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Impact of a Structured Lifestyle Program on Patients with Metabolic Syndrome Complicated by Non-alcoholic Fatty Liver Disease

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ABSTRACT

Background: Lifestyle interventions are first line therapy for non-alcoholic fatty liver disease (NAFLD). **Aim:** To examine the prevalence of NAFLD among participants of the University of Michigan Metabolic Fitness Program (MetFit) and to assess the impact of this program on weight, metabolic, and liver-related parameters among patients with and without NAFLD.

Methods*:* Adults who completed the program between 2008-2016 were analyzed. Clinical and laboratory data were collected at enrollment, 12 and 24 weeks. NAFLD was defined based on liver biopsy, imaging or clinical diagnosis.

Results*:* The cohort (N= 403; 253 12-week, 150 24-week) consisted primarily of middle-aged (median 54 years) white (88%) men (63%) with severe obesity (median BMI 37.4). 47.6% met criteria for NAFLD. At baseline, NAFLD patients were younger (52 vs 55 years), had higher weights, and more metabolic derangements (higher fasting insulin and triglyceride, lower HDL-C). At program completion, 30% achieved weight reduction ≥5%, 62% resolution of hypertriglyceridemia, 33% resolution of low HDL, 27% resolution of impaired fasting glucose, and 43% normalization of ALT. Endpoints were unaffected by NAFLD. Longer program duration (OR 6.7, 95% CI 3.6-12.3) and white race (OR 3.83, 95% CI 1.04-1.76) were independent predictors of ≥5% weight loss.

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Conclusions*:* Nearly half the patients referred to a structured lifestyle program for metabolic syndrome had NAFLD. Although baseline metabolic derangements were more pronounced among NAFLD patients, the program was equally efficacious in achieving weight loss and resolving metabolic syndrome components. Program duration was the most important predictor of response.

Keywords: NAFLD, NASH, diet, exercise, metabolic syndrome

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INTRODUCTION

Obesity has become a worldwide public health crisis given its prevalence and multiple associated complications including non-alcoholic fatty liver disease (NAFLD). Metabolic syndrome (MetSyn) is highly correlated with prevalent and incident NAFLD. Approximately 46% of patients with NAFLD have concomitant MetSyn and odds of developing NAFLD are significantly higher among patients with baseline MetSyn [odds ratios (OR) 4 for men and 11.2 for women].[1,2] Presence of MetSyn has been identified as a predictor for underlying non-alcoholic steatohepatitis (NASH) among patients with NAFLD and the total number of metabolic risk factors in an individual NAFLD patient is correlated with risk of liver disease progression.[3,4] First line treatment for metabolic disease associated with obesity including NAFLD is lifestyle interventions. From a liver perspective, multiple studies have demonstrated improvement in hepatic steatosis and histologic components of NASH among patients who are able to achieve weight loss.[5,6] While 10% reduction in body weight is generally required to resolve steatosis, inflammation and fibrosis, a more modest reduction (3-5%) has been shown to decrease steatosis.

In clinical practice it can be challenging for patients to implement lifestyle changes. Highly structured lifestyle programs often have the highest efficacy for weight loss. One such program is the University of Michigan Metabolic Fitness (MetFit) Program. Although many regimented lifestyle programs were initially targeted for patients with MetSyn with cardiology and endocrinology referral bases, these types of programs represent potential therapeutic options for patients with NAFLD. The aims of this study were (1) to evaluate the prevalence of NAFLD among participants enrolled in the MetFit Program and to characterize their patterns of clinical care, and (2) to assess the impact of the MetFit Program among

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participants with and without NAFLD and to identify predictors of achieving significant weight loss at program completion.

MATERIALS AND METHODS

Metabolic Fitness Program

The University of Michigan's MetFit program was initially designed for patients with MetSyn, with detailed description of the program design previously described, but reviewed here.[7] MetSyn was defined as having at least three of the five following variables: waist circumference of ≥40 inches in men and ≥35 inches in women, triglycerides (TG) ≥150 mg/dL or treatment targeting triglycerides, high density lipoprotein-cholesterol (HDL-C) <40 mg/dL in men and <50 mg/dL in women, fasting glucose ≥100 mg/dL or diabetes, and systolic blood pressure (SBP) ≥130mmHg or diastolic blood pressure (DBP) ≥85 mmHg or on treatment for hypertension (HTN).[8] Indications for referral have expanded and include NAFLD with or without MetSyn. Both a 12 and 24 week program are offered.[9]

The program was designed to maximize cost effective and time efficient real-world delivery of care and thus utilizes an interactive small group design (rather than costly and less efficient one-on-one design). Sessions occur once per week with each session comprised of a 45-minute educational lecture and a 45-minute supervised exercise session. Lectures are given in small group settings (roughly 10-15 patients per session), with an interactional model that allows individual participants to discuss their personal goals and barriers and receive feedback from the instructor. Lecture topics include the following: an orientation lecture on the program, several lectures on nutritional topics, several lectures on the impact of stress and behavior change, dedicated lectures on exercise, and lectures on clinical impact of metabolic syndrome. Nutritional lecture topics reviewed included the Mediterranean diet, reducing sodium intake, meal planning, portion control, eating health while dining out and interpreting food labeling to tailor to a healthy eating plan. The topics for the stress/behavioral educational lecture series included emotional barriers to lifestyle change, strategies to increase awareness of emotional needs, and strategies to decrease the impact of psychosocial stressors on food choices.

Two exercise physiologists were available during exercise sessions to monitor safety, and educate and encourage participants. Aerobic exercise intensity was prescribed based on heart rate from entry graded

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exercise testing. Exercise intensity was prescribed based upon the symptom-limited stress test [treadmill exercise electrocardiogram (ECG)] and provided as 50% to 75% of predicted maximal heart rate and perceived exertion as moderately hard. Heart rate targets were 60%–85% of heart rate reserve formula (difference between resting heart rate and maximum predicted heart rate). When graded exercise testing was not indicated or not available, Borg ratings of perceived exertion scale was used.[10] The Borg rating ranges from 6 (no exertion) to 20 (maximal exertion). Participants were encouraged to target exertion levels between 11 (fairly light) and 13 (somewhat hard). Some low risk participants were allowed to exercise to intensities of 15. BMI and central obesity were taken into account for exercise regimen on an individual, as needed basis according to participant's report to the exercise physiologists who monitored each session with alternative exercises provided based on participant reported limitations.[11,12] Participants were asked to keep a logbook of aerobic exercise equipment used and total dedicated aerobic and resistance training each day. Supervised exercise sessions include aerobic exercise (typically lasting 30 to 40 minutes) using equipment of participant choice (treadmill, bike, elliptical), exercise tubes, and free-weight strength training. The remaining 5-10 minutes included stretching exercises. As a complement to aerobic exercise, participants engaged in a full-body strengthening program [free weight, resistance bands, or combination circuit training targeting all major muscle groups (legs, chest, back, shoulders, core, biceps, and triceps)]. In addition to these supervised sessions, participants were advised to engage in 150 to 300 minutes of exercise per week consisting of a combination of moderate/vigorous intensity aerobic activity and strength/resistance training. Each session of exercise was recommended to last a minimum of 20 minutes with a maximum of 60 minutes per session. In addition to this moderate to vigorous intensity exercise, a full-body strengthening program (free weight, resistance bands, or combination circuit training) was recommended minimum two times weekly targeting all major muscle groups. Participants had access to the exercise facility throughout the course of the program to use for this purpose.

