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Effects of a community-based weight loss intervention on adipose tissue circulating factors

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Abstract

Background/Objectives—Obesity is associated with metabolic dysfunctions, which may be mediated by changes in adipose tissue signaling factors. These molecules are denoted as Adipose Tissue Generated Mediators of CardioVascular Risk (ATGMCVR) here, and include leptin, adiponectin, C-reactive protein (CRP), interleukin 6 (IL-6), tumor necrosis factor alpha (TNFα), and plasminogen activator inhibitor 1 (PAI-1). This study examined the effect of a weight loss program on ATGMCVR in obese adults with prediabetes.

Subjects/Methods—Subjects were randomized to usual care (UC; n=15) or lifestyle weight loss groups (LWL; n=15). LWL was a community-based weight loss intervention to promote physical activity and healthy eating. ATGMCVR at 1-yr were compared between groups by analysis of covariance; baseline value of the mediator was the covariate. Baseline means for

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Conflicts of Interest
Other authors declare no conflict of interest.

Authors Contributions
Design and conduct of the study: GDM, TMM, MZV, JAK, DG
Data collection and analysis: SI, TMM, CB, KBB, DID
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ATGMCVR were compared between those with (n=21) and without (n=9) metabolic syndrome (MetS).

Results—At baseline, subjects were 58±9 (SD) yrs, 70% female, with a BMI of 34±4 kg/m^2. One-yr weight loss (%) was 7.8±6.0% for LWL and 1.7±4.5% for UC. Group differences at 1-yr were noted (adjusted means [95%CI] for UC and LWL, respectively) for adiponectin (8526.3 [7397.7,9827]; 10870.9 [9432.0,12529.3] ng/ml; p=0.02), leptin (30.4 [26.1,35.4]; 23.7 [20.3,27.5] ng/ml; p=0.02), IL-6 (0.4 [0.3,0.5]; 0.2 [0.1,0.2] pg/ml; p=0.001), and PAI-1 (50 [42.7,58.7]; 36.2 [30.8,42.4] pg/ml; p=0.01). No differences in baseline ATGMCVR were seen between subjects with and without MetS.

Conclusions—These findings suggest ATGMCVR can be improved with weight loss; larger studies are needed to determine if improvements in metabolic dysfunction are related to changes in ATGMCVR.

Keywords

Obesity; diabetes; metabolic syndrome; prediabetes; adipose tissue; weight loss

1. Introduction

Obesity is associated with a number of metabolic dysfunctions, including impaired fasting glucose, insulin resistance, dyslipidemia, type 2 diabetes mellitus (T2DM), and hypertension or other cardiovascular disease (CVD). The mechanisms leading to these conditions in obesity are not entirely known, but it has been proposed that these may be mediated by changes in circulating factors released from adipose tissue. Adipose tissue has recently been recognized as a significant endocrine organ[1, 2]; it secretes bioactive molecules in a paracrine, autocrine, and endocrine fashion[2, 3]. These adipose tissue derived molecules number more than 100 and include nonesterified fatty acids (NEFA), pro- and anti-inflammatory cytokines and hormones (ex. tumor necrosis factor alpha (TNFα), interleukin (IL)-6, TNFαSR, IL-6SR, leptin, adiponectin), procoagulants (plasminogen activator inhibitor 1 (PAI-1), insulin sensitizers (adiponectin, resistin, and retinol binding protein 4 (RBP-4)), and components of the renin/angiotensin/aldosterone axis (angiotensin II, renin, angiotensin converting enzyme (ACE) 1 and 2)[4–7]. Although acute phase reactant proteins, such as C-reactive protein (CRP), amyloid A, and transferrin, are not released from adipose tissue, their plasma concentrations are mediated by adipose tissue derived signaling molecules. Collectively, this research refers to these signaling molecules as Adipose Tissue Generated Mediators of CardioVascular Risk (ATGMCVR).

