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Relationship Between Metabolic and Histological Responses in People With Metabolic Dysfunction–Associated Steatohepatitis With and Without Type 2 Diabetes: Participant-Level Exploratory Analysis of the SYNERGY-NASH Trial With Tirzepatide

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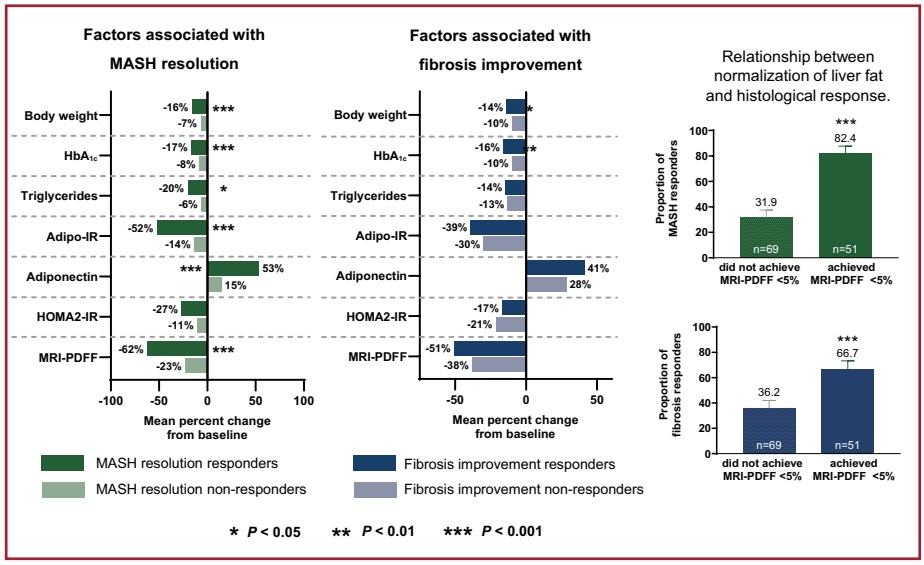
Body Weight Reduction, Improved Glycemic Control, and Normalization of Liver Fat Were Associated With Resolution of MASH and Fibrosis Improvement: A Post Hoc Analysis From the SYNERGY-NASH Trial

Background : In a phase 2 trial of MASH, tirzepatide resolved MASH in up to 62% and improved fibrosis in up to 55% of participants

Objective : To explore the relationship between metabolic and histological responses in participants with MASH from the SYNERGY-NASH trial

Research Design

- Participant-level post hoc analysis of 154 participants who completed the study from the phase 2 52-week SYNERGY-NASH trial of patients with MASH and stage 2 or 3 fibrosis
- All treatment groups pooled for responder analysis



Adipo-IR, adipose tissue insulin resistance index; PDFF, proton density fat fraction.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  In patients with metabolic dysfunction–associated steatohepatitis (MASH), tirzepatide was superior to placebo for MASH resolution in the SYNERGY-NASH trial. We hypothesized that hepatic histological responses may be associated with metabolic improvements in patients with MASH.

- **What is the specific question we wanted to answer?**
  Are weight or HbA_{1c} reductions associated with histological improvements in participants with MASH from the SYNERGY-NASH trial?

- **What did we find?**
  In the overall study population, responders for both MASH resolution and fibrosis improvement had greater reductions in weight, HbA_{1c}, and normalization of liver fat compared with nonresponders.

- **What are the implications of our findings?**
  These findings provide new insight into the clinical benefits of tirzepatide, suggesting that improvements in weight, glycemic control, and liver fat potentially contribute to disease modification in MASH.

ORIGINAL ARTICLE

Relationship Between Metabolic and Histological Responses in People With Metabolic Dysfunction–Associated Steatohepatitis With and Without Type 2 Diabetes: Participant-Level Exploratory Analysis of the SYNERGY-NASH Trial With Tirzepatide

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OBJECTIVE

To explore the relationship between metabolic and histological responses in a phase 2 trial of tirzepatide in metabolic dysfunction–associated steatohepatitis (MASH).

RESEARCH DESIGN AND METHODS

This is a participant-level post hoc analysis of the 52-week, double-blind, randomized, placebo-controlled SYNERGY-NASH trial (NCT04166773). Participants (n = 190) with MASH and stage 2/3 fibrosis were randomly assigned to receive tirzepatide (5, 10, or 15 mg) or placebo once weekly. The primary end point was MASH resolution without worsening of fibrosis. Secondary end points included fibrosis improvement by at least one stage without worsening of MASH. Metabolic changes were evaluated in responders and nonresponders for histological end points in 154 participants who completed the study on treatment.

RESULTS

At baseline, 59% had type 2 diabetes and mean BMI was 35.7 kg/m^2. Compared with nonresponders, greater body weight reductions were observed in responders for MASH resolution (−16.0% vs. −7.0%; $P < 0.001$) and for fibrosis improvement (−13.6% vs. −9.8%; $P = 0.023$). Reductions in HbA_{1c} were greater for MASH responders (−1.2% vs. −0.6%; $P < 0.001$) and fibrosis responders (−1.2% vs. −0.7%; $P = 0.004$) than for nonresponders. Compared with nonresponders, greater improvements in liver fat and measures of adipose tissue insulin sensitivity (adipose tissue insulin resistance index and adiponectin) were observed with MASH responders ($P < 0.001$). In causal mediation analyses, normalization of liver fat was a significant mediator of both MASH resolution and fibrosis improvement.

CONCLUSIONS

In this post hoc exploratory analysis, MASH resolution and fibrosis improvement were associated with body weight reduction, improved glycemic control, and normalization of liver fat. Weight reduction and metabolic improvements with tirzepatide treatment potentially contributed to disease modification in MASH.

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Metabolic dysfunction–associated steatohepatitis (MASH) is the progressive form of metabolic dysfunction–associated steatotic liver disease (MASLD) (1–3). MASH is strongly associated with obesity, type 2 diabetes (T2D), insulin resistance, dyslipidemia, and hypertension and increases the risk of liver-related complications, including cirrhosis, hepatic decompensation, hepatocellular carcinoma and death (1). T2D is a recognized independent risk factor for the transition from simple hepatic steatosis to fibrotic MASH and subsequent progression to liver-related complications (4–6). Body weight reduction of at least 10%, achieved by either lifestyle modification or bariatric surgery, is associated with MASH resolution and regression of liver fibrosis (7–9).

