sought to determine the prevalence of dyslipidemia in children with NAFLD, assess dyslipidemia by liver histology and histologic changes.

Methods—Individuals in the Treatment of NAFLD in Children (TONIC) trial were included (N=173). In the TONIC trial children with NAFLD were randomized to vitamin E, metformin or placebo for 96 weeks. Nonalcoholic steatohepatitis (NASH) improved in 56 individuals. Change in lipid levels from baseline and 96 weeks was compared between subjects with and without histologic improvement and with and without NASH.

Results—Dyslipidemia was frequent, with low high-density lipoprotein (HDL) (<40 mg/dL) in 61.8%, hypertriglyceridemia (≥130 mg/dL) in 50.3%, hypercholesterolemia (≥200 mg/dL) in 23.7%, elevated low-density lipoprotein (LDL) (≥130 mg/dL) in 21.5%, elevated non-HDL

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cholesterol (non-HDL-C) (≥145 mg/dL) in 35.2%, and triglycerides/HDL>3.0 in 57.2% of subjects.

Histologic improvement was associated with significant decreases in cholesterol (−11.4 mg/dL vs. −1.9 mg/dL, p=0.04), LDL (−11.2 mg/dL vs. −2.1 mg/dL, p=0.04) and non-HDL-C (−8.8 mg/dL vs. 0.5 mg/dL, p=0.03) compared to those without improvement. Children with NASH resolution had significant decreases in cholesterol (−10.0 mg/dL vs. −0.9 mg/dL, p=0.02) and non-HDL-C (−7.3 mg/dL vs. 1.1 mg/dL, p=0.01) compared to those without NASH resolution. Neither triglycerides, HDL level nor triglycerides/HDL ratio improved in either group.

Conclusions—Dyslipidemia is frequent in children with NAFLD. NASH resolution and histologic improvement are associated with improvements in some forms of dyslipidemia.

Keywords

nonalcoholic fatty liver disease; nonalcoholic steatohepatitis; lipids; vitamin E; metformin; non-high density lipoprotein cholesterol; cardiovascular disease risk

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease among children, affecting 10% of American youth.[2,3] Nonalcoholic steatohepatitis (NASH), the progressive form of NAFLD, is well-described in children and can result in cirrhosis.[4] In addition, NAFLD confers an independent risk for cardiovascular disease (CVD) in adults.[5–9] Children with NAFLD have an increased prevalence of risk factors for CVD including elevated low-density lipoprotein (LDL), increased total cholesterol, and decreased high-density lipoprotein (HDL), when compared to matched controls.[10–12] The severity of NASH, as assessed by the NAFLD activity score (NAS) is associated with increased triglyceride/HDL, total cholesterol/HDL, and LDL/HDL ratios.[13] Furthermore, children with NAFLD have greater carotid arterial intima-media thickness (CIMT), a risk factor for CVD development, as compared to obese children without NAFLD.[14–16] Studies of dietary and pharmacologic interventions in children with NAFLD have shown conflicting effects on CVD risk factors.[17–20] Thus, the impact of NAFLD and NASH regression on CVD risk factors in children remains uncertain.

The development of NASH is associated with dyslipidemia and alterations in hepatic lipid metabolism. The liver secretes triglyceride rich lipoproteins in the form of very low-density lipoproteins (VLDL) and, less frequently, intermediate-density lipoproteins (IDL). Increased levels of VLDL and IDL have been described in NAFLD and are also associated with increased CVD risk.

Non high-density lipoprotein cholesterol (non-HDL-C) is a composite measure that encompasses VLDL, LDL, IDL and lipoprotein (a).[21] Non-HDL-C is easily calculated from a commonly available lipid profile by subtracting HDL cholesterol from the total cholesterol level (Non-HDL-C = total cholesterol – HDL) and can be performed with no additional cost. We have recently shown that non-HDL-C is significantly higher in adults with NASH compared to those with steatosis alone.[22] Further, non-HDL-C is a risk factor for CVD development, and is a superior predictor of CVD in adults when compared to the widely

used LDL.[23] Non-HDL-C is now considered an important secondary target of lipid lowering therapy.[2425]

Non-HDL-C levels in childhood also predict cardiovascular disease risk factors in adults. The Bogalusa Heart Study followed 1163 children age 5–14 years over a 27-year period. Childhood non-HDL-C was not only a predictor of adult non-HDL-C but adult dyslipidemia, hyperinsulinemia and hyperglycemia, all important CVD risk factors.[26] Further, increased non-HDL-C levels correlate with the extent of coronary and aortic atherosclerotic disease in youth found on autopsy.[27]

Similar to non-HDL-C, Triglycerides(TG)/HDL ratio correlates with small, dense, LDL particles in children and adolescents and a ratio ≥ 3 predicts increased concentrations of small dense LDL.[28,29] TG/HDL is strongly associated with insulin resistance and independently predicts arterial stiffness in obese youth.[30, 31, 32] TG/HDL ratio is also significantly associated with increased carotid arterial intima-media thickness in youth with type II diabetes, although HDL cholesterol was the only lipid to independently contribute to the prediction of CIMT.[33] Both high triglycerides and non-HDL cholesterol that persist into adulthood are a strong predictive risk factor for cardiovascular disease and development of type II diabetes in adulthood.[34]

While studied in adults with NAFLD, non-HDL-C as a CVD risk factor has not been assessed in children with NAFLD. Furthermore, the impact of histologic improvement in NASH and regression of NASH on lipid profiles including non-HDL-C and TG/HDL ratio has not been evaluated.