The consequence of metabolic dysfunction in obesity is an increased risk for CVD, occurring through several mechanisms. ATGMCVR are stimuli for central and peripheral organs; there is evidence that they may initiate this metabolic dysfunction[1–3]. The clustering of several CVD risk factors, principally abdominal obesity, T2DM, dyslipidemia, and hypertension is termed metabolic syndrome (MetS).[8] It has been suggested that the development of insulin resistance in obesity is the underlying cause for MetS.[9] Metabolic syndrome (MetS) increases the risk for T2DM and CVD[10–17] and affects over one-third of US adults[18]. Imbalances in these biomarkers are thought to mediate comorbidities of

obesity, and pharmacologic alterations of selected ATGMCVR have already been shown to provide substantial cardiovascular health benefits[19, 20]. At present, the primary management of MetS or any of the criterion for MetS involves healthy lifestyle promotion through weight management, dietary energy restriction and increased physical activity.[21] Previous work with the Diabetes Prevention Program[22] and the Finish Diabetes Prevention Study[23] showed that weight loss using lifestyle changes to diet and physical activity reduced the development of T2DM in those with impaired fasting glucose. Furthermore, both of these clinical trials showed lifestyle changes improved inflammatory markers[24, 25].

However, it is not known whether weight loss in response to successful behavioral interventions corrects or reverses these ATGMCVR. Thus, the overall goal of this analysis is to understand the effect of a community delivered behaviorally based weight loss program on potential mediators of obesity related vascular conditions. These data can then be used in optimizing adjunct therapies for obesity comorbidities. We propose that the metabolic dysfunctions of obesity are associated with ATGMCVR and that weight loss improvements in cardiometabolic functions are induced through correction of metabolic dysfunction of ATGMCVR. Thus, this study explores: 1) the impact of a weight loss intervention on ATGMCVR; and 2) the associations of these signaling molecules on obesity metabolic disturbances.

2. Materials and Methods

2.1 Subjects and Design

We utilized stored plasma samples from baseline and at 1-year follow-up from a subsample of HELP PD (Healthy Living Partnerships to Prevent Diabetes, HELP PD), a translational, randomized study in obese older adults with impaired fasting glucose to more extensively investigate the changes in ATGMCVR, markers of cardiovascular risk. The 2-armed, NIDDK-funded HELP PD trial was a 2-year study that tested the relative effectiveness of a lifestyle weight loss intervention (LWL) or an enhanced usual care comparison condition (UC) on fasting blood glucose in individuals with prediabetes. The primary hypothesis of HELP PD was that a lifestyle weight loss intervention consisting of healthy eating and increased physical activity will have a beneficial and clinically meaningful impact on glucose and insulin metabolism, as well as improvements in markers of the metabolic syndrome[26]. This trial was unique in that the intervention was administered through a community-based diabetes education program model using community health workers and delivered through a diabetes care center. Details on the design, methods, recruitment procedures, and participant baseline characteristics have previously been reported and are summarized below[26]. The study was approved by the Wake Forest Baptist Health Institutional Review Board and all participants in HELP PD consented to the study. Beneficial effects of the HELP PD intervention have been demonstrated on body weight, fasting glucose, and other elements of MetS after 1 and 2 years[27, 28]. Briefly, trial enrollment began in 2007 and 301 participants were enrolled over a 2-year period with the following eligibility criteria: overweight or obese (BMI=25 to 40 kg/m^2); blood glucose of 95 mg/dl ≤ 125 mg/dl following at least an 8-hour fast; and ≥ 21 years of age. Individuals

were excluded if they had been diagnosed with diabetes, recent history of cardiovascular disease, or had uncontrolled hypertension. There were 273 participants for the 1-year follow-up, greater than 90% retention rate.

2.2 Measures

A random subsample of participants was obtained from the LWL and UC groups (n=15 per group). Anthropometric variables of height, weight, and waist circumference were determined at both time points using standard techniques. For each assessment, measurements were taken in duplicates with the means used in analyses. Participants wore lightweight clothing and without shoes using a Cardinal Detecto Digital Scale (758 C Series). Outer garments (i.e. jackets and sweaters) were removed before measurements. Waist circumference was assessed using a Gulick II 150-cm anthropometric tape with the participant in a recumbent position and was taken without clothing directly touching the skin. The tape measure was placed around the torso at the midpoint between the inferior margin of the last rib and the crest of the ilium[29]. Body height was assessed by having participants stand erect on the floor with their backs against a vertical stadiometer (Accu-Hite Measure device with level bubble).