Incretin-based therapy has demonstrated beneficial effects in MASH. In a phase 3 trial, a higher proportion of participants treated with semaglutide, a glucagon-like peptide 1 (GLP-1) agonist, achieved MASH resolution and improvement in liver fibrosis compared with placebo (10). A phase 2 trial of survodutide, a GLP-1 and glucagon receptor agonist, demonstrated significant improvement in MASH without worsening of fibrosis compared with placebo (11). Tirzepatide, a glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, demonstrated resolution of MASH without worsening of fibrosis in up to 62% of patients with MASH and significant fibrosis in the phase 2 SYNERGY-NASH trial (12). Moreover, all doses of tirzepatide were associated with improvement of fibrosis without worsening of MASH, although no adjustments were made for multiple comparisons (12). Interestingly, the percentage of responders for both histological end points, stratified by categories of percentage weight reduction and presented in a supplementary figure in the report, suggested an association between histological response and the magnitude of weight loss, warranting further in-depth assessment (12).

In clinical trials of patients with T2D and/or obesity, tirzepatide treatment was associated with significant weight reduction, improvements in glycemic control and insulin resistance, and reductions in visceral and subcutaneous abdominal adipose tissue (13–17). Given these multiple beneficial metabolic effects, we hypothesized that hepatic histological responses to tirzepatide may be associated with metabolic improvement in patients with MASH. Therefore, the aim of these participant-level exploratory analyses was to assess the relationship between metabolic and histological responses in patients with fibrotic MASH in the SYNERGY-NASH trial. In addition, we assessed whether these associations were influenced by T2D status.

RESEARCH DESIGN AND METHODS

Study Design and Participants

SYNERGY-NASH (NCT04166773) was a phase 2, multicenter, double-blind, randomized, placebo-controlled, 52-week trial conducted at 130 sites in 10 countries. The study design, protocol, and principal findings have been reported previously (12,18). Briefly, randomized participants were 18 to 80 years of age, with or without T2D, and had a BMI of 27–50 kg/m^2. A histological diagnosis of MASH with stage 2 or 3 fibrosis was confirmed by two central pathologists based on a liver biopsy performed at or within 6 months of screening. A nonalcoholic fatty liver disease (NAFLD) activity score (NAS) of $\geq$4 was required, with at least 1 point for each subcomponent (steatosis, hepatocellular ballooning, and lobular inflammation), using the nonalcoholic steatohepatitis (NASH) Clinical Research Network scoring system. Key exclusion criteria included other chronic liver diseases; cirrhosis; evidence of hepatic decompensation; alcohol consumption exceeding 14 or 21 standard drinks per week for women and men, respectively; and uncontrolled T2D (i.e., HbA_{1c} >9.5%). Doses of glucose-lowering agents were required to be stable for at least 3 months (6 months for thiazolidinediones) prior to study entry. Patients treated with insulin, a GLP-1 receptor agonist, or other medications with potential to result in weight gain or loss were excluded from the study. The primary outcome was resolution of MASH without worsening of fibrosis after 52 weeks of treatment with tirzepatide. Several secondary end points were assessed; this analysis considered the secondary end point of an improvement in fibrosis stage by at least one stage without worsening of MASH.

All participants provided written informed consent for participation in the study. The protocol was approved by local institutional ethical review boards at each participating site and was conducted according to International Conference on Harmonization Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.

Randomization and Masking

Participants were randomly assigned (1:1:1:1) to receive a once-weekly subcutaneous injection of tirzepatide (maintenance doses of 5, 10, or 15 mg) (Eli Lilly and Company, Indianapolis, IN) or placebo by use of an interactive web-response system with stratification by T2D status and geographic region. The starting dose of tirzepatide or placebo was 2.5 mg, which was increased by 2.5 mg every 4 weeks, in a blinded manner, until the target maintenance dose was achieved.

Procedures

All participants in this post hoc analysis underwent the previously described trial procedures (12,18). These analyses focused on results obtained at baseline and after 52 weeks of treatment for liver histology; magnetic resonance imaging (MRI) used to measure liver fat content (proton density fat fraction [PDFF] and liver fibro-inflammation [iron-corrected T1 image (cT1)]); vibration-controlled transient elastography (VCTE) (FibroScan) used to measure liver stiffness; body weight; and fasting blood samples to measure levels of glucose, HbA_{1c}, insulin, C-peptide, lipids, free fatty acids, liver enzymes, and biomarkers of MASH disease activity and liver fibrosis, including the Enhanced Liver Fibrosis (ELF) test, N-terminal type III collagen propeptide (PRO-C3), and noninvasive test 4 (NIS4) score.

Statistical Analyses

The efficacy analysis set, with any insulin-rescued participants removed, was used in these post hoc statistical analyses. Only participants who completed the study with both baseline and postbaseline measures were analyzed. All treatment groups were pooled for responder versus nonresponder status for the primary end point of resolution of MASH and no worsening of fibrosis and the secondary end point of fibrosis improvement by at least one stage with no worsening of MASH. Baseline characteristics are

presented for all participants included in these post hoc analyses and based on participants' T2D status and responder status for both histological end points.

We used *t* tests and χ^2 tests to compare continuous and categorical variables, respectively. A *t* test was used to compare the week 52 change or percent change from baseline for body weight and metabolic measures in histological responders versus nonresponders. Metabolic measures assessed included HbA_{1c}, fasting triglyceride levels, and insulin sensitivity according to the adipose tissue insulin resistance index (Adipo-IR) (computed with fasting free fatty acids and insulin levels), HOMA of insulin resistance (HOMA2-IR) (computed with fasting glucose and insulin levels), and adiponectin. Correlations between percentage change of weight or change in HbA_{1c} and changes in imaging and serum biomarkers of MASH disease activity and fibrosis were assessed. Histograms and smoothed density curves for tirzepatide-treated participants (all doses pooled) are presented to illustrate the relationship between percent change in body weight and responder status for histologic end points.

Correlations between the primary or secondary histologic end points and percent change in weight and other metabolic factors were evaluated with and without adjustment for percent change of weight. Causal mediation analyses were conducted to investigate the mediating effects of changes in metabolic parameters on the relationship between treatment (pooled tirzepatide vs. placebo) and the primary and secondary histological outcomes (19–22), and the percentage mediated by the metabolic measure was estimated (19). Detailed methods are provided in the Supplementary Material.

Data and Resource Availability

A statement on data and resource availability is provided in the Supplementary Material.

RESULTS

Baseline Characteristics

In the SYNERGY-NASH trial, 190 participants were randomly assigned to treatment with once-weekly tirzepatide 5 mg (*n* = 47), 10 mg (*n* = 47), 15 mg (*n* = 48), or placebo (*n* = 48). The population for these post hoc analyses comprised 154 participants who completed study treatment, had an end-of-treatment liver biopsy, and were not treated with insulin.