The Treatment for Nonalcoholic Fatty Liver Disease in Children (TONIC) trial was a randomized, double blinded, placebo-controlled trial to evaluate the efficacy of vitamin E and metformin for 96 weeks in children with biopsy-proven NAFLD and elevated alanine aminotransferase (ALT) levels. Neither metformin nor vitamin E was found to be superior to placebo in improving ALT levels, the primary endpoint, although vitamin E was associated with an improvement in NAFLD activity score (NAS) and resolution of NASH. The TONIC trial, with its use of serial liver biopsies, allows for the evaluation of the impact NASH resolution on lipid levels including non-HDL-C and TG/HDL.

The present study is based on post-hoc analyses of children who participated in the TONIC trial and aims to examine the frequency of dyslipidemia in children and adolescents with NASH, evaluate the relationship between baseline liver histology and lipid levels including non-HDL-C and TG/HDL in children with NAFLD, and assess the impact of the resolution of NASH and histologic improvement on lipids levels including non-HDL-C and TG/HDL.

Materials and Methods

Study Design

Data for this study were obtained from participants in the TONIC Trial.[35] TONIC was a pediatric treatment trial of NAFLD conducted by the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN). The TONIC trial study design has been previously

described and the ClinicalTrials.gov identifier is NCT00063635.[36] Briefly, children aged 8 to 17 years with biopsy-confirmed NAFLD within 6 months of randomization and persistently elevated ALT levels were eligible for study inclusion. NAFLD was defined as liver histology with >5% of hepatocytes exhibiting macrovesicular steatosis. Children with diabetes mellitus, monogenic inborn errors of metabolism, viral hepatitis, alcohol use, pregnancy, cirrhosis or other causes of chronic liver disease were excluded. Children with biopsy-proven NAFLD were randomized at a 1:1:1 ratio to vitamin E 400 units twice daily, metformin 500 mg twice daily or double-dummy placebo for 96 weeks. The primary endpoint was significant and sustained reduction in ALT level compared to placebo. Secondary endpoints included the resolution of NASH in individuals with NASH on baseline biopsy and histologic improvement.

Liver Histology

Participants underwent biopsies within 6 months prior to study randomization and 96 weeks later. Biopsies were centrally evaluated by a panel of NASH CRN pathologists. Liver biopsies were assessed using the NAFLD Activity Score (NAS). The NAS is a composite score ranging from 0 to 8 points composed of steatosis (0–3), hepatocyte ballooning (0–2) and lobular inflammation scores (0–3).[37] Fibrosis stage was scored on a scale of 0–4. The presence of NASH was assessed independently of the NAS score based on the pattern of injury and was categorized as definite, borderline, or no NASH.

Laboratory Analyses

Fasting serum total cholesterol, HDL, triglyceride and LDL levels were measured locally at baseline and week 96. From these measurements, non-HDL-C was calculated (Non-HDL-C=total cholesterol – HDL). Definitions for high, borderline-high, acceptable and low lipid levels were derived from the National Heart, Lung and Blood Institute (NHLBI) Expert Panel Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.[1]

Statistical Analysis

Histologic improvement was defined by a decrease in the NAS of ≥2 with no worsening of fibrosis. Resolution of NASH was defined as a diagnosis of no steatohepatitis at 96 weeks among children with borderline or definite NASH at baseline. An example of the histology of NASH and subsequent NASH resolution are presented in Figure 1.

Mean lipid levels and lipid level elevations were compared between children with NASH and children with borderline or no NASH at baseline using t-tests and Fisher's exact test. Linear regression was used to assess the association between histologic improvement and resolution of NASH and mean baseline and 96 week lipid levels Treatment group (Metformin of Vitamin E) versus placebo, baseline body mass index (BMI), and ethnicity were included in the multivariable model. For the comparison of the mean change in lipid levels between groups, P values were derived in the same manner with the addition of baseline value of the lipid measure to the multivariable model. All analyses were carried out using SAS 9.3 (SAS Institute, Cary, NC) and Stata 12 (Stata Corp., College Station, TX).

Nominal, two-sided *P* values were used and were considered statistically significant if $P<0.05$.

Results

Baseline Characteristics

All children included in this study have been described in a previous publication.[35] Baseline demographics, anthropometrics, laboratory data and liver histologic characteristics were evenly distributed across treatment groups. In the TONIC trial, no significant difference in sustained reduction of ALT was seen among the vitamin E, metformin and placebo groups. Significant differences were found in the vitamin E–treated group compared to placebo in significant histologic measures such as resolution of NASH and decrease in NAS score. Altogether, 56 of 146 subjects (38%) who underwent repeat liver biopsy had histologic improvement in NASH (defined as a decrease of ≥2 points on NAS and without worsening fibrosis). Fifty-two of 121 subjects (43%) with NASH at baseline experienced resolution of NASH.

Baseline Lipid Levels

Dyslipidemia was frequent in this cohort at baseline. (Table 1) Definitions for high and low lipid levels were derived from the NHLBI Expert Panel Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.[1] Hypertriglyceridemia and low HDL levels were the most common abnormalities. High triglyceride levels (triglycerides ≥130 mg/dL) were present in 50.3% of subjects. The mean triglyceride level was 153 mg/dL (acceptable <90 mg/dL). Low HDL levels (<40 mg/dL) were found in 61.8% of individuals with a mean HDL of 38 mg/dL. Elevated total cholesterol (total cholesterol ≥200 mg/dL) was present in 23.7% of subjects and mean total cholesterol was 176 mg/dl (acceptable <170 mg/dL). Elevated LDL (LDL≥130 mg/dL) was present in 21.5% although the mean LDL was within the acceptable range at 109 mg/dL (acceptable<110 mg/dL). Elevated non-HDL-C (non-HDL≥145 mg/dL) was found in 35.2% of subjects. Mean non-HDL-C was 138.5mg/dL (acceptable <120mg/dL). Triglycerides/HDL>3.0 was present in 57.2% of subjects. Baseline lipid levels did not differ by three treatment groups at baseline or at 96 weeks. One hundred forty-four individuals (83%) had some form of lipid abnormality. During the course of the mean total cholesterol, LDL and HDL decreased significantly while triglyceride levels increased significantly.