Phlebotomy was performed after at least an 8-hour fast in accordance with the American Diabetes Association guidelines[30]. Plasma measures of ATGMCVR included leptin (RIA, Millipore, Billerica, MA), adiponectin (ELISA – Millipore, Billerica, MA), CRP (c-reactive protein (High Sensitivity ELISA – American Laboratory Products Company (ALPCO), Windham, NH), TNFα (ELISA – Biosource, Grand Island, NY), IL-6 (High Sensitivity ELISA – R & D Systems, Minneapolis, MN), and PAI-1 (ELISA – eBioscience, San Diego, CA), and were determined at both baseline and 1-year for the subsample of participants that had stored plasma samples at both baseline and 1-year follow-up.

Additionally, measures for the criterion of MetS were performed. These included waist circumference as described above, plasma fasting glucose, high density lipoproteins (HDL), plasma triglycerides, and resting systolic and diastolic blood pressure. Glucose was measured using a timed endpoint method supplied by Beckman Coulter for the Synchron LX Analyzer. This method has been accepted as a reference method for glucose determination. Within-run coefficients of variation for this method are ≤ 3.9%, and total coefficient of variation are ≤ 6.45%. HDL and triglycerides were also measured using a timed endpoint method supplied by Beckman Coulter for serum samples for the Synchron LX Analyzer. Blood pressure was measured using an automated blood pressure monitor (Omron HEM 907XL) following the recommendations outlined in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). Participants were seated for a 5-minute rest period prior to the first measurement; two measurements were taken and the mean of these measurements was recorded.

2.3 Interventions

Lifestyle Weight Loss—The lifestyle weight loss intervention was a translation of the Diabetes Prevention Program utilizing community-based sites via a local diabetes education program and community health workers (CHWs). Registered dietitians employed by the

diabetes education program trained the CHWs. Principle components of the intervention were a targeted decrease in calorie intake (goal of 1200–1800) and increase in calorie expenditure (goal of > 180 min/wk) with a weight loss goal of 5–7% during months 0–6 with continued loss or maintenance during months 7–24. Participants had weekly group sessions (months 0–6) and 3 individual sessions with a dietitian. During the second 6-months, participants were encouraged to continue to meet or maintain their weight loss goals. They also maintained two times a month contact with their community health worker (one group and one phone contact).

Enhanced Usual Care—This intervention arm of the study was designed to exceed the usual care provided to patients with prediabetes and to enhance retention. There were 2 individual sessions with dietitian in months 0–3 with monthly newsletter to support weight loss.

2.4 Statistical Analysis

Although the HELP PD intervention lasted for 24-months, we report only 12-month follow up data here. Demographic characteristics of the study population were calculated and presented as means ± standard deviation or frequency (percent). A log transformation was used for ATGMCVR measures to normalize the distributions for analysis that required a normality assumption. Baseline means for ATGMCVR are presented with comparisons between those with (n=21) and without (n=9) metabolic syndrome (MetS) using a t-test. Spearman correlations were used to describe the associations of ATGMCVR with components of metabolic syndrome, body weight, and BMI at baseline. Pearson correlations were used to investigate the association between one year change in ATGMCVR and one year change in components of metabolic syndrome. ATGMCVR measures at 1-yr were compared between randomized groups by analysis of covariance using the baseline value as a covariate. Adjusted means and corresponding confidence intervals are presented in original units.

3. Results

3.1 Subject characteristics and 1-year weight loss

There were no differences between groups in this subanalysis for demographic variables. The mean age for the UC group was 54.9±7.2 years and 60.3±9.8 years for the LWL group. Most participants were female (70%) and white (70%). At baseline, BMI was 33.0±3.2 kg/m^2 for LWL and 34.2±4.1 for UC. At 1-year, weight loss was 7.8±6.0% for LWL and 1.7±4.5% for UC. This compared to the 1-year weight loss for the entire HELP PD cohort of 7.2±6.6% for LWL and 1.3±4.6% for UC.