Analyzed participants had mean age of 55 years and BMI of 35.7 kg/m^2; 59% had T2D and 57% had stage 3 fibrosis. Compared with participants without T2D, those with T2D were significantly older (56.7 vs. 52.4 years), had higher mean HbA_{1c} (7.15% vs. 5.70%) and serum triglyceride levels (187 mg/dL vs. 155 mg/dL), and had higher prevalences of hypertension (78% vs. 48%) and dyslipidemia (75% vs. 48%). In contrast, participants with T2D had lower mean ALT (57 units/L vs. 67 units/L) and AST (45 units/L vs. 56 units/L) than non-T2D participants (Supplementary Table 1). The most common glucose-lowering agent was metformin, predominantly in participants with T2D (76%) (Supplementary Table 2). Lipid-lowering therapy was taken by 59% and 27% of participants with T2D and those without T2D, respectively (Supplementary Table 3).

Baseline characteristics for responders versus nonresponders for the primary outcome of MASH resolution without worsening of fibrosis did not differ significantly except that nonresponders had higher mean ELF (9.98 vs. 9.65) and cT1 (933.57 vs. 887.67 ms) values than responders (Supplementary Table 4). For the secondary outcome of fibrosis improvement by at least one stage with no worsening of MASH, nonresponders were significantly more likely than responders to have stage 3 fibrosis (66% vs. 48%) and higher mean values for fibrosis biomarkers, including Fibrosis-4 score (1.72 vs. 1.43), PRO-C3 (148.54 vs. 111.81 μg/L), ELF (10.06 vs. 9.56), and VCTE liver stiffness measurement (13.21 vs. 10.15 kPa) (Supplementary Table 5). For both outcomes, baseline weight, BMI, diabetes status, glycemic control, measures of insulin sensitivity, fasting lipid levels, and adipokines did not differ between responders and nonresponders.

MASH Resolution Responders

Overall, there were 80 responders (52%) (tirzepatide, *n* = 76; placebo, *n* = 4) and 74 (48%) nonresponders (tirzepatide, *n* = 44; placebo, *n* = 30) for the primary outcome of MASH resolution without worsening of fibrosis. Responders achieving this outcome had a significantly greater mean percent decrease from baseline in body weight compared with nonresponders (−16.0% [SE 1.1] vs. −7.0% [1.1]; $P < 0.001$) (Fig. 1*A*). This finding was statistically significant in both the T2D population (−14.3% [1.3] vs. −6.5% [1.4]; $P < 0.001$) (Fig. 1*B*) and the non-T2D population (−19.3% [1.9] vs. −7.6% [1.6]; $P < 0.001$) (Fig. 1*C*). Greater reductions in HbA_{1c} were observed in responders compared with nonresponders for the overall population (−1.2%, [SE 0.1] vs. −0.6% [0.1]; $P < 0.001$) (Fig. 1*D*), the T2D population (−1.5% [SE 0.1] vs. −0.9% [0.2]; $P = 0.007$) (Fig. 1*E*), and the non-T2D population (−0.6% [0.1] vs. −0.3% [0.1]; $P = 0.020$) (Fig. 1*F*). Among participants with T2D, MASH responders were more likely to achieve a normal HbA_{1c} of <5.7% compared with MASH nonresponders (64.0%, [SE 6.8] vs. 35.9% [7.7]; $P = 0.009$) and those who achieved HbA_{1c} of <5.7% were more likely to be MASH responders compared with participants with HbA_{1c} ≥5.7% at week 52 (69.6% [SE 6.8] vs. 41.9% [7.5]); $P = 0.009$) Supplementary Fig. 1). Participant-level changes from baseline in weight and HbA_{1c} at week 52 by responder status are presented with waterfall plots in Supplementary Figs. 2 and 3, respectively. Greater reductions in fasting triglyceride levels were observed for responders compared with nonresponders for the overall population (−20.4% [SE 4.3] vs. −6.5% [3.9]; $P = 0.018$) (Fig. 1*G*) and the T2D population, (−24.0% [3.2] vs. −5.8% [6.3]; $P = 0.007$) (Fig. 1*H*) but not for the non-T2D population (Fig. 1*I*). Compared with nonresponders, responders had greater percent reductions in liver fat (MRI-PDFF) in the overall population (−62.4% [3.2] vs. −22.9% [8.1]; $P < 0.001$) (Fig. 1*J*), the T2D population (−59.6% [4.4] vs. 31.1% [9.3]; $P = 0.003$) (Fig. 1*K*), and the non-T2D population (−67.2% [4.0] vs. −13.7% [13.6]; $P < 0.001$) (Fig. 1*L*).

Greater improvements in measures of insulin sensitivity were observed in MASH responders compared with nonresponders (Fig. 2). Mean percent decrease from baseline in Adipo-IR was significantly greater for responders compared with nonresponders for the overall population (−52.4% [SE 4.7] vs. −13.7% [7.7]; $P < 0.001$) (Fig. 2*A*), the T2D population (−46.4% [6.6] vs. −5.3% [12.0]; $P = 0.002$) (Fig. 2*B*), and the non-T2D