Dietitians provided nutritional recommendations based on a Mediterranean diet targeted towards a 12-week weight loss goal of 5% and 24-week weight loss goal of 10% of enrollment body weight. Nutrition data was collected at entry and at completion of the program using a food frequency assessment focusing on a Mediterranean eating pattern. As part of the initial intake evaluation, personalized energy intake guidelines were calculated by a registered dietitian, as estimated by the Mifflin-St Jeor equation based on sex, age, height, weight, and activity level.[13] Resting energy equivalent as determined by the Mifflin-St Jeor equation was multiplied by an activity factor of 1.3 for participants who fully participated

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in the exercise portion of the program. For less active participants, an activity factor of 1.2 was recommended to estimate energy needs.

Data Collection

Patients complete an initial one-hour assessment including a history and physical, and evaluation for barriers to participation. Potential barriers include severe orthopedic, musculoskeletal or cardiopulmonary disease, or any other self-reported barriers that would preclude the individual from completing components of the program. A Framingham risk assessment and the Patient Health Questionnaire-9 (PHQ-9) was completed.[14] The PHQ-9 is a 9-item depression score with each item rated 0 (not at all) to 3 (nearly every day), with total scores of 5-9 representing possible depression, 10-14 high probability of depression, and >14 high probability of major depression. Baseline height, weight, BMI, waist circumference, body composition percentage (assessed using bioelectrical impedance, Tanita Body Composition Analyzer Model TBF-310; Tanita, Arlington Heights, IL, USA), blood pressure (systolic and diastolic per American Heart Association standard protocol), glucose, insulin, total cholesterol, TG, HDL-C, and low density lipoprotein-cholesterol (LDL-C) were obtained after a 12-hour fast. Hemoglobin A1c (A1c) and alanine aminotransferase (ALT) were also obtained. The baseline assessment was repeated at 12-weeks and then again at 24 weeks for those in the 24-week program. Ethics approval was regulated by the University of Michigan health system Institutional Review Board (HUM0045929) and all participants provided written informed consent.

Study Inclusion and Exclusion Criteria

To be included in the primary analysis for this outcome study, patients had to complete the program, as defined by attending >75% of sessions and needed to complete the end of program data collection for biometrics and laboratory studies.

Definition of NAFLD and Outcomes of Interest

The diagnosis of NAFLD was ascertained using a natural language processing program (University of Michigan EMERSE) and manual chart review by a hepatologist (MAK).[15] A patient was classified as meeting criteria for NAFLD if they had any of the following in the absence of significant alcohol use (defined at >14 drinks per week in men and >7 drinks per week in women; alcohol use was obtained via self-report at time of program enrollment): evidence of steatosis or steatohepatitis on liver biopsy; imaging including ultrasound (US), computed tomography (CT) scan or magnetic resonance imaging

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(MRI) noting hepatic steatosis; a clinical diagnosis code (ICD-9 or 10) for NAFLD or NASH; or a combination of the above. We also assessed proportion of patients with NAFLD referred and managed by hepatology and/or gastroenterology (GI). In addition, we analyzed differences in baseline clinical characteristics and the impact of the program between patients with and without NAFLD. Specifically, we investigated percentage weight loss and predictors of weight loss, and changes in metabolic and liver-related parameters and change in depression scores. Insulin resistance was assessed by homeostasis model assessment-estimated insulin resistance (HOMA-IR) among patients without baseline diabetes, and defined as (fasting plasma insulin x fasting plasma glucose) / 22.5, with a value >2.9 indicative of significant insulin resistance.[16]

Statistical Analyses

Descriptive and bivariate analyses were performed to assess baseline characteristics and impact of the MetFit program on outcomes of interest. Chi-square tests and Fisher exact tests were used for categorical variables and t-tests were used for continuous variables. Variables with distributions that deviated from normality were reported by median and interquartile range (Q1, Q3) and were compared using the Kruskal-Wallis test. Intention to treat analysis was performed for primary outcomes of interest to account for program drop out using multiple variable imputation. Multivariate analysis was performed to identify predictors of weight loss. Candidate covariates were assessed for inclusion into the multivariable model based on p values <0.10 in the univariate analysis and biologic plausibility. P values ≤0.05 were considered statistically significant. All analyses were performed in STATA 14 (StataCorp, College Station, TX).

RESULTS

Program Adherence and Drop Out

Overall completion rate for the MetFit Program was approximately 79% (defined as percentage of participants who complete≥ 75% of sessions). Drop out occurred mostly in the second half of the program. Characteristics of patients who did versus those who did not complete the program are detailed in **Supplement Table 1**. Overall, there was a higher proportion of females among the population of participants who did not complete the program (among participants who did not complete the program, 69% were female whereas 37.5% of program completers were female, p=<0.001). There was a similar proportion of patients with NAFLD who dropped out vs completed the

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program, (41.6% vs 47.6%). Participants who dropped out of the program had a higher prevalence of central obesity (95.5% vs 88.1%, p=0.03) but a lower prevalence of hypertriglyceridemia (42.2% vs 54.1%, p=0.04) and low HDL-C (38.9% vs 57.3%, p=0.002). Of note, those who dropped out had higher baseline PHQ-9 depression scores [7 vs 5, p=0.04] and tended to have more extensive formal educational backgrounds. Baseline characteristics were otherwise similar between those who dropped out and those who completed the program.

NAFLD Prevalence and Care Patterns

Within this cohort, 47.6% of patients had evidence of NAFLD. 16 (8.3%) met criteria based on a combination of imaging, clinical and histologic criteria, 96 (50%) met criteria based on a combination of imaging and clinical diagnosis, 45 (23.4%) by clinical diagnosis alone, and 35 (18.2%) by imaging criteria alone. Among those meeting diagnostic criteria for NAFLD, only 47 (25%) were managed by GI/Hepatology for NAFLD. Of note, an additional 31% of patients with NAFLD had established care with a GI provider for other conditions, but did not have their NAFLD managed or addressed by the GI provider (**Figure 1**).