Lipid Levels in Relation to Liver Histology

There was no difference in the proportion of children with definite NASH and those with borderline or no NASH with elevated LDL (LDL ≥ 110mg/dL or LDL ≥ 130 mg/dL), total cholesterol (total cholesterol ≥ 170 mg/dL) or elevated non-HDL-C (non-HDL-C ≥ 120mg/dL or non-HDL-C ≥ 145 mg/dL) at baseline.(Table 2) There was a non-significant increase in the proportion of individuals with NASH who had triglyceride levels ≥ 130mg/dL compared to those with borderline or no NASH (58.9 % vs. 44.0%, p=0.06). There was a significant increase in the proportion of individuals with NASH with HDL ≤ 40 mg/dL compared to those with borderline or no NASH (75.3% vs. 52.0%, p=0.003). In

addition, TG/HDL > 3 was more frequent in individuals with NASH than those without NASH (65.8% vs. 51.0%, p=0.05).

Lipid Levels and Resolution of NASH

While baseline lipid levels did not differ significantly by histology, subjects whose NASH resolved experienced an improvement in multiple lipid parameters compared to those without resolution of NASH (Table 3, Figure 2). Resolution of NASH was associated with a significant decrease in total cholesterol levels from baseline compared to those who did not experience a resolution of NASH (mean change [95% CI] −10.0 mg/dL [−18.0, −2.0] vs. −0.9 mg/dL [−8.0, 6.3], p=0.02). Furthermore, individuals whose NASH resolved had a significant decrease in non-HDL-C levels compared to subjects without resolution of NASH who had no change in non-HDL-C from baseline (mean [95% CI] change −7.3 mg/dL [−14.9, 0.2] vs. 1.1 [−5.7, 7.9], p=0.01). These results remained significant when controlled for baseline lipid level, BMI, ethnicity and treatment group. Resolution of NASH was associated with a non-significant decrease in LDL when compared to subjects whose NASH did not resolve (mean change [95% CI] −11.2mg/dL [−19.1, −3.3] vs. −2.1mg/dL [−7.6, 3.4], p=0.06). Triglyceride levels increased in subjects with and without resolution of NASH but the increase did not differ between the two groups (mean change [95% CI] 21.7 mg/dL [−2.2, 45.6] vs. 18.9mg/dL [−1.7, 39.5]. p=0.28). There was no significant change in HDL or TG/HDL over the study period or difference in HDL or TG/HDL change by histologic response (p=0.42 and p=0.35, respectively).

Lipid Levels and Histologic Improvement

Histologic improvement was also associated with an improvement in multiple lipid parameters (Table 4, Figure 3). Individuals who experienced histologic improvement had a significant decrease in total cholesterol levels from baseline compared to those who did not experience histologic improvement (mean change [95% CI] −11.4 mg/dL [−18.9, −3.9] vs. −1.9 mg/dL [−7.7, 3.9], p=0.04). In addition, LDL significantly decreased in those with histologic improvement compared to those without improvement (mean change [95% CI] −11.2 mg/dL [−19.1, −3.3] vs. −2.1 mg/dL [−7.6, 3.4], p=0.04). Non-HDL-C levels also decreased significantly in children with histologic improvement in NASH when compared to children without histologic improvement (mean [95% CI] change −8.8 mg/dL [−15.5, −2.0] vs. 0.5 [−5.1, 6.2], p=0.03). There was no significant change in triglyceride, HDL or TG/HDL levels by histologic improvement.

Change in BMI and Change in Lipid Levels

Change in BMI over the study duration was positively correlated with changes in non-HDL-C (p=0.02). There was no correlation between change in BMI and change in LDL and total cholesterol levels (p=0.13, p=0.09, respectively). Thus, while change in non-HDL-C may be driven by change in BMI, change in total cholesterol and LDL were independent of change in BMI. No difference was seen in change in BMI by treatment group.

Discussion

The results of this study demonstrate that dyslipidemia, characterized by hypertriglyceridemia, hypercholesterolemia, elevated non-HDL-C and low HDL levels, is frequent in children and adolescents with NAFLD. Further, this study demonstrates that non-HDL-C, a powerful cardiovascular risk marker, is elevated in children and adolescents with NAFLD. Finally, our study establishes that both resolution of NASH and histologic improvement in NASH are associated with improvements in non-HDL-C, LDL and total cholesterol. Interestingly, while multiple lipid parameters improved in the setting of histologic improvement and NASH resolution, no change was seen in HDL, triglycerides or TG/HDL. Thus, while histologic improvement and NASH resolution improves some measures of CVD risk, other important risk factors persist.

Limited data has suggested that NAFLD in children is associated with dyslipidemia. Schwimmer et al evaluated 150 adolescents with biopsy-proven NAFLD and 150 overweight control individuals for cardiovascular risk factors.[10] Children with NAFLD had higher total cholesterol, LDL and triglyceride levels compared with BMI-matched controls. Nobili et al evaluated 118 children with biopsy-proven NAFLD. This group found that NAS and fibrosis stage were positively correlated with triglyceride/HDL, total cholesterol/HDL, and LDL/HDL ratio and were predictors of an atherogenic lipid profile. Our study confirms these findings, demonstrating a high prevalence of dyslipidemia in children with biopsy-proven NAFLD and NASH. Our study also provides longitudinal data on children with NAFLD and NASH that adds to these cross-sectional studies and demonstrates the impact of NASH resolution and histologic improvement on CVD risk factors. While several studies have assessed the impact of weight loss interventions in children with NAFLD none have been performed with serial liver biopsies and thus, could not assess the relationship between histologic changes and lipid parameters.[17,18] Our study addresses these limitations by assessing biopsy-proven NASH serially, allowing for assessment of the relationship between histologic changes in NASH and improvement in lipid parameters. We were able to show that resolution of NASH and histologic improvement in NASH are associated with parallel improvements in LDL and total cholesterol with persistence of low HDL levels and hypertriglyceridemia.