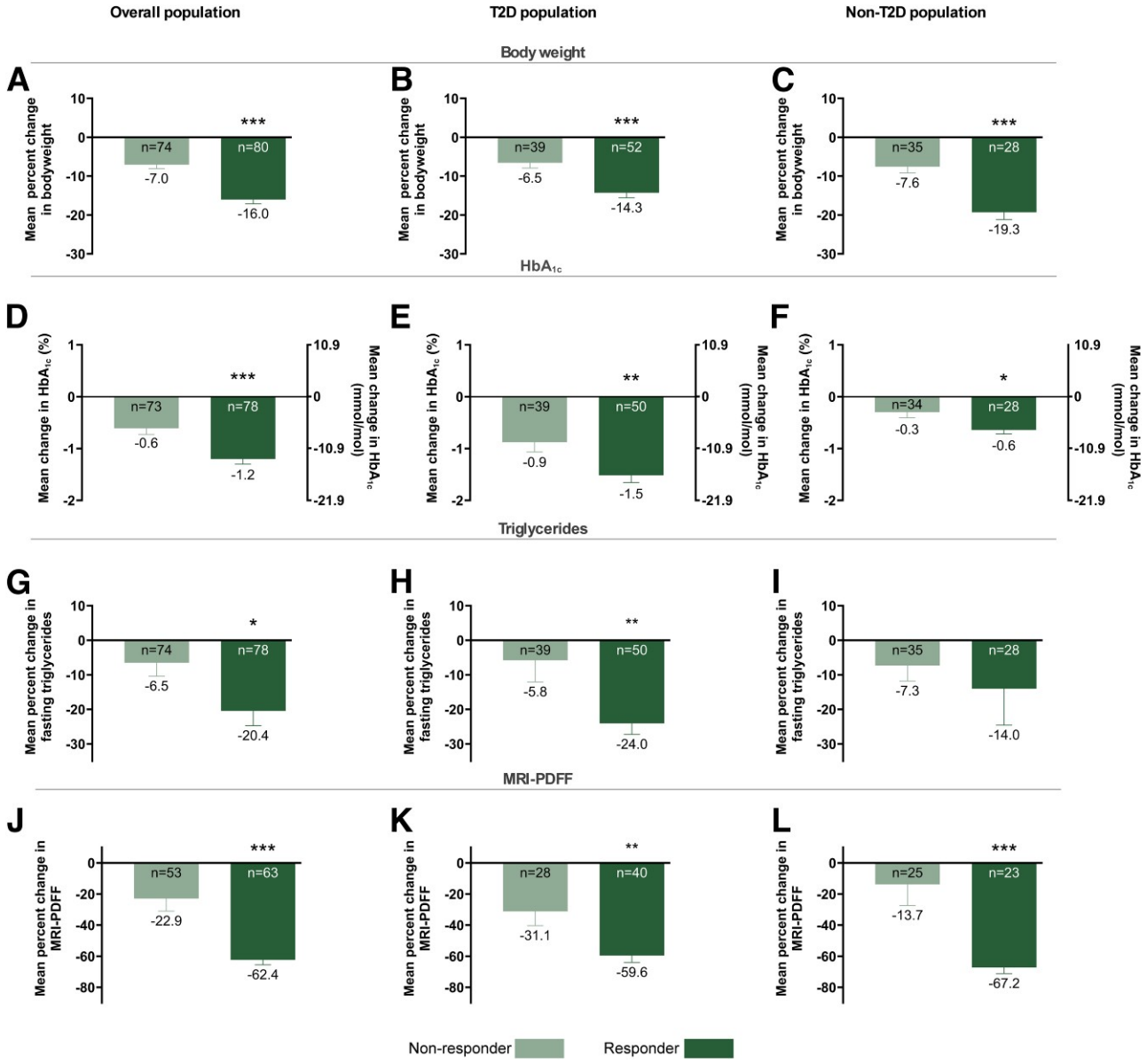

Figure 1—Change in metabolic parameters among the overall (*A*, *D*, *G*, *J*), T2D (*B*, *E*, *H*, *K*), and non-T2D (*C*, *F*, *I*, *L*) populations by responder status for the primary end point of resolution of MASH and no worsening of fibrosis. All treatment groups (including placebo) were pooled for the responder vs. nonresponder analysis of meeting each of two histologic end points. Data are observed means (error bars represent the SE). **P* < 0.05; ***P* < 0.01; ****P* < 0.001 vs. nonresponder, by *t* test using the efficacy analysis set excluding one insulin-rescued participant.

population (−64.5% [4.4] vs. −23.2 [8.9]; *P* < 0.001) (Fig. 2*C*). The reduction in HOMA2-IR was significantly greater in responders than in nonresponders only in the non-T2D population (−38.1% [SE 8.4] vs. −13.7% [6.8]; *P* = 0.028) (Fig. 2*F*). Greater increases in adiponectin were observed for responders compared with nonresponders in the overall population (53.4% [SE 6.9] vs. 14.6% [3.4]; *P* < 0.001) (Fig. 2*G*), the T2D population (47.3% [7.3] vs. 17.0% [4.9]; *P* = 0.002) (Fig. 2*H*), and the non-T2D population (64.3% [14.0] vs. 11.8 [4.6]; *P* < 0.001) (Fig. 2*I*).

Fibrosis Improvement Responders

There were 77 responders (50%) (tirzepatide, *n* = 67; placebo, *n* = 10) and 77 nonresponders (50%) (tirzepatide, *n* = 53; placebo, *n* = 24) for the secondary end point of improvement in fibrosis stage by at least one stage without worsening of MASH. Participants achieving this outcome had a significantly greater mean percent decrease from baseline in body weight compared with nonresponders in the overall population (−13.6% [SE 1.1] vs. −9.8% [1.2]; *P* = 0.023) (Fig. 3*A*) and the T2D population (−13.7% [SE 1.4] vs. −7.7% [1.4]; *P* = 0.003) (Fig. 3*B*) but not in the non-T2D population (Fig. 3*C*). Greater reductions in HbA_{1c} (% units) were observed in responders compared with nonresponders in the overall population (−1.2% [SE 0.1] vs. −0.7% [0.1]; *P* = 0.004) (Fig. 3*D*) and the T2D population (−1.6% [0.2] vs. −0.9 [0.2]; *P* = 0.002) (Fig. 3*E*) but not in the non-T2D population (Fig. 3*F*). There were no significant differences among fibrosis responders and nonresponders regarding achievement of HbA_{1c} <5.7% (Supplementary Fig. 1). Participant-level changes from baseline in weight and HbA_{1c} at week 52 by responder status are presented with