Baseline Patient Characteristics

The baseline characteristics of patients are displayed in **Table 1.** Overall the cohort consisted primarily of middle-aged (median 54 years) white (88.6%) men (62.5%) with severe obesity (median BMI 37.4). All 5 components of MetSyn were present in 19.9%, 4 components in 26.9% and 3 components in 27.9%. NAFLD patients had higher numbers of components of the MetSyn (median 4 vs 3, p=0.001). At baseline, patients with NAFLD were younger (52 vs 55 years, P=0.004) and more likely to have higher weight (242 vs 227 lb, p=0.01) and maximum lifetime weight (250 vs 231 lb, P=.008). NAFLD patients also had higher prevalence of features of the metabolic syndrome and insulin resistance, and higher prevalence of abnormal ALT. There were no significant differences in baseline characteristics between participants who completed the 12-week versus 24-week program aside from a higher prevalence of baseline HTN in the 24-week program (75% vs 57.8%, P=0.001) (**Supplement Table 2**). Baseline NAFLD Fibrosis Score (NFS), a non-invasive biomarker of fibrosis in NAFLD, was available in 90 (47%) NAFLD patients. The median NFS was -0.62 (IQR -1.56 to 0.26), with a value of <-1.455 consistent with no to minimal fibrosis and a score of >0.675 consistent with advanced fibrosis. [17]

Impact of Program on Outcomes of Interest

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Results of the impact of the MetFit program are outlined in **Table 2**. At 12-weeks a weight reduction ≥5% was achieved in 23% of participants and weight reduction≥10% in 3.4% of participants. The program was efficacious in eliminating components of the MetSyn, with resolution of hypertriglyceridemia (62%) being most common. The degree of change in triglyceride level was not significantly different based on use of statin at enrollment (N=168 on statins). The distribution of number of components of the MetSyn at 12 weeks was similar among those with and without NAFLD (median=3 for both, p=0.19). Also of note, 36% of patients with baseline abnormal ALT had normalized ALT and median PHQ-9 score improved by 2 points. When the impact of the program at 12-weeks was stratified by the presence of NAFLD, weight loss and improvement in metabolic parameters were similar in patients with and without NAFLD but patients with NAFLD had a greater decrease in percentage of body fat (-1.5 vs -0.9, p=0.009), and a larger reduction in ALT (-5.5 vs -2 U/L, p=0.004) (**Figure 2**). Pre and post NFS was available in 36 (19%) NAFLD patients, with a median change in NFS of -0.21 (IQR -0.73 to 0.77).

In the 24-week program, weight reduction ≥5% was achieved in 53% of participants and weight reduction ≥10% in 16% of participants. At week 24, median weight loss was 12.5 lb (IQR 5-20.5), resolution of hyperTG was observed in 35%, low HDL-C in 34%, impaired fasting glucose in 30.6% and insulin resistance in 28.7%. The distribution of number of components of the MetSyn at 24 weeks was similar among those with and without NAFLD (median=3 for both, p=0.32). Roughly half (54%) of patients with an abnormal ALT had normalized their ALT. Median PHQ-9 score remained improved by 2 points compared to baseline. Weight loss and improvement in metabolic parameters were similar in patients with and without NAFLD, but patients with NAFLD were noted to have a greater decrease in TG (-45mg/dL vs -23 mg/dL, p=0.05) and a larger reduction in ALT (-11 U/L vs -3 U/L, p=0.003) (**Figure 2**).

Intention to treat analysis to evaluate impact of outcomes at week 12 demonstrated similar overall trends in change in weight, fasting glucose, triglycerides, HDL and ALT (**Supplement Table 3**). There were more pronounced reductions in weight and resolution of low HDL among participants with NAFLD in this subanalysis.

Predictors of Weight Loss

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Characteristics of patients who did and those who did not achieve ≥5% weight reduction by program completion are displayed in **Table 3.** Those with ≥5% weight reduction were more likely to be women and to be white, and had a higher baseline weight (241 lb vs 235.5 lb, P=0.05) and a higher median ALT (35 vs 30 IU/L, p=0.03) compared to those with <5% weight reduction. Likelihood of achieving ≥5% weight reduction was similar in patients with or without NAFLD. The most striking variable associated with achieving ≥5% weight reduction was duration of program participation . As expected, individuals who were able to achieve ≥5% weight loss were more likely to have improvement in metabolic parameters including resolution of central obesity (19.3% vs 6.9%, P=0.001) and impaired fasting glucose (38.4% vs 23.2%, P=0.01), and more pronounced reductions in A1c, fasting glucose, fasting insulin, insulin resistance and TG. They also had more pronounced reduction in ALT.

A sub-analysis of individuals with and without ≥10% weight loss noted that participants with a higher maximum weight (p= 0.04) and those who completed the 24-week program were significantly more likely to achieve ≥10% weight loss (82.7% vs 33.7%, P=<0.001). Participants who achieved ≥10% weight loss had higher rates of resolution of central obesity (26.9% vs 9.5%, P=0.006), impaired fasting glucose (76.5% vs 24%, P=<0.001), insulin resistance (70.6% vs 14.6%, P=<0.001) and more pronounced improvements in A1c, TG and ALT (**Supplemental Table 4**).

Multivariate analysis of predictors of ≥5% weight loss is demonstrated in **Supplement Table 5.** Duration of program participation was the strongest independent predictor [odds ratio (OR) 6.79 95% CI 3.7-12.4, P=<0.001]. White race was the only other significant variable with an OR of 3.83 (95%CI 1.04-14.03, P=0.04). Additional analysis of characteristics based on race was performed to evaluate if any other covariates may be mediators of this relationship (**Supplement Table 6**). Participants of white race (N=349, 87%) were older (55 vs 48.8), had less college/post graduate education (68.6% vs 88.6%), a higher prevalence of HTN (66.5% vs 48.8%), larger waist circumference (46 vs 43 in), higher percentage body fat (45.5 vs 43%) and higher TG (160 vs 123) at baseline compared to participants of other races.

DISCUSSION

NAFLD is one of the most common forms of chronic liver disease, affecting 25-30% of the United States' population.[18,19] Weight loss through lifestyle changes is a proven therapy for this highly prevalent disease. Unfortunately, implementation of lifestyle changes and achievement of sustained weight loss remains challenging for many patients. Structured lifestyle programs often result in higher rates of weight loss due to regimented recommendations and follow-up. These types of programs have long

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been designed and targeted for patients with cardiac or endocrine disease, but due to the underlying metabolic nature of NAFLD, lifestyle programs are also relevant for patients with NAFLD.