We also demonstrate that elevated non-HDL-C is frequent in NAFLD and declines with histologic improvement. Non-HDL-C is an accepted risk factor for the development of CVD in adults and a target of lipid lowering therapy.[24,25] Childhood non-HDL-C predicts dyslipidemia, hyperglycemia and hyperinsulinemia in adulthood and correlates with atherosclerosis on autopsy. [27] Thus, improvement in liver histology in children with NASH is not only associated with an improvement in traditional lipid parameters but also with an improvement in non-HDL-C, a powerful predictor of future CVD.

Interestingly, the triglyceride levels increased in all groups over the study duration and no improvement was seen in TG/HDL. The methods used for triglyceride measurement vary and the final triglyceride value can exclude or include free glycerol level, altering the final value.[3839] Following NAFLD and NASH resolution there may be a decrease in triglyceride formation due to alterations in available free fatty acids. This would result in increased

levels of free glycerol and using a one step method, falsely elevate TG measurements. Further evaluation of triglyceride levels using both methods is needed to clarify this issue.

This study has several important limitations. While dyslipidemia and elevated non-HDL-C are validated markers of CVD risk, they remain surrogate markers of CVD. Long term follow-up is needed in children with NAFLD and NASH to determine whether resolution of NAFLD and/or NASH decreases CVD events and CVD-related mortality in adulthood. Further, our study demonstrates only an association between liver histology and lipid levels and cannot demonstrate causality. Improvements in dyslipidemia may be the result of improvements in insulin resistance and the metabolic syndrome in addition to alterations in hepatic lipid metabolism. In addition, the change in dyslipidemia may be impacted by vitamin E use. While data exists to suggest that vitamin E supplementation may make LDL particles more resistant to oxidative stress, clinical trials of vitamin E supplementation in adults at risk for or with CVD have shown no impact on circulating lipid levels.[32–34] Further, evaluation of the impact of vitamin E on lipid levels in children is needed. Finally, while the present study demonstrated an improvement in non-HDL-C, LDL and total cholesterol, triglyceride and HDL levels did not improve. Adolescents with NAFLD tend to have delayed clearance of plasma TG, likely from intestinal chylomicrons.[40] In the groups with improvement and/or resolution of NASH, one would expect the kinetics of chylomicron TG to have been normalized. This, however, was not the finding in the present study. The fact that TG remain high in the responders would suggest that the kinetics of intestinal TG may not have been normalized (or affected) by the intervention or that production of TG from the liver remains elevated despite the improvement in the liver disease.

In summary, we have demonstrated that dyslipidemia including elevated non-HDL-C levels and increased TG/HDL are frequent in children with NAFLD and NASH. We have also shown that resolution of NASH and histologic improvement are independently associated with improvement in non-HDL-C, total cholesterol and LDL levels suggesting that improvement in NASH and NASH resolution may improve CVD risk in children with NAFLD. While improvement was shown in non-HDL-C a similar improvement in TG and TG/HDL was not seen and the data remain inconclusive for long term atherosclerotic risk. Further studies will be needed utilizing direct measurement of lipoprotein particle size and characteristics. While the improvement in non-HDL cholesterol is promising, the lack of improvement in TG/HDL demonstrates complexity in the relationship between peripheral lipids and NAFLD. Larger sample sizes would allow improved comparison between improvements in steatosis vs. inflammation in the liver and the relationship with peripheral lipids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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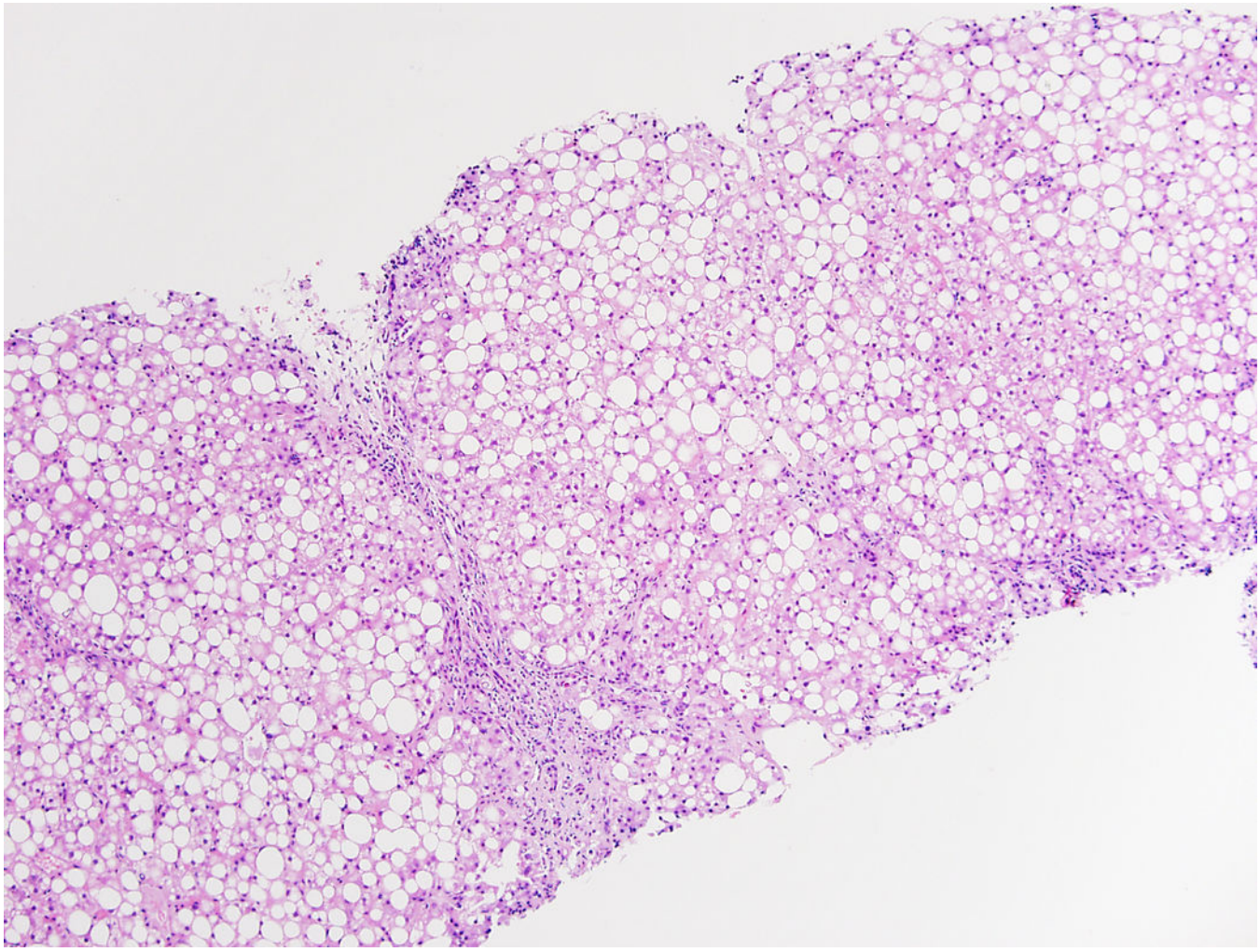