3.2 Differences in ATGMCVR between groups

No differences were observed between groups at baseline for ATGMCVR (Table 1). The 1-year adjusted means (95% confidence intervals) for ATGMCVR comparing UC with LWL are shown in Table 2. Statistical analysis was performed on the log transformed values, but for ease of interpretation, the non-transformed adjusted means are shown. The LWL group had statistically significantly ($p<0.05$) lower measures of leptin, IL-6, and PAI-1 compared

to UC, whereas adiponectin was statistically significantly higher in the LWL vs. UC. There was a trend for TNFα to be higher in the LWL than UC, but this did not reach significance (p=0.0834). There was no difference between groups for CRP at 1-year.

3.3 Prevalence of metabolic syndrome in subjects

Nearly all participants had a waist circumference larger than the sex-dependent criteria (n=27 (90%). Low HDL levels were seen in 15 or 50% of the cohort. Hypertension was present in 16, about 53% of participants. More than 80% had fasting glucose above 100 mg/dl (n=25), with only 6 of the 30 having high triglyceride concentrations. Participants were classified as having metabolic syndrome (n=21) and not having metabolic syndrome (n=9) using the National Cholesterol Education Program's Adult Treatment Panel III guidelines[31, 32]. Thus, in the participants meeting all 5 criteria, a further analysis was performed to examine the differences in the ATGMCVR between participants with and without metabolic syndrome (Table 3). For each biomarker assessed, there were no differences between groups, although IL-6 showed a trend towards being higher in those with metabolic syndrome (0.19 pg/ml vs. 0.39 pg/ml; p=0.07).

3.4 Correlations between metabolic syndrome components and ATGMCVR, BMI, and body weight at baseline and 1-year

As indicated above, almost all subjects had one or more components of the metabolic syndrome. Therefore, Spearman correlations were performed for the components of metabolic syndrome, BMI, and weight with ATGMCVR at baseline (Table 4) and for their one-year change (Table 5). For each participant's assessment of the metabolic syndrome components, a numerical value of 0 or 1 was assigned if their measure for that component met the NCEP/ATP III metabolic syndrome definition. A sum of these were determined for each individual, which ranged from 0 to 5, and comprised the MetS summary measure in the first column of Table 4. Additionally, a summary measure of the ATGMCVR (last column of Table 4), as calculated by summing the standardized value of each of the six ATGMCVR measures, was correlated with the MetS components, summary measure for MetS, weight, and BMI. Several metabolic syndrome components, as well as the metabolic syndrome summary score were statistically ($p<0.05$) correlated or showed strong trends for significance ($p<0.10$) with ATGMCVR measures. For baseline, adiponectin was negatively correlated with plasma triglycerides ($r=-0.34$; $p=0.07$), plasma glucose ($r=-0.48$; $p<0.01$), diastolic blood pressure ($r=-0.49$; $p<0.01$), and the summary score ($r=-0.38$; $p=0.04$), and positively correlated with HDL cholesterol ($r=0.35$; $p=0.06$). Leptin was positively correlated with BMI ($r=0.35$; $p=0.06$) and negatively correlated with plasma glucose ($r=-0.44$; $p=0.01$). CRP was also positively correlated with BMI ($r=0.47$; $p<0.01$). TNFα was correlated with the summary score for metabolic syndrome ($r=0.42$, $p=0.02$). Interleukin 6 was positively correlated with waist circumference ($r=0.48$, $p<0.01$), the summary score for metabolic syndrome ($r=0.37$, $p=0.04$), body weight ($r=0.41$; $p=0.03$), and BMI ($r=0.41$; $p=0.03$). PAI-1 was positively associated with waist circumference ($r=0.39$, $p=0.03$), triglycerides ($r=0.75$, $p<0.01$), diastolic blood pressure ($r=0.40$, $p=0.03$) and metabolic syndrome summary score ($r=0.40$, $p=0.03$). Finally, the summary measure for the ATGMCVR measures was negatively correlated with glucose ($r=-0.53$, $p<0.01$) and positively correlated with BMI ($r=0.48$; $p<0.01$). For the correlations between the one-year