The results of our study mirror findings of other investigations of prevalence of NAFLD among patients with metabolic disease.[1,20] In this cohort, just under half of the patients had evidence of NAFLD. This is likely an underestimate as not all patients had undergone testing to evaluate for possible NAFLD. Another finding of note is that only one quarter of patients with NAFLD were referred to and managed by a GI or liver specialist for their NAFLD. Also of note, an additional one third of NAFLD patients were under the care of a GI provider for other conditions (e.g. acid reflux, diarrhea), but they did not receive care related to NAFLD. Taken together this pattern of care reflects low disease awareness among patients and providers, even in the face of multiple metabolic risk factors.[21,22] These care patterns also reflect perceptions regarding the clinical significance and treatment options for NAFLD held by many providers.[23] This low rate of referral to GI/Hepatology is in line with data from prior studies where 71% of providers reported that they did not refer patients with suspected NAFLD to GI/Hepatology. [24,25]These deficiencies in the care cascade represent key areas for improvement in order to optimize long term outcomes for this burgeoning patient population. It is important to note the potential implications of low rates of referral including the potential to make accurate diagnoses of NAFLD and NASH and risk stratification for stage of liver disease. Although routine screening among high risk patients is not currently recommended due to uncertainties around diagnostic approaches and cost-effectiveness of screening, the role for screening will continue to evolve as additional therapeutic options and predictive models for advanced or rapidly progressive NAFLD become available.[26-28]

We also highlighted the differences in baseline characteristics of patients with and without NAFLD among patients with the MetSyn. Patients with NAFLD were younger and more likely to have higher baseline weight, maximum lifetime weight and central obesity. They were also more likely to have hyperTG, low HDL-C and higher HOMA-IR. These unique characteristics underscore the importance of central adiposity and insulin resistance in NAFLD as metabolic health has been independently associated with risk of NASH and significant fibrosis.[29,30] Despite having more pronounced metabolic derangements at baseline, NAFLD patients were equally likely to respond to the lifestyle program. This finding is of note given concerns that NAFLD patients may have different uptake and response rates to lifestyle changes stemming from different baseline motivation to change and lower confidence to exercise.[31-33] In

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this study, we found that duration of program participation was the strongest predictor of weight loss. In our prior studies, we had demonstrated that the number of MetS criteria was correlated with the number of program sessions attended (OR 2.27), highlighting a potential predictor of program completion that can be used to help target interventions to increase adherence among participants. [34] Although race was an independent predictor of weight loss, we are limited in our ability to draw conclusions from this finding given that 88% of participants were of white race. However, this finding has been previously described in the literature with higher rates of success in weight loss in part attributed to differences in basal metabolic rates. [35-37] On sub-analysis, those of non-white race appeared to have more favorable baseline metabolic characteristics (younger age, lower baseline waist circumference, percentage body fat and TG). These racial differences for propensity for weight loss are particularly interesting given the variable prevalence rates of NAFLD across different races and ethnicities.[38,39]

There are several limitations to note for our study. First, the diagnosis of NAFLD was made based on chart review and natural language processing and is inherently prone to both over and under classification. Second, our patient population is relatively homogenous and thus the results of this study may not generalize to the larger population of patients with NAFLD. Additionally, our current program design does not include structured, prospective follow-up post-program completion, so we are unable to speak to the durability of the benefits achieved through this program. Our recent retrospective study of participants with follow-up data available in our health system (N=225) demonstrated that at 12 months after program completion, while the majority of parameters were still improved compared to baseline, only change in LDL-C remained significantly improved compared to end of 12-week program.[40-42] These findings echo those reported in follow-up after completion of most structured lifestyle intervention programs where participants regain weight over time, but the majority are able to remain below program entry weight.[43] While program design varies widely in terms of duration and intensity of follow-up, most programs are designed for 3-6 months and do not incorporate post-program follow-up. Overall, these findings of difficulty with maintenance of benefit post program completion highlights the primary limitation of these interventions and the need for maintenance interventions over the long term. [44] Incorporation of follow-up touch points using eHealth modalities have been shown to be a potentially beneficial mechanism to sustain improvements over time, and as such warrant further investigation.[45] A strength of our study in terms of NAFLD prevalence assessment was our ability to rule

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out heavy alcohol use in this cohort as an alcohol use assessment was performed as a standard part of enrollment into the program. Another key strength is the detailed clinical, anthropometric and HRQOL assessments at baseline and program completion that enabled us to conduct in depth analysis of the different types of benefits of fitness programs in patients with MetSyn and NAFLD. While weight loss and improvements in metabolic parameters have been reported in many lifestyle intervention programs, ours is one of the few demonstrating a decrease in PHQ-9, a measure of depression.

In conclusion, we demonstrated that roughly one-half of patients participating in a structured lifestyle intervention program predominantly referred because of cardiovascular or endocrine diseases had evidence of underlying NAFLD, but only a quarter of the NAFLD patients were being specifically managed for their NAFLD by a specialist. We also found that metabolic derangements were more pronounced at baseline in NAFLD patients, but despite this NAFLD patients were equally responsive to the lifestyle program. As expected, we found that a longer duration of program participation was the most important predictor of significant weight loss. Our data can be used to help counsel NAFLD patients regarding expectations and timeline for lifestyle interventions to achieve target weight loss. It can also provide a framework for the design of future lifestyle intervention programs targeted specifically for NAFLD patients. Future prospective assessment of for baseline NAFLD with detailed liver-specific endpoints including elastography would add to our knowledge of the disease specific benefits of structured lifestyle programs for this population.

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REFERENCES

1. Chen SH, He F, Zhou HL, Wu HR, Xia C, Li YM. Relationship between nonalcoholic fatty liver disease and metabolic syndrome. *Journal of digestive diseases.* 2011;12(2):125-130.
2. Hamaguchi M, Kojima T, Takeda N, et al. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Annals of internal medicine.* 2005;143(10):722-728.