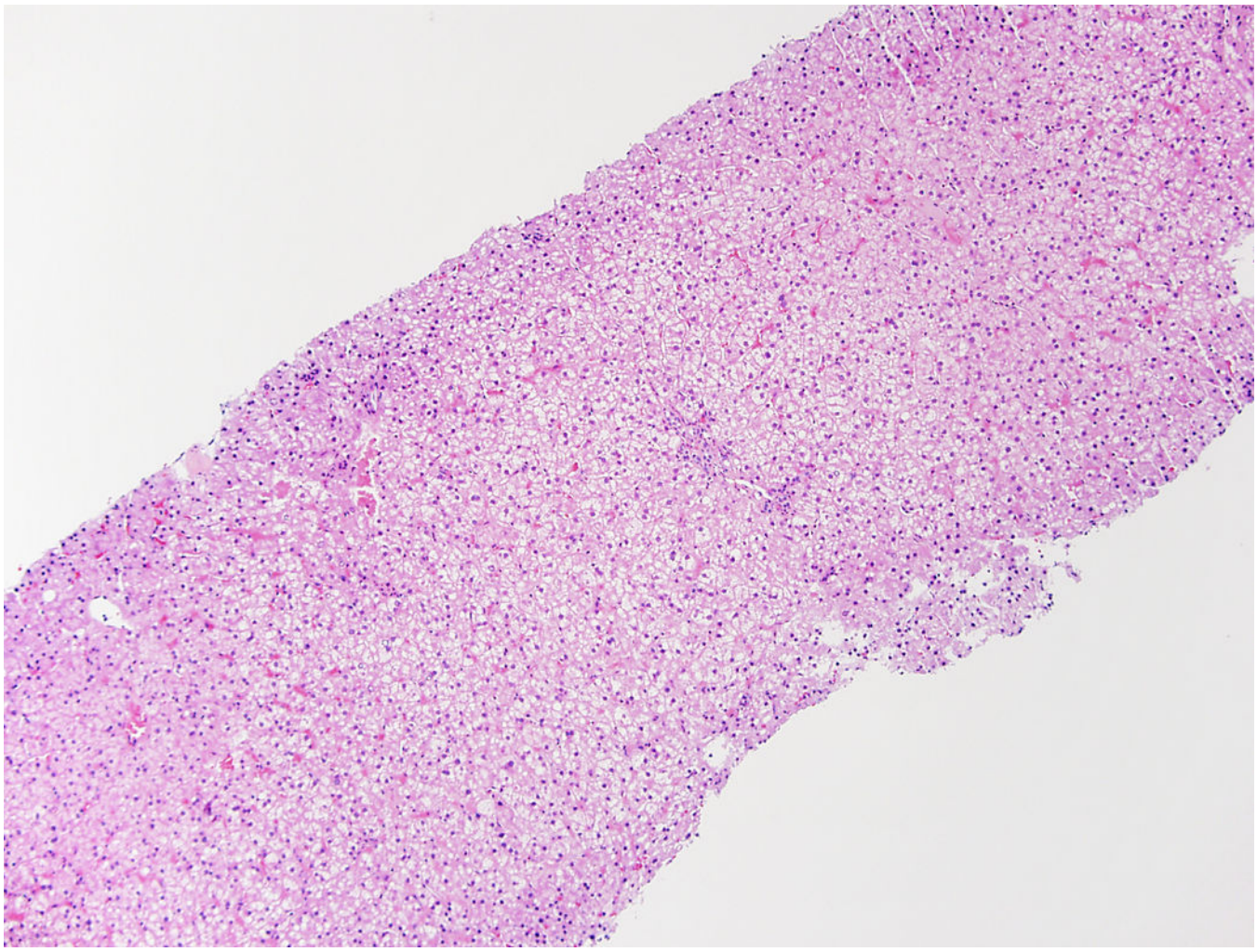


Figure 1.