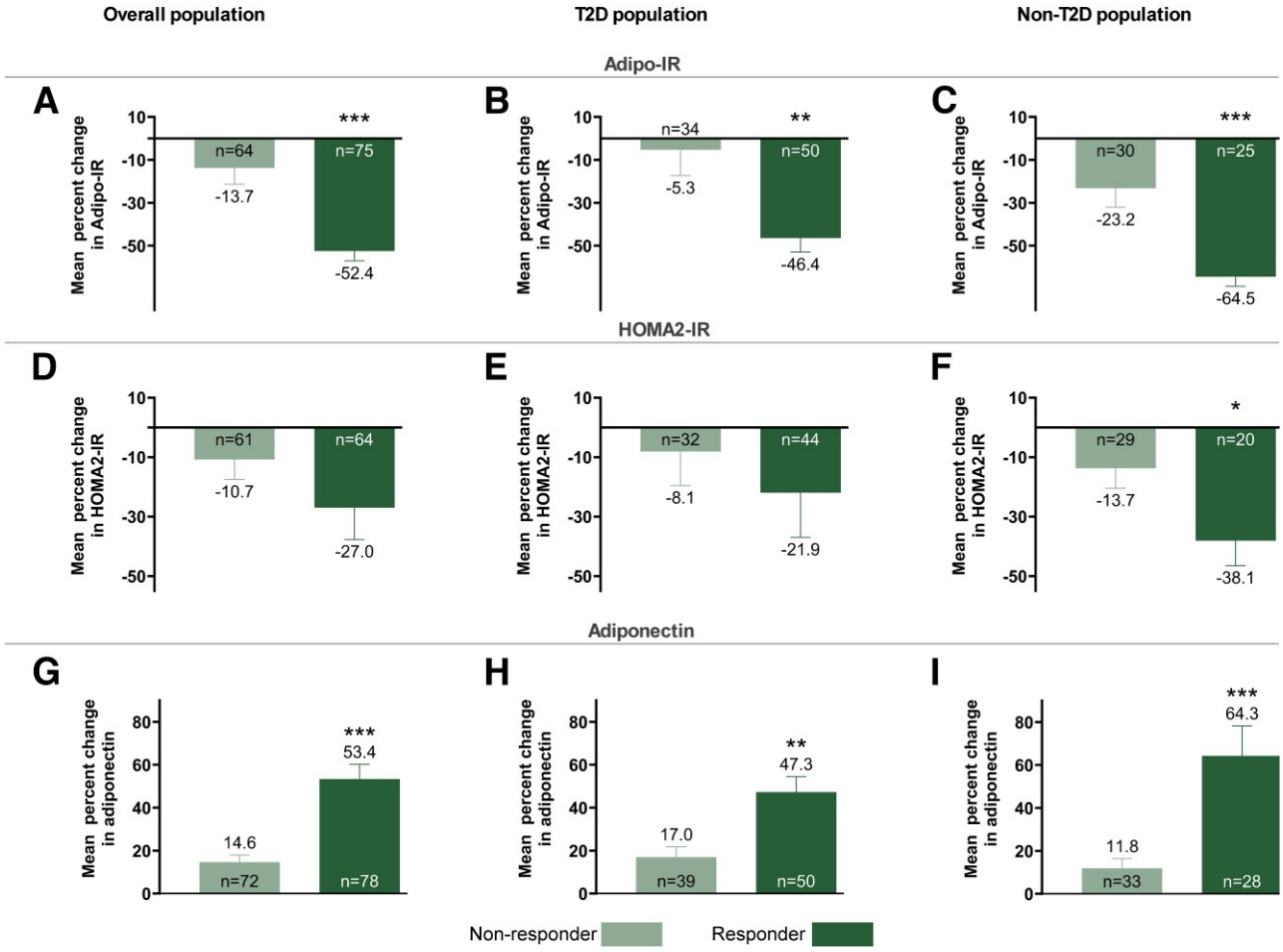

Figure 2—Change in insulin resistance serum biomarkers among the overall (*A*, *D*, *G*), T2D (*B*, *E*, *H*), and non-T2D (*C*, *F*, *I*) populations by responder status for the primary end point of resolution of MASH and no worsening of fibrosis. All treatment groups (including placebo) were pooled for the responder vs. nonresponder analysis of meeting each of two histologic end points. Data are observed means (error bars represent the SE). *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ vs. nonresponder, *t* test using the efficacy analysis set excluding one insulin-rescued participant.

waterfall plots in Supplementary Figs. 2 and 3, respectively. Greater increases in fasting adiponectin levels were observed for responders compared with nonresponders in the T2D population (44.2% [SE 7.7] vs. 22.5% [5.1]; $P = 0.025$) (Fig. 3*H*), but this was not statistically significant in the overall population (Fig. 3*G*) or the non-T2D population (Fig. 3*I*). No significant differences in mean percent changes in Adipo-IR, HOMA2-IR, triglycerides, or liver fat (MRI-PDFF) were observed between fibrosis responders and nonresponders (Supplementary Fig. 4).

Normalization of Liver Fat

For the outcome of MASH resolution without worsening of fibrosis, 65.6% of responders achieved MRI-PDFF <5% compared with 16.1% of nonresponders ($P < 0.001$) (Supplementary Fig. 5). Similarly, for the outcome of fibrosis improvement by at least one stage without worsening of MASH, 57.6% of responders achieved MRI-PDFF <5% compared with 27.9% of nonresponders ($P = 0.001$) (Supplementary Fig. 6). Additionally, participants achieving MRI-PDFF <5% were significantly more likely to achieve MASH resolution and fibrosis improvement by at least one stage than participants not achieving this threshold (82.4% vs. 31.9%, $P < 0.001$; and 66.7% vs. 36.2%, $P < 0.001$, respectively). These findings were statistically significant for the T2D and non-T2D populations for both outcomes.

Relationships With Changes in Body Weight and Metabolic Measures

To explore the relationship between histological responses and changes in body weight or other metabolic factors, we performed correlation analyses. We found that changes in body weight ($r = -0.43$), HbA_{1c} ($r = -0.30$), Adipo-IR ($r = -0.36$), triglycerides ($r = -0.19$), and adiponectin ($r = 0.38$) were significantly ($P < 0.05$) correlated with MASH resolution and changes in weight ($r = -0.18$) and HbA_{1c} ($r = -0.24$) were significantly ($P < 0.05$) correlated with fibrosis improvement (Supplementary Tables 6 and 7). When adjusting for percent change of weight, the correlation between change in Adipo-IR and MASH resolution remained statistically significant ($r = -0.19$; $P = 0.0298$); changes in HbA_{1c} ($r = -0.16$; $P = 0.0539$) and adiponectin ($r = 0.13$; $P = 0.1196$) had strong trends but did not reach statistical significance, and the correlation with triglycerides was not significant ($P = 0.4979$). Interestingly, the correlation between change in HbA_{1c} and fibrosis improvement remained statistically significant after adjusting for percent change in weight ($r = -0.18$; $P = 0.0256$).