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3. Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Annals of medicine.* 2011;43(8):617-649.
4. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology (Baltimore, Md).* 2016;64(1):73-84.
5. Promrat K, Kleiner DE, Niemeier HM, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. *Hepatology (Baltimore, Md).* 2010;51(1):121-129.
6. Tamura Y, Tanaka Y, Sato F, et al. Effects of diet and exercise on muscle and liver intracellular lipid contents and insulin sensitivity in type 2 diabetic patients. *The Journal of clinical endocrinology and metabolism.* 2005;90(6):3191-3196.
7. Rubenfire M, Mollo L, Krishnan S, et al. The Metabolic Fitness Program: LIFESTYLE MODIFICATION FOR THE METABOLIC SYNDROME USING THE RESOURCES OF CARDIAC REHABILITATION. *Journal of Cardiopulmonary Rehabilitation and Prevention.* 2011;31(5):282-289.
8. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106(25):3143-3421.
9. Walden P, Jiang Q, Jackson EA, Oral EA, Weintraub MS, Rubenfire M. Assessing the incremental benefit of an extended duration lifestyle intervention for the components of the metabolic syndrome. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy.* 2016;9:177-184.
10. Borg G. *Borg's perceived exertion and pain scales.* Champaign, IL, US: Human Kinetics; 1998.
11. American College of Sports M, Thompson WR, Gordon NF, Pescatello LS. *ACSM's guidelines for exercise testing and prescription.* Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2010.
12. Ehrman J GP, Visich P, Keteyian S. . Clinical Exercise Physiology 4th Edition. 2018.
13. Frankenfield D, Roth-Yousey L, Compher C. Comparison of predictive equations for resting metabolic rate in healthy nonobese and obese adults: a systematic review. *Journal of the American Dietetic Association.* 2005;105(5):775-789.
14. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a Brief Depression Severity Measure. *Journal of General Internal Medicine.* 2001;16(9):606-613.
15. Engine E-UoMRS.

This article is protected by copyright. All rights reserved

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16. Qu H-Q, Li Q, Rentfro AR, Fisher-Hoch SP, McCormick JB. The Definition of Insulin Resistance Using HOMA-IR for Americans of Mexican Descent Using Machine Learning. *PloS one.* 2011;6(6):e21041.
17. Angulo P, Hui JM, Marchesini G, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology (Baltimore, Md).* 2007;45(4):846-854.
18. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Alimentary pharmacology & therapeutics.* 2011;34(3):274-285.
19. Wong RJ, Liu B, Bhuket T. Significant burden of nonalcoholic fatty liver disease with advanced fibrosis in the US: a cross-sectional analysis of 2011-2014 National Health and Nutrition Examination Survey. *Alimentary pharmacology & therapeutics.* 2017;46(10):974-980.
20. Gerber L, Otgonsuren M, Mishra A, et al. Non-alcoholic fatty liver disease (NAFLD) is associated with low level of physical activity: a population-based study. *Alimentary pharmacology & therapeutics.* 2012;36(8):772-781.
21. Wieland A, Mettler P, McDermott M, Crane L, C Cicutto L, M Bambha K. *Low Awareness of Nonalcoholic Fatty Liver Disease Among Patients at High Metabolic Risk.* Vol 492014.
22. Ghevariya V, Sandar N, Patel K, et al. Knowing What's Out There: Awareness of Non-Alcoholic Fatty Liver Disease. *Frontiers in medicine.* 2014;1:4.
23. Wieland AC, Quallick M, Truesdale A, Mettler P, Bambha KM. Identifying practice gaps to optimize medical care for patients with nonalcoholic fatty liver disease. *Digestive diseases and sciences.* 2013;58(10):2809-2816.
24. C.-J. B, R. S, L. H, D. CA, R. JJ, E. PE. Awareness and opinions of non-alcoholic fatty liver disease by hospital specialists. *Internal Medicine Journal.* 2013;43(3):247-253.
25. Said A, Gagovic V, Malecki K, Givens ML, Nieto FJ. Primary care practitioners survey of non-alcoholic fatty liver disease. *Annals of hepatology.* 2013;12(5):758-765.
26. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology (Baltimore, Md).* 2018;67(1):328-357.
27. Corey KE, Klebanoff MJ, Tramontano AC, Chung RT, Hur C. Screening for Nonalcoholic Steatohepatitis in Individuals with Type 2 Diabetes: A Cost-Effectiveness Analysis. *Digestive diseases and sciences.* 2016;61(7):2108-2117.

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28. Wong VW, Chalasani N. Not routine screening, but vigilance for chronic liver disease in patients with type 2 diabetes. *Journal of hepatology.* 2016;64(6):1211-1213.
29. Pang Q, Zhang J-Y, Song S-D, et al. Central obesity and nonalcoholic fatty liver disease risk after adjusting for body mass index. *World Journal of Gastroenterology : WJG.* 2015;21(5):1650-1662.
30. Ampuero J, Aller R, Gallego-Durán R, et al. The effects of metabolic status on non-alcoholic fatty liver disease-related outcomes, beyond the presence of obesity. *Alimentary pharmacology & therapeutics.*0(0).
31. Frith J, Day CP, Robinson L, Elliott C, Jones DE, Newton JL. Potential strategies to improve uptake of exercise interventions in non-alcoholic fatty liver disease. *Journal of hepatology.* 2010;52(1):112-116.
32. Centis E, Moscatiello S, Bugianesi E, et al. Stage of change and motivation to healthier lifestyle in non-alcoholic fatty liver disease. *Journal of hepatology.* 2013;58(4):771-777.
33. Stewart KE, Haller DL, Sargeant C, Levenson JL, Puri P, Sanyal AJ. Readiness for behaviour change in non-alcoholic fatty liver disease: implications for multidisciplinary care models. *Liver international : official journal of the International Association for the Study of the Liver.* 2015;35(3):936-943.
34. Walden P, Jiang Q, Jackson EA, Oral EA, Weintraub MS, Rubenfire M. Assessing the incremental benefit of an extended duration lifestyle intervention for the components of the metabolic syndrome. *Diabetes, metabolic syndrome and obesity : targets and therapy.* 2016;9:177-184.
35. DeLany JP, Jakicic JM, Lowery JB, Hames KC, Kelley DE, Goodpaster BH. African American women exhibit similar adherence to intervention but lose less weight due to lower energy requirements. *International Journal Of Obesity.* 2013;38:1147.
36. Gannon B, DiPietro L, Poehlman ET. Do African Americans have lower energy expenditure than Caucasians? *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity.* 2000;24(1):4-13.
37. Davis KK, Tate DF, Lang W, et al. Racial Differences in Weight Loss Among Adults in a Behavioral Weight Loss Intervention: Role of Diet and Physical Activity. *Journal of physical activity & health.* 2015;12(12):1558-1566.
38. Schneider ALC, Lazo M, Selvin E, Clark JM. Racial Differences in Nonalcoholic Fatty Liver Disease in the U.S. Population. *Obesity (Silver Spring, Md).* 2014;22(1):292-299.
39. Pan J-J, Fallon MB. Gender and racial differences in nonalcoholic fatty liver disease. *World journal of hepatology.* 2014;6(5):274-283.