A. Screening biopsy showing grade 3 large droplet, pan-acinar fat. There is peri-portal and peri-sinusoidal fibrosis and moderate lobular inflammation. B. Follow up biopsy of the same patient at the same magnification. The large droplet fat has cleared. The inflammation and fibrosis have also improved.

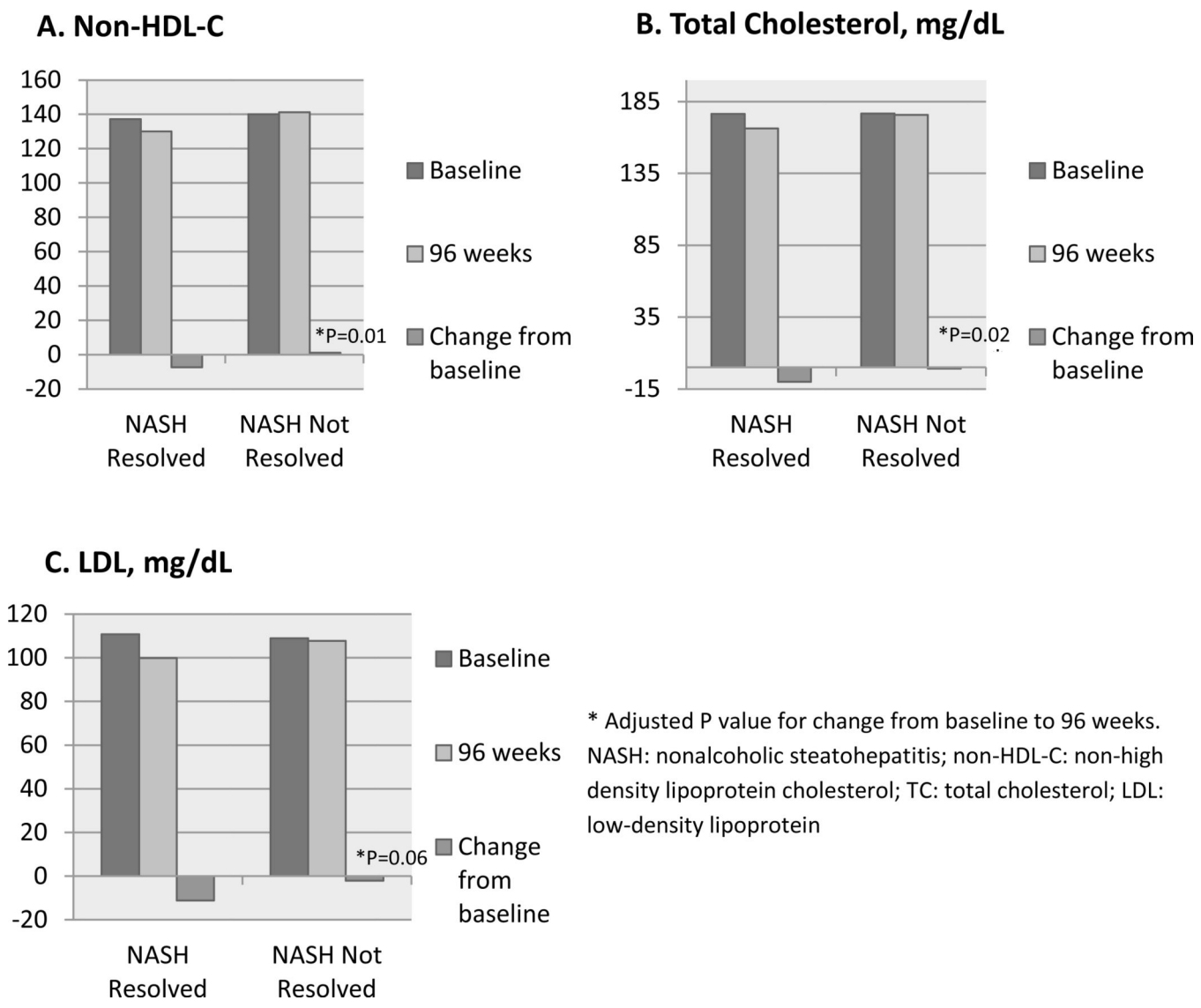
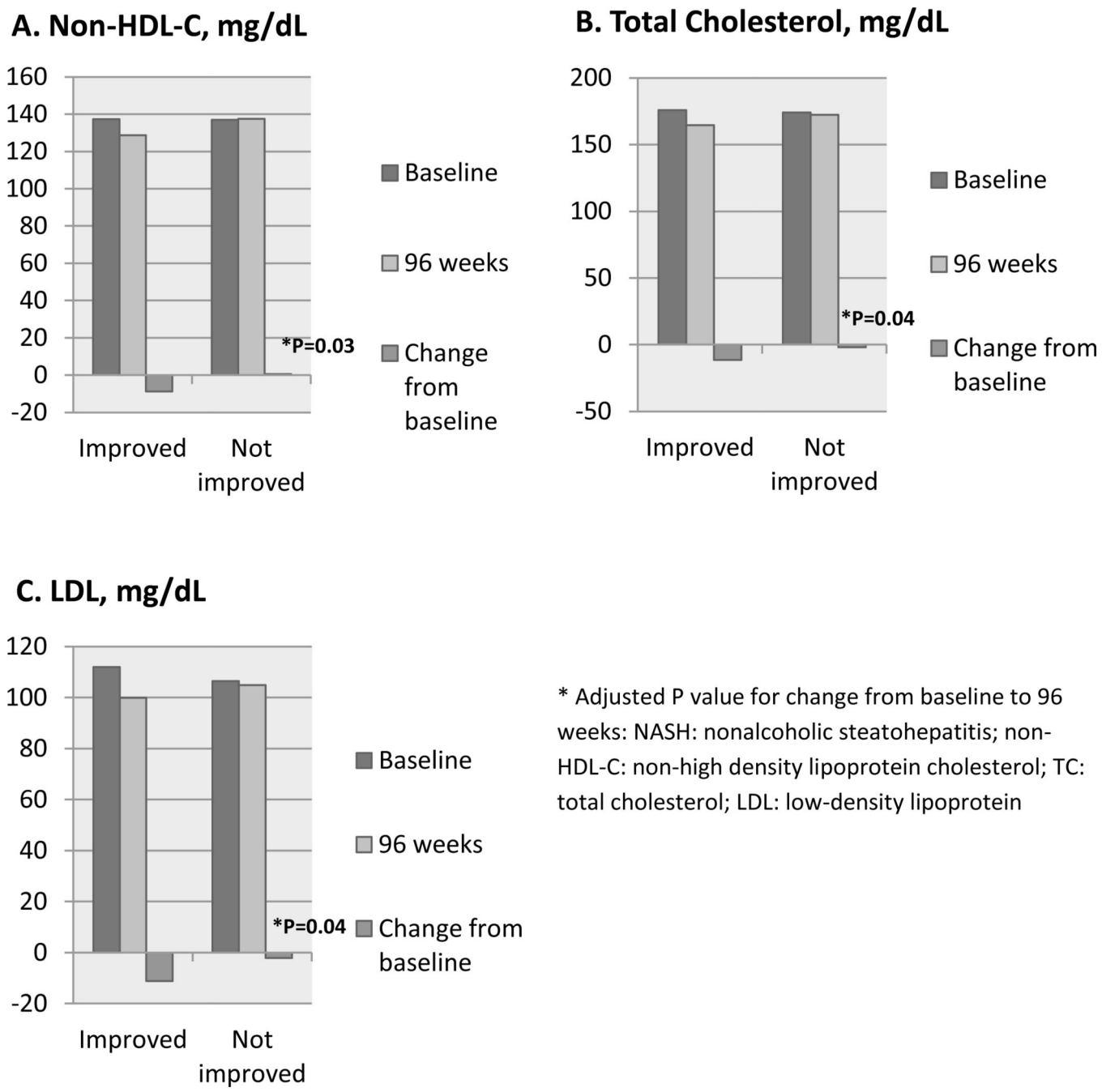