Significant ($P < 0.001$) direct linear correlations were observed between

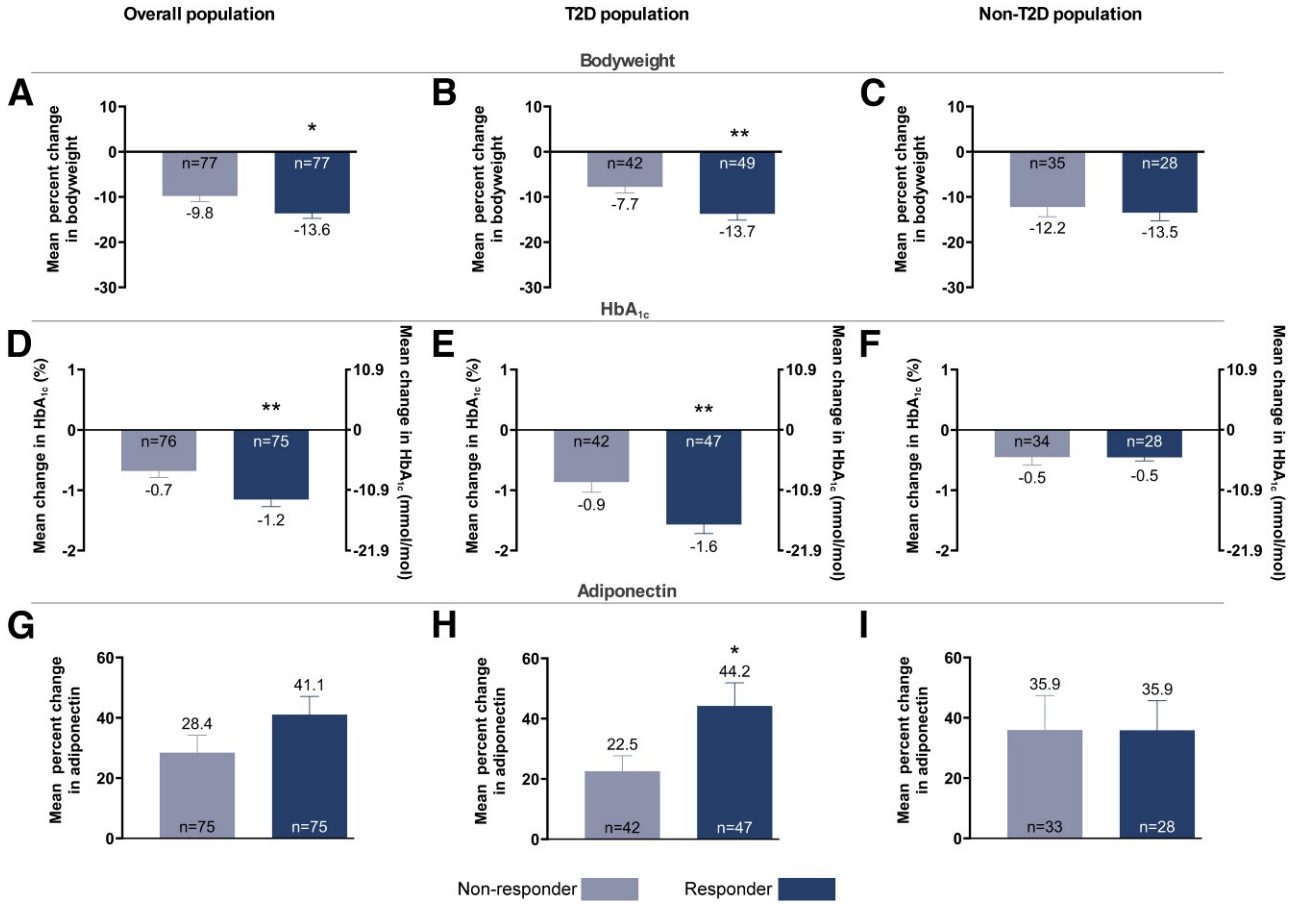

Figure 3—Change in metabolic parameters among the overall (*A*, *D*, *G*), T2D (*B*, *E*, *H*), and non-T2D (*C*, *F*, *I*) populations for the secondary end point of fibrosis improvement by at least one stage without worsening of MASH. All treatment groups (including placebo) were pooled for the responder vs. nonresponder analysis of meeting each of two histologic end points. Data are observed mean (error bars represent the SE). *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ vs. nonresponder, by *t* test using the efficacy analysis set excluding one insulin-rescued participant.

reductions in body weight and reductions in liver fat (MRI-PDFF; $r = 0.653$), liver fibro-inflammation (MRI-cT1; $r = 0.614$), NAS score ($r = 0.616$), ALT ($r = 0.468$), AST ($r = 0.372$), ELF ($r = 0.410$), Pro-C3 ($r = 0.394$), NIS4 ($r = 0.566$), and liver stiffness (VCTE; $r = 0.216$, $P = 0.008$) (Supplementary Fig. 7). Significant ($P < 0.001$) direct correlations were also observed between reductions in HbA_{1c} (%) and reductions in liver fat ($r = 0.469$), liver fibro-inflammation ($r = 0.379$), NAS score ($r = 0.406$), ALT ($r = 0.302$), AST ($r = 0.255$; $P = 0.002$), ELF ($r = 0.346$), Pro-C3 ($r = 0.261$; $P = 0.001$), and liver stiffness (VCTE; $r = 0.242$, $P = 0.003$) (Supplementary Fig. 8). Finally, percent changes in adiponectin and Adipo-IR were inversely correlated ($r = -0.26$; $P = 0.0023$).

Causal Mediation Analyses of Metabolic Factors on Tirzepatide Effect

To further assess the metabolic mediators of the tirzepatide treatment effect, we performed exploratory causal mediation analyses (Fig. 4). We found that body weight, percent change in liver fat, and normalization of liver fat were significant ($P < 0.05$) mediators of the tirzepatide treatment effect on MASH resolution without worsening of fibrosis. Although the odds of MASH resolution with tirzepatide treatment versus placebo was reduced when accounting for changes in weight or liver fat, the unmediated tirzepatide treatment effect for this end point remained statistically significant. Changes in Adipo-IR ($P = 0.070$) and adiponectin ($P = 0.051$) approached statistical significance as mediators, but this was not the case for changes in HbA_{1c} and triglycerides ($P > 0.3$). For the end point of fibrosis improvement without worsening of MASH, only normalization of liver fat was a statistically significant mediator. After accounting for normalization of liver fat, the unmediated tirzepatide treatment effect was not statistically significant. Change in HbA_{1c} approached statistical significance as a mediator ($P = 0.114$), but this was not the case for change in weight, Adipo-IR, triglycerides, or adiponectin ($P > 0.5$ for all).

Finally, in separate mediation analyses, change in weight was a significant mediator of changes in liver fat ($P < 0.001$) and HbA_{1c} ($P = 0.007$). The relationships between percent change in body weight and responder status of participants achieving histologic end points are illustrated with smoothed density curves in Supplementary Fig. 9.