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40. Joseph M KM, Zhang M, Wei B, Brinza E, Walden P, Jackson E, Rubenfire M. Long-term outcomes following completion of a structured nutrition and exercise lifestyle intervention program for patients with metabolic syndrome. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy.* 2018;accepted.

41. Dalzill C, Nigam A, Juneau M, et al. Intensive lifestyle intervention improves cardiometabolic and exercise parameters in metabolically healthy obese and metabolically unhealthy obese individuals. *The Canadian journal of cardiology.* 2014;30(4):434-440.

42. Pettman TL, Buckley JD, Misan GM, Coates AM, Howe PR. Health benefits of a 4-month group-based diet and lifestyle modification program for individuals with metabolic syndrome. *Obesity research & clinical practice.* 2009;3(4):221-235.

43. Svetkey LP, Stevens VJ, Brantley PJ, et al. Comparison of strategies for sustaining weight loss: the weight loss maintenance randomized controlled trial. *Jama.* 2008;299(10):1139-1148.

44. Colombo CM, de Macedo RM, Fernandes-Silva MM, et al. Short-term effects of moderate intensity physical activity in patients with metabolic syndrome. *Einstein (Sao Paulo, Brazil).* 2013;11(3):324-330.

45. Wing RR, Tate DF, Gorin AA, Raynor HA, Fava JL. A self-regulation program for maintenance of weight loss. *The New England journal of medicine.* 2006;355(15):1563-1571.

FIGURE LEGENDS

Figure 1. NAFLD Prevalence and Care Patterns Among Participants in Metabolic Fitness Program

Pie chart depicting percentage of participants in Metabolic Fitness Program with evidence of underlying non-alcoholic fatty liver disease (NAFLD) and distribution of NAFLD patients who received specialty care for their NAFLD.

GI, gastroenterology; Hep, hepatology

Figure 2. Changes in Metabolic, Liver and Depression Parameters Based on Underlying NAFLD and Program Duration

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Bar charts show changes in weight, central obesity, triglycerides (TG), homeostasis model assessment-estimated insulin resistance (HOMA-IR), alanine aminotransferase (ALT) and patient health questionnaire 9 (PHQ-9) from baseline to 12 and 24 weeks of the Metabolic Fitness Program, stratified by non-alcoholic fatty liver disease (NAFLD) status. Improvements were similar in patients with and without NAFLD, but patients with NAFLD had a greater decrease in TG and a larger reduction in ALT.Values represent median with brackets representing interquartile ranges.

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Table 1. Baseline Patient Characteristics According to NAFLD Diagnosis

Variables Median (IQR) or N (%)	NAFLD N=192	No NAFLD N=211	P Value
Clinical Characteristics			
Age, years	52 (45-59.9)	55 (49-63)	**0.004**
Male Gender	116 (60.4%)	136 (64.5%)	0.40
White Race	167 (89.3%)	182 (87.9)	0.67
Medical Co-Morbidities			
CAD	9 (4.7%)	15 (7.1%)	0.29
Diabetes	65 (33.8%)	54 (25.7%)	0.07
Metabolic Syndrome			
Central Obesity	179 (93.2%)	176 (83.4%)	**0.002**
Hypertension	122 (67.4%)	120 (61.2%)	0.21
Impaired Fasting Glucose or DM	133 (69.3%)	132 (63.5%)	0.22
Hypertriglyceridemia	116 (60.4%)	102 (48.3%)	**0.01**
Low HDL-C	122 (63.5%)	109 (51.6%)	**0.01**
Systolic Blood Pressure (mmHg)	120 (110-130)	120 (110-136)	0.12
Diastolic Blood Pressure (mmHg)	70 (66-80)	72 (66-80)	0.43
Duration of Program: 24- week	77 (40.1%)	73 (34.6%)	0.25
Psychosocial Assessment			
PHQ-9 Depression Score	5 (2-9)	4 (2-8)	0.15
Employment Status, (employed)	108 (56.2%)	147 (69.6%)	**0.005**
Financial Stressors, (yes)	9 (7.1%)	11 (5.8%)	0.66
Educational Background			0.46
High School or some post High School	55 (28.9%)	59 (28.6%)	
College Graduate	64 (33.7%)	59 (28.6%)	
Post Graduate/ Professional	71 (37.4%)	88(42.7%)	
Anthropometrics			
Baseline BMI	38.4 (34.4-42.6)	36.6 (31.9-42.7)	0.06
Baseline Weight, (lb)	242.2 (210.7-276.3)	227 (191.5-278)	**0.01**
Waist Circumference, (inches)	46.7 (43-51)	45 (40.5-50)	**0.01**

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% Body Fat	45.6 (39-49.3)	44.6(39.2-49.2)	0.74
Max Lifetime Weight, (lb)	250 (220-290)	231 (200-285)	**0.008**
Labs			
A1c	5.9 (5.6-6.7)	5.9 (5.6-6.5)	0.45
Fasting Glucose, mg/dL	108.9 (98.5-127)	105 (95-123)	0.15
Fasting Insulin, umol/mL	21.6 (14.5-29.8)	16.2 (10.7-25.1)	**<0.001**
HOMA IR (non-DM), mU mmol/L^2	5.23 (3.36-7.79)	3.69 (2.47-6.26)	**0.002**
TG, mg/dL	172.5 (120.5-273.5)	146(104-230)	**0.002**
LDL-C, mg/dL	100 (77-122)	104 (80-130)	0.35
HDL-C, mg/dL	42 (35-50)	45 (37-54)	**0.005**
ALT, U/L	41(26-57)	27 (20-35)	**<0.001**
Abnormal ALT (>35 U/L)	109 (62.6%)	46 (24.6%)	**<0.001**

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Change in Variable from Baseline to End of Program Median (IQR) or N (%)	NAFLD	No NAFLD	P Value

BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; TG, triglycerides; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; ALT, alanine aminotransferase; HOMA-IR, homeostasis model assessment-estimated insulin resistance. Central obesity defined as ≥40 inches in men and ≥35 inches in women; Hypertension defined as SBP >130mmHg, DBP >85mmHg or on anti-hypertensive; Impaired fasting glucose defined as >100mg/dL or DM; hyperTG defined as ≥150 mg/dL or on treatment for triglycerides; Low HDL-C defined as <40mg/dL men and <50mg/dL women.