Figure 2.
Change in Lipid Level from Baseline to Week 96 by Resolution of NASH



* Adjusted P value for change from baseline to 96 weeks: NASH: nonalcoholic steatohepatitis; non-HDL-C: non-high density lipoprotein cholesterol; TC: total cholesterol; LDL: low-density lipoprotein

Figure 3.
Change in Lipid Levels by Improvement in Histology

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Table 1

Proportion of children in the TONIC Trial with Dyslipidemia and Mean Lipid Levels(N=173)

	Baseline		96 Weeks		
Lipid type and cutoff for dyslipidemia	Mean (95% CI)	Dyslipidemic N(%)	Mean (95% CI)	Dyslipidemic N(%)	P Value
Triglycerides, mg/dL **Dyslipidemic: ≥130 mg/dL**	152.5 (137.5, 167.6)	87(50.3%)	165.0 (149.0, 180.9)	80(53.3%)	0.006
HDL, mg/dL **Dyslipidemic: <40 mg/dL**	37.9 (36.6, 39.2)	107(61.8%)	35.1 (33.9, 36.3)	110(73.3%)	<0.001
Total cholesterol,mg/dL **Dyslipidemic: ≥200 mg/dL**	176.3 (170.3,182.4)	41(23.7%)	169.8 (163.6,175.9)	25(16.7%)	0.02
LDL, mg/dL **Dyslipidemic: ≥130 mg/dL**	108.8 (104.3,113.4)	37(21.5%)	103.4 (98.2,108.7)	26(17.9%)	0.004
Non-HDL-C, mg/dL **Dyslipidemic: ≥145 mg/dL**	138.5 (132.6,144.3)	61(35.2%)	134.6 (128.6,140.7)	54(36.0%)	0.15
Triglycerides/HDL **Combined dyslipidemia of obesity: >3.0**	4.3 (3.8, 4.8)	99(57.2%)	5.0 (4.4, 5.5)	103(59.5%)	<0.001

Adapted from the National Heart, Lung and Blood Institute(NHLBI) Expert Panel Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.[1]

Table 2

Baseline Lipid Levels Stratified by Presence or Absence of NASH

	NASH diagnosis at baseline		
	Definite NASH (N=73)	**Borderline/ Not NASH (N=100)**	**P***
Lipids at Baseline – N(%)			
LDL Cholesterol			
Mean(95% CI)	108.6 (101.7, 115.5)	109.0 (102.8, 115.2)	0.93
≥ 110 mg/dL	29(39.7%)	46(46.5%)	0.44
≥ 130 mg/dL	18(24.7%)	19(19.2%)	0.45
Total Cholesterol			
Mean(95% CI)	175.8(167.1, 184.6)	176.1(168.2, 185,2)	0.89
≥170 mg/dL	39(53.4%)	54(54.0%)	1.0
≥200 mg/dL	20(27.4%)	21(21.0%)	0.37
Non-HDL Cholesterol			
Mean(95% CI)	140.4(132.0, 148.9)	137.0(128.9, 145.2)	0.57
≥ 120 mg/dL	54(74.0%)	63(63.0%)	0.14
≥ 145 mg/dL	26(35.6%)	35(35.0%)	1.0
Triglycerides			
Mean(95% CI)	164.6(143.9, 185.4)	143.7(122.4, 165.0)	0.18
≥ 90 mg/dL	61(83.6%)	71(71.0%)	0.07
≥ 130 mg/dL	43(58.9%)	44(44.0%)	0.06
HDL Cholesterol			
Mean(95% CI)	35.4(33.8, 37.0)	39.7(37.8, 41.6)	**0.0008**
< 45 mg/dL	65(89.0%)	77(77.0%)	**0.04**
< 40 mg/dL	55(75.3%)	52(52.0%)	**0.003**
Triglycerides/HDL-C			
Mean(95% CI)	4.8(4.2, 5.5)	4.0(3.3, 4.7)	0.07
≥3.0	48(65.8%)	51(51.0%)	**0.05**

PP-values derived from t tests or Fisher's Exact Test.