CONCLUSIONS

These participant-level exploratory analyses of data from the SYNERGY-NASH trial expand upon previous findings of a higher proportion of MASH resolution and fibrosis improvement observed with the GIP/GLP-1 receptor agonist tirzepatide, compared with placebo, among participants with MASH and fibrosis stages 2 or 3 (12). The present analysis demonstrates

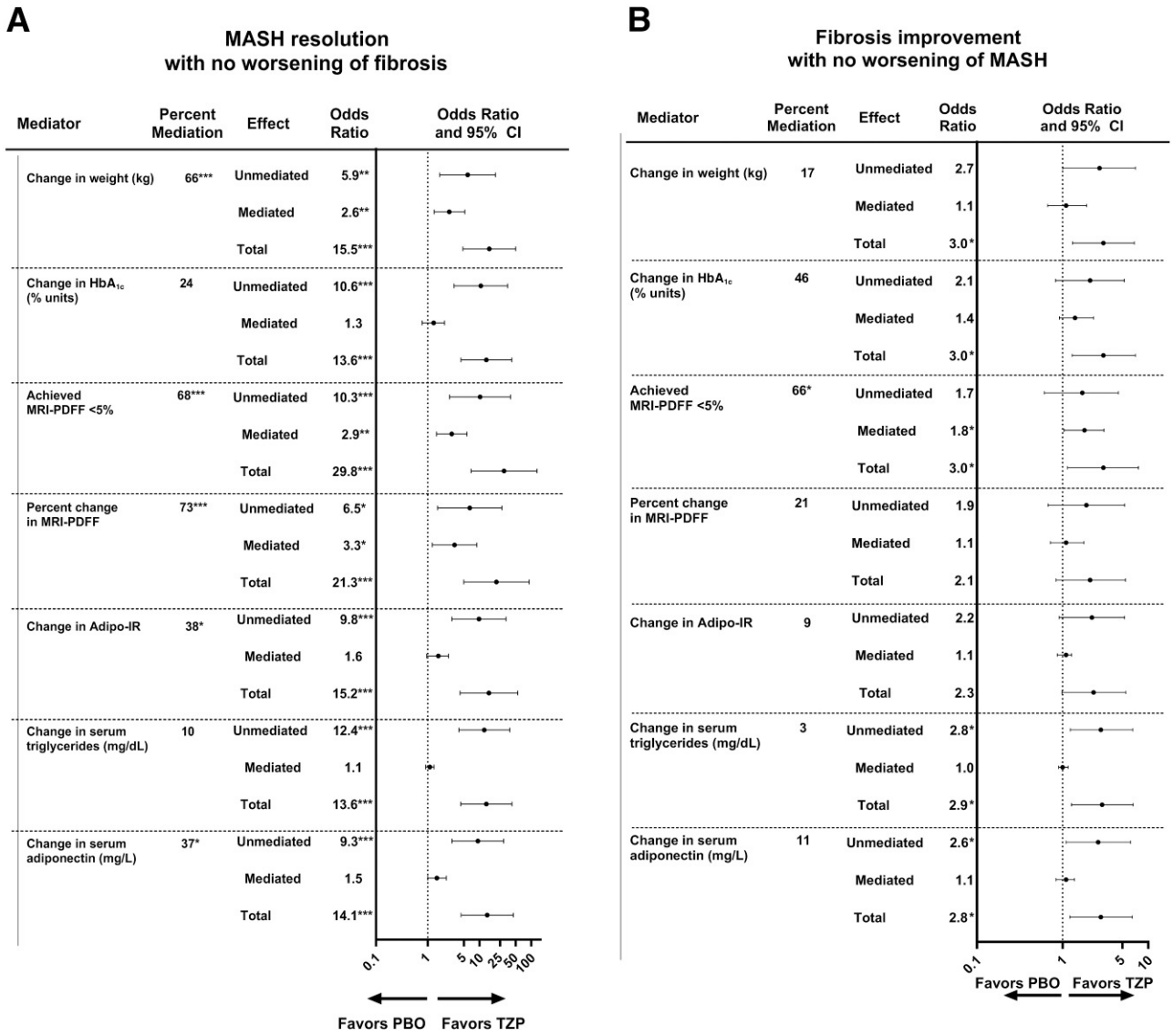

Figure 4—Causal mediation analyses of the mediating effects of changes in metabolic measures after tirzepatide treatment for 52 weeks on MASH resolution with no worsening of fibrosis (*A*) and fibrosis improvement with no worsening of MASH (*B*). The dashed line indicates an odds ratio equal to 1. The odds ratio with 95% CIs and *P* values are provided for the natural direct effects (unmediated; tirzepatide treatment effect not explained by the metabolic mediator), natural indirect effects (mediated; effect mediated by the metabolic measure), and total effects. A logarithmic scale is used due to the wide 95% CIs, but the *x*-axis numbers reflect the odds ratios. The percentages mediated by the metabolic measures, calculated using the formula of VanderWeele and Vansteelandt (19), are shown with *P* values. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. PBO, placebo.

that achievement of both of these histologic end points was associated with larger mean reductions in body weight and HbA_{1c}, normalization of liver fat, and improvements in adipose tissue insulin sensitivity, compared with nonresponders.

Body weight reduction is associated with improvement in histological lesions of MASH and liver fibrosis induced by lifestyle modification (9), bariatric surgery (7,8), or incretin-based therapy, including semaglutide, survodutide, or tirzepatide (10–12). This study demonstrates that in the SYNERGY-NASH trial, reductions in body weight were significantly correlated with reductions in hepatic fat content (MRI-PDFF), liver fibro-inflammation (MRI-cT1), MASH disease activity (NAS score), and improvements in biomarkers of fibrosis, including ELF, PRO-C3, NIS4, and liver stiffness (VCTE). These observations suggest that body weight reduction with tirzepatide treatment may play a key role in MASH resolution and fibrosis improvement. However, the relationship between percent change of weight and histological responder status was less apparent for fibrosis improvement (Fig. 4). These findings suggest differential impacts of the magnitude of body weight change with tirzepatide for MASH resolution compared with fibrosis improvement. Of note, nonresponders for fibrosis improvement had higher baseline fibrosis stage and liver stiffness measures, consistent with greater severity of liver disease. In this trial, the response to tirzepatide treatment appeared to be dose-dependent for MASH resolution but not for fibrosis improvement (12). This suggests either a ceiling effect for the relationship between body weight reduction and

fibrosis improvement or that a longer exposure to treatment or greater body weight reduction is needed to observe a potential dose-response relationship. A higher percentage of patients with MASH had an improvement of fibrosis 5 years after bariatric surgery than after 1 year (7). In the 72-week A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight (SURMOUNT-1) trial of tirzepatide in participants with obesity, additional body weight reduction was observed beyond 52 weeks (15). Further studies with larger sample size and longer duration are needed to determine whether body weight reduction could be used as a predictor of histological response.