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12-week	N= 192	N=211	
BMI	-1.2 (-0.4;-2)	-0.9.(-0.3;-1.6)	0.10
Weight (lb)	-6.8 (-2; -12.7)	-5.5 (-1.6; -10)	0.08
≥5% Reduction Weight	48 (25%)	44 (20.9%)	0.32
≥10% Reduction Weight	6 (3.1%)	8 (3.8%)	0.70
Waist Circumference (in)	-1.5 (0;-3)	-1.3 (0;-2.7)	0.48
% body fat	-1.5 (-0.2;-2.9)	-0.9 (0; -2.2)	**0.009**
Features of Metabolic Syndrome			
Loss of Central Obesity	11 (6.1%)	18 (10.3%)	0.15
Resolution of Hypertension	9 (7.6%)	7 (5.8%)	0.59
Resolution of Impaired of Fasting Glucose	31 (24.1%)	28 (22.5%)	0.73
Resolution of Hypertriglyceridemia	65 (56%)	68 (68%)	0.07
Resolution of Low HDL	44 (36.1%)	35 (32.7%)	0.59
Systolic Blood Pressure (mmHg)	-4 (-12;+5)	-6 (-18;+2)	0.29
Diastolic Blood Pressure (mmHg)	-2 (-8;+4)	-3 (-10; +2)	0.35
A1c	-0.2 (0;-0.5)	-0.1 (0;-0.3)	0.15
Fasting Glucose, mg/dL	-5 (+4; -14)	-3 (+3; -11)	0.21
Insulin, umol/mL	-2.4 (+2.4; -9.2)	-0.8 (+2.4; -6.3)	0.09
HOMA-IR (non DM), mU mmol/L^2	-0.73 (+0.44; -2.44)	-0.16 (+0.49; -1.49)	0.17
TG, mg/dL	-32.5 (+10;-93)	-22 (+3;-57)	0.28
LDL-C, mg/dL	0 (+10; -11)	-3 (+9; -14)	0.18
HDL-C, mg/dL	-1 (+2; -4)	0 (+3; -4)	0.69
ALT, U/L	-5 5 (+2; -16)	-2 (+3; -7)	**0.004**
Normalization of ALT (<35)	30/102 (29.4%)	21/39 (53.8%)	**0.007**
PHQ-9 Score	-2 (0;-4)	-2 (0;-4)	0.69
24-week	N=77	N=73	
BMI	-2.2 (-0.6; -3.4)	-1.9 (-0.8;-3.0)	0.75
Weight (lb)	-13.5 (-3.5; -22.5)	-11.7 (-5.5; -18.5)	0.72
≥ 5% Reduction Weight	43(55.8%)	36 (49.3%)	0.42
≥10% Reduction Weight	12 (15.6%)	12 (16.4%)	0.88
Waist Circumference	-2.9 (-0.7; -4.5)	-2.5 (-0.5;-4)	0.59
% body fat	-1.9 (-0.3; -4.1)	-1.9 (-0.7;-3.4)	0.94
Features of Metabolic Syndrome			
Loss of Central Obesity	11 (15.1%)	10 (16.4%)	0.83
Resolution of Hypertension	6 (10.7%)	3 (6.3%)	0.44
Resolution of Impaired of Fasting Glucose	13 (27.1%)	17 (34%)	0.46
Resolution of Hypertriglyceridemia	18 (35.9%)	14 (35.9%)	0.89
Resolution of Low HDL	15 (30.6%)	15 (37.5%)	0.49
Systolic Blood Pressure (mmHg)	-3 (-18; +6)	-8 (-18;+6)	0.42
Diastolic Blood Pressure (mmHg)	-2 (-12; +6)	-2 (-14;+4)	0.66

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A1c ,%	-0.2 (0; -0.5)	-0.1 (0; -0.6)	0.88
Fasting Glucose, mg/dL	-6 (+4; -17)	-4 (+3;-11)	0.58
Insulin, umol/mL	-2.5(-0..5; -9.1)	-4.9 (-1.5; -9.8)	0.06
HOMA-IR (non DM), mU mmol/L^2	-0.72 (+0.35; -2.21)	-1.38 (-0.30; -3.15)	0.06
TG, mg/dL	-45 (-9; -113)	-23 (+3; -58)	**0.05**
LDL-C, mg/dL	0 (+13;-18)	-4 (+6; -13.5)	0.34
HDL-C, mg/dL	+1 (+6;-4)	0 (+3;-3)	0.51
ALT, U/L	-11 (-0.5; -28.5)	-3 (+1;-9)	**0.003**
Normalization of ALT (<35)	22/46 (47.8%)	9/11 (81.8%)	**0.04**
PHQ-9 Score	-2 (0;-5)	-2 (0;-5)	0.79

Table 2. Metabolic Fitness Program on Metabolic, Liver-Related and Depression Parameters Stratified by NAFLD Status

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BMI, body mass index; TG, triglycerides; HDL-C, high density lipoprotein- cholesterol; LDL-C, low density lipoprotein-cholesterol; ALT, alanine aminotransferase; HOMA-IR, homeostasis model assessment-estimated insulin resistance. Central obesity defined as ≥40 inches in men and ≥35 inches in women; Hypertension defined as SBP >130mmHg, DBP >85mmHg or on anti-hypertensive; Impaired fasting glucose defined as >100mg/dL or DM; hyperTG defined as ≥150 mg/dL or on treatment for triglycerides; Low HDL-C defined as <40mg/dL men and <50mg/dL women.

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Variable Median (IQR) or N (%)	≥ 5% Weight Loss N=121	<5% Weight Loss N=282	P value