Table 3

Lipid measures by resolution of NASH at 96 weeks

Mean(95% CI)	Resolution of NASH at 96 weeks: Resolved (N=52)	Resolution of NASH at 96 weeks: Not resolved (N=69)	P*	Adjusted P†
Non HDL-C(mg/dL)				
Baseline	137.3(127.4,147.2)	140.1(130.9,149.2)	0.69	0.71
96 weeks	130.0(120.1,139.9)	141.2(131.7,150.7)	0.11	0.05
Change from baseline	−7.3(−14.9,0.2)	1.1(−5.7,7.9)	0.1	0.01
Triglycerides(mg/dL)				
Baseline	139.7(113.7, 165.7)	152.5(127.4, 177.5)	0.49	0.72
96 weeks	161.4(132.3,190.6)	171.4(148.0,194.7)	0.59	0.3
Change from baseline	21.7(−2.2,45.6)	18.9(−1.7,39.5)	0.86	0.28
HDL(mg/dL)				
Baseline	39.1(36.7,41.6)	36.5(34.3,38.7)	0.12	0.09
96 weeks	36.4(34.5,38.4)	34.5(32.8,36.2)	0.14	0.07
Change from baseline	−2.7(−4.5,−0.8)	−2.0(−3.6,−0.4)	0.56	0.42
LDL(mg/dL)				
Baseline	110.8(101.5,120.2)	109.0(102.5,115.4)	0.73	0.97
96 weeks	99.8(90.6,109.1)	107.7(99.5,115.8)	0.21	0.16
Change from baseline	−11.2(−19.1,−3.3)	−2.1(−7.6,3.4)	0.05	0.06
Total cholesterol(mg/dL)				
Baseline	176.4(166.0, 186.9)	176.6(166.8, 186.3)	0.99	0.96
96 weeks	166.4(156.5, 176.3)	175.7(165.8, 185.6)	0.2	0.11
Change from baseline	−10.0(−18.0,−2.0)	−0.9(−8.0,6.3)	0.09	**0.02**
Triglycerides/HDL				
Baseline	4.0(3.0,5.0)	4.4(3.7,5.1)	0.48	0.62
96 weeks	4.8(3.8,5.9)	5.1(4.4,5.7)	0.69	0.31
Change from baseline	0.9(0.2,1.5)	0.7(0.04,1.3)	0.72	0.35

*P-values derived from univariable linear regression models.

†Adjusted p-values derived from linear regression models and included treatment group, baseline BMI, ethnicity, and for change measures, the baseline value of the lipid measure

Table 4

Lipid measures by histological improvement at 96 weeks

Mean(95% CI)	Improvement in histology at 96 weeks: Improved (N=56)	Not improved (N=90)	P*	Adjusted P†
Non HDL-C(mg/dL)				
Baseline	137.4(129.0, 145.8)	137.0(128.5, 145.4)	0.94	0.78
96 weeks	128.7(119.5, 137.8)	137.5(129.1, 145.9)	0.17	0.23
Change from baseline	−8.8(−15.5, −2.0)	0.5(−5.1, 6.2)	**0.04**	**0.03**
Triglycerides(mg/dL)				
Baseline	128.8(112.5, 145.0)	154.6(131.4, 177.7)	0.07	0.17
96 weeks	146.9(125.2, 168.6)	175.6(152.7, 198.5)	0.07	0.08
Change from baseline	18.2(−3.1, 39.4)	21.0(3.4, 38.6)	0.84	0.26
HDL(mg/dL)				
Baseline	38.5(36.3, 40.7)	37.3(35.4, 39.1)	0.41	0.34
96 weeks	35.9(34.0, 37.7)	34.8(33.2, 36.4)	0.41	0.48
Change from baseline	−2.6(−4.6, −0.7)	−2.4(−3.7, −1.2)	0.86	0.95
LDL(mg/dL)				
Baseline	111.9(103.8, 120.0)	106.5(100.4, 112.6)	0.28	0.25
96 weeks	99.9(91.6, 108.3)	104.8(97.8, 111.9)	0.38	0.53
Change from baseline	−11.2(−19.1, −3.3)	−2.1(−7.6, 3.4)	**0.01**	**0.04**
Total cholesterol(mg/dL)				
Baseline	175.9(166.9, 185.0)	174.2(165.5, 183.0)	0.8	0.64
96 weeks	164.5(155.2, 173.8)	172.3(163.9, 180.8)	0.23	0.3
Change from baseline	−11.4(−18.9, −3.9)	−1.9(−7.7, 3.9)	**0.05**	**0.04**
Triglycerides/HDL				
Baseline	3.6(3.0, 4.2)	4.4(3.7, 5.2)	0.07	0.16
96 weeks	4.3(3.6, 5.0)	5.3(4.6, 6.1)	0.04	0.06
Change from baseline	0.7(0.05, 1.4)	0.9(0.3, 1.4)	0.68	0.21

*P-values derived from univariable linear regression models.

†Adjusted p-values derived from linear regression models and included treatment group, baseline BMI, ethnicity, and for change measures, the baseline value of the lipid measure