The effect of improved glycemic control on the histological response to treatment of fibrotic MASH has been studied less extensively. The present analysis demonstrates that beyond associations between the reduction in HbA_{1c} and both MASH resolution and fibrosis improvement, reductions in HbA_{1c} were significantly correlated with reductions in hepatic fat content (MRI-PDFF), liver fibro-inflammation (MRI-cT1), MASH disease activity (NAS score), and improvements in biomarkers of fibrosis, including ELF, PRO-C3, and liver stiffness (VCTE). This suggests that improvement in glycemic control may contribute to improvement of MASH. These findings are consistent with those of a retrospective study reporting an association between glycemic control and severity of ballooned hepatocytes and steatosis in patients with MASLD (23). This possibility is also supported by the high proportion of patients with T2D who were MASH responders who achieved a normal HbA_{1c} of <5.7%, which is usually considered a marker of diabetes remission. Similarly, achievement of an HbA_{1c} <5.7% was associated with a higher odds of MASH resolution. These observations are consistent with epidemiological data demonstrating that T2D is a risk factor for progressive disease in MASH (4–6). However, in the causal mediation analysis, change in HbA_{1c} was not a statistically significant mediator of the treatment effect of tirzepatide on both MASH resolution and fibrosis improvement.

MASH resolution was associated with significant improvements in markers of insulin sensitivity. A greater reduction in Adipo-IR and a greater increase in plasma adiponectin were observed in the responders for MASH resolution compared with nonresponders in the overall, T2D, and non-T2D populations. These findings are consistent with improved adipose tissue insulin sensitivity. However, the changes in Adipo-IR and adiponectin did not reach statistical significance in the causal mediation analysis, potentially due to a lack of statistical power. The mean reduction in HOMA2-IR (a marker of whole-body insulin resistance) was greater in responders for MASH resolution compared with nonresponders but reached statistical significance only in the subgroup without T2D, likely due to high variability in the fasting insulin levels in participants with T2D treated with a variety of glucose-lowering medications. In the T2D population, the greater reduction in serum triglyceride levels among MASH resolution responders compared with nonresponders is consistent with improved insulin sensitivity. Previous studies in T2D reported improvements in insulin sensitivity with tirzepatide treatment as assessed by HOMA2-IR (13,17) and insulin clamp studies (24). The association between markers of adipose tissue insulin resistance and MASH resolution is in line with studies highlighting the importance of dysfunctional adipose tissue in MASLD and previous pharmacological studies in participants with MASH reporting associations between improvement in adipose tissue insulin sensitivity and liver histology (25–29). GIP receptors are present in adipose tissue; preclinical studies demonstrate that activation of these receptors increases lipoprotein lipase activity, which promotes postprandial triglyceride clearance while also augmenting insulin-dependent glucose uptake (30). Improvements in adipose tissue insulin sensitivity contribute to improved whole-body insulin sensitivity and reducing triglyceride levels by suppression of lipolysis (30,31). Moreover, improved lipid storage in white adipose tissue may result in a reduction in hepatic fat content deposition (32). Consistent with this hypothesis, normalization of liver fat content (i.e., MRI-PDFF <5%) in SYNERGY-NASH was strongly associated with histological response for both end points in the overall, T2D, and non-T2D populations. Together these observations support the hypothesis that tirzepatide is contributing to MASH resolution in part through GIP receptor agonism in adipose tissue.

Few MASH studies have compared histological responses in participants with T2D with those who do not have T2D. Therefore, we investigated the association between metabolic factors and histological response by T2D status. This is particularly relevant in the context of incretin-based therapies, because indirect comparisons of clinical trial and real-world data have suggested that patients with T2D lose less body weight compared with those without T2D in response to treatment with semaglutide (33–35) and tirzepatide (15,16). In participants included in the present analyses, placebo-adjusted body weight reduction with tirzepatide 15 mg was nonsignificantly (P = 0.128 for interaction term) lower in participants with T2D (−14.5%) versus those without T2D (−22.5%). The associations between MASH resolution response and change in body weight and metabolic factors (HbA_{1c}, Adipo-IR, and adiponectin) were observed in both T2D and non-T2D groups, suggesting a robust association between these metabolic parameters and MASH resolution independently of T2D status. However, the association between fibrosis improvement response and changes in metabolic parameters such as HbA_{1c}, body weight, and adiponectin were driven mainly by significant associations in the T2D group and were not observed in the non-T2D group. This suggests that metabolic dysfunction may be a larger contributor to hepatic fibrosis for individuals with T2D than in those without T2D. Alternatively, it is possible that, among responders for fibrosis improvement at 52 weeks, patients with T2D may have an enhanced and early metabolic response compared with patients without T2D. However, these emerging hypotheses need confirmation in studies with larger sample size and longer treatment duration.

An important question is whether tirzepatide-associated effects in MASH are related only to weight reduction and other metabolic improvements. Although the odds of meeting the end point of MASH resolution without worsening of fibrosis with tirzepatide versus placebo were reduced after controlling for reduction in body weight or for improvements in HbA_{1c}, liver fat, Adipo-IR, adiponectin, or triglycerides, the unmediated treatment

effect of tirzepatide versus placebo remained statistically significant (Fig. 4). This finding suggests that reduction in body weight and metabolic improvements contribute to MASH resolution but do not completely account for the treatment effects observed with tirzepatide in MASH. Given the complex pathophysiology of MASH, it is possible that other factors not measured in our study, such as changes in systemic inflammation, may contribute to the effect of tirzepatide in MASH. In contrast, the odds of fibrosis improvement with tirzepatide versus placebo were no longer statistically significant after controlling for changes in weight, HbA_{1c}, liver fat, or Adipo-IR (Fig. 4). These findings are consistent with the hypothesis that tirzepatide may have an indirect antifibrotic effect in the liver. However, studies with larger sample sizes are needed to confirm these findings.

Key limitations of this study include that this was a post hoc exploratory analysis of a single trial with a relatively small sample size that may have limited the statistical power of the mediation analyses. No adjustments were made for multiple comparisons. Furthermore, it was a per-protocol analysis, because only participants who completed the study with both baseline and postbaseline measures were included. The results, therefore, are preliminary and can only be regarded as hypothesis generating. Second, the trial duration was too short to fully assess the effects of weight reduction and metabolic improvements on fibrosis regression and major adverse liver outcomes.

In conclusion, this post hoc exploratory analysis of the SYNERGY-NASH trial data demonstrated strong associations between responses for both MASH resolution and fibrosis improvement and improvements in body weight, glycemic control, liver fat normalization, and biomarkers of insulin resistance, particularly adipose tissue insulin resistance. These observations support the hypothesis that metabolic improvements associated with tirzepatide treatment contribute to disease modification in MASH. Of note, several therapies are currently under development for the treatment of MASH; they target various pathways that do not necessarily induce weight reduction or glycemic control improvement. Indeed, the first U.S. Food and Drug Administration–approved therapy for MASH, resmetirom, does not induce weight reduction or glycemic control improvement (36). More investigations are warranted to fully decipher the relationship between metabolic and histological improvements in patients with fibrotic MASH treated with tirzepatide.

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