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Baseline Characteristics			
Age	56 (48.5-62.5)	53.7 (46-61)	0.19
Male Gender	67 (55.4%)	186 (65.6%)	**0.05**
White Race	112 (93.3%)	237 (86.5%)	**0.05**
Medical Co-Morbidities			
CAD	8 (6.6%)	16 (5.6%)	0.70
Diabetes	33 (27.5%)	85 (30%)	0.54
Metabolic Syndrome Components			
Central Obesity	110 (90.9%)	245 (86.9%)	0.25
Hypertension	76 (67.8%)	166 (62.6%)	0.33
Impaired Fasting Glucose or DM	75 (61.9%)	192 (68.1%)	0.23
Hypertriglyceridemia	68 (56.2%)	150 (53.2%)	0.57
Low HDL-C	71 (58.6%)	160 (56.8%)	0.72
NAFLD	63 (52.1%)	129 (45.7%)	0.24
PHQ-9 Depression Score	4 (2-8)	5 (2-8)	0.11
Program Duration: 24-week	79 (65.3%)	71 (25.2%)	**<0.001**
Baseline Psychosocial Assessment			
Financial Stressors, yes	3 (3.3%)	17 (7.6%)	0.15
Educational Background			0.98
High School or some post High School	34 (28.8%)	80 (28.8%)	
College Graduate	36 (30.5%)	87 (31.3%)	
Post Graduate/ Professional	48 (40.6%)	111 (39.9%)	
Baseline Anthropometrics			
Baseline BMI	38.5 (33.7-41.9)	36.9 (32.6-42.9)	0.52
Baseline Weight, lb	241(210-284)	235.5 (200.5-276)	**0.05**
Waist Circumference, in	46.3 (43-50)	46 (41-50.5)	0.22
% Body Fat	44.5 (37.4-49)	45.3 (39.8-49.5)	0.28
Max Lifetime Weight, lb	250 (219-300)	241 (205-285)	0.06
Baseline Labs			
A1c	5.9 (5.6-6.5)	5.9 (5.6-6.5)	0.39
HOMA-IR (non DM), mU mmol/L^2	4.73 (2.89-7.09)	4.44 (2.76-6.81)	0.67
TG, mg/dL	161 (112-268)	157 (111-238)	0.45
LDL-C, mg/dL	96 (77-121)	103 (80-128)	0.18
HDL-C, mg/dL	43 (36-49)	43.5 (36-52)	0.74
ALT, U/L	35 (23-53)	30 (22-42)	**0.03**
Abnormal ALT (>35 U/L)	52 (49.5%)	103 (40.2%)	0.11
Change in Clinical Parameters			
Features of Metabolic Syndrome			
Loss of Central Obesity	21 (19.3%)	17 (6.9%)	**0.001**
Resolution of Hypertension	6 (8.1%)	13 (7.9%)	0.97

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Resolution of Impaired of Fasting Glucose	28 (38.4%)	42 (23.2%)	**0.01**
Resolution of Hypertriglyceridemia	37 (55.2%)	95 (65.1%)	0.16
Resolution of Low HDL	28 (39.4%)	49 (31.2%)	0.22
A1c	-0.2 (-0.1; -0.8)	-0.1 (+0.1; -0.3)	**<0.001**
Fasting glucose, mg/dL	-6 (+3; -16)	-3 (+4; -12)	**0.03**
Fasting Insulin, umol/mL	-5.9 (-0.7; -10.5)	-1.1 (+2.6; -5.8)	**<0.001**
HOMA-IR (non DM), mU mmol/L^2	-1.49 (-0.20; -3.01)	-0.27 (+0.64; -1.38)	**<0.001**
TG, mg/dL	-38 (-13;-119)	-16 (+18; -52)	**<0.001**
HDL-C, mg/dL	0 (+4; -3)	1 (+3; -4)	0.30
LDL-C, mg/dL	-3 (+10; -17)	-1 (+11; -13)	0.26
ALT, U/L	-10 (-3; -27)	-2 (+4; -10)	**<0.001**
Normalization of ALT (<35 IU/L)	27 (57.4%)	34 (35.7%)	**0.01**
Change in PHQ-9 Score	2 (0;5)	2(0;4)	0.19

Table 3. Baseline Characteristics and Change in Metabolic, Liver-Related and Depression Parameters Stratified by Achievement of ≥5% Weight Loss

BMI, body mass index; TG, triglycerides; HDL-C, high density lipoprotein- cholesterol; LDL-C, low density lipoprotein-cholesterol; ALT, alanine aminotransferase; HOMA-IR, homeostasis model assessment-estimated insulin resistance. Central obesity defined as ≥40 inches in men and ≥35 inches in women; Hypertension defined as SBP >130mmHg, DBP >85mmHg or on anti-hypertensive; Impaired fasting glucose defined as >100mg/dL or DM; hyperTG defined as ≥150 mg/dL or on treatment for triglycerides; Low HDL-C defined as <40mg/dL men and <50mg/dL women.

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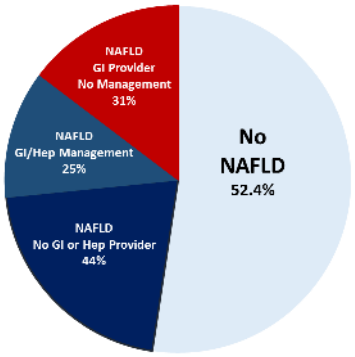

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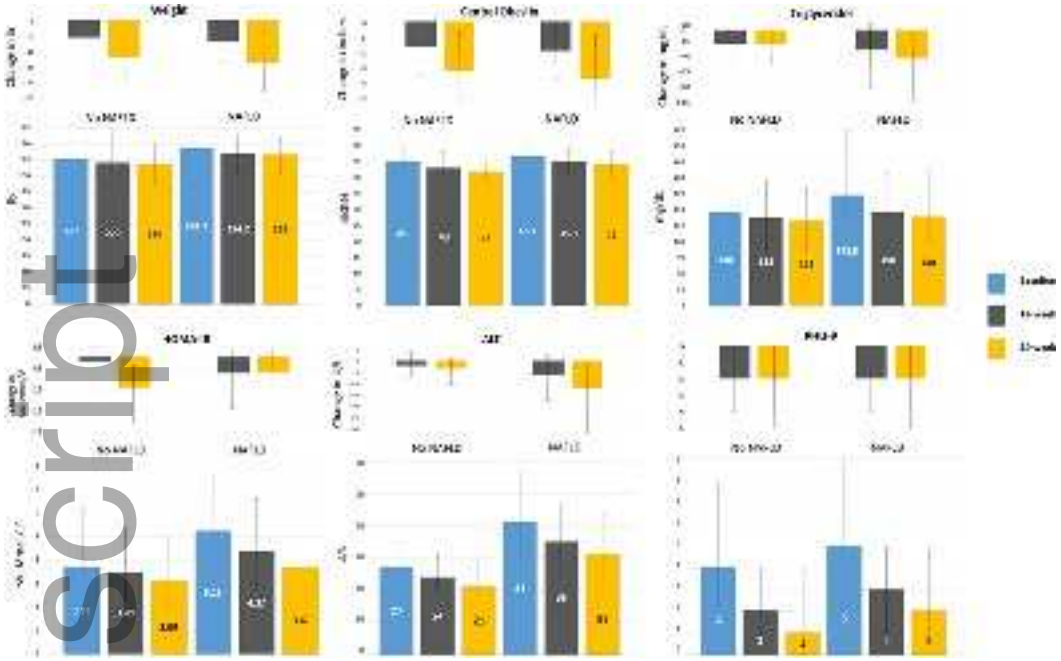

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