changes in the MetS components and the ATGMCVR (Table 5), the change in adiponectin was negatively correlated with the change in waist circumference (r=−0.49, p=<0.01) and positively correlated with the change in HDL-C (r=0.31, p=0.09). The change in leptin was positively correlated with the change in waist circumference (r=0.33, p=0.08) and the change in CRP was negatively correlated with the change in HDL-C (r=−0.30, p=0.10). The change in TNFα was negatively correlated with the change in diastolic blood pressure (r=−0.33, p=0.07), whereas the change in PAI-1 was positively associated with the change in waist circumference (r=0.36, p=0.05) and change in triglycerides (r=0.47, p<0.01), and negatively correlated with the change in HDL-C (r=−0.34, r=0.07).

4. Discussion

The aims of these analyses were to study the impact of a community-based weight loss intervention on ATGMCVR in a cohort with pre-diabetes, and to examine the associations of these signaling molecules on obesity driven metabolic disturbances. There was a statistically significant difference between treatment groups at 1-year for several ATGMCVR, including higher adiponectin and lower leptin, IL-6, and PAI-1 for LWL compared to UC. Furthermore, a number of significant correlations were apparent between measures of metabolic syndrome, blood pressure and the signaling molecules. These results are unique with regards to the community-based intervention delivery, as well as the extent of various ATGMCVR measured. These findings suggest that most ATGMCVR can be improved in individuals with pre-diabetes through a community-based moderate weight loss intervention, which suggests that the health benefits afforded by healthy lifestyle may, in part, be attributed to alterations in these biomarkers. However, further studies are needed to determine if metabolic dysfunction as defined by presence of metabolic syndrome is also improved.

Insulin resistance is characterized by impaired glucose tolerance[33] and is a predisposing factor for development of type 2 diabetes as well as being a major component of MetS. Metabolic syndrome increases the risk for CVD. While a number of the biomarkers from adipose tissue, including the molecules assessed in the current analysis, have been linked with CVD and/or its risk factors in other studies, the impact of a pragmatic intervention centered on a community-driven weight loss program is not as well described. HELP PD, the parent study from which these samples were drawn, is a community administered weight loss program that is a realistic application of the Diabetes Prevention Program (DPP) in the community. Since the findings demonstrating the success of behavioral interventions of physical activity and dietary restriction in DPP for reducing the incidence of T2DM in individuals with prediabetes,[22] scientists have developed and implemented interventions to translate the DPP clinical trial into real-world application into a number of targeted cohorts. In a recent meta-analysis, Ali et al found a mean one-year weight loss or 3.99% across 28 trials that used a variety of strategies to implement the weight loss[34]. The greater than 7% weight loss obtained from our cohort was among the largest of the 28 published trials, making this an ideal opportunity to study the impact of the weight loss intervention on the ATGMCVR.

Altered secretion of adipose tissue derived molecules in obesity is a proposed mechanism for the development of insulin resistance and impaired insulin signaling[35, 36]. The development of insulin resistance and type 2 diabetes is associated with higher concentrations of proinflammatory markers in the circulation, including PAI-1, IL-6, and CRP[37, 38]. Inflammation has been found to be activated by obesity and hyperlipidemia, causing expression of genes encoding TNFα and IL-6[39–41]. Infiltrated macrophages in adipose tissue are the responsible cell type for the production of a majority of inflammatory cytokines, and these immune cells are increased with obesity, thus providing a link between obesity and insulin resistance. Both weight loss and pharmacological intervention (thiazolidinediones) to improve insulin resistance decreases adipose tissue macrophage infiltration, and is accompanied by reductions in inflammatory markers[42–45]. The novel community-based delivery of the weight loss intervention implemented by HELP PD supports this earlier work with improvements in the majority (5 out of 6) of the ATGMCVR selected for analysis.

In DPP, biomarkers of inflammation and coagulation were improved in the weight loss group, and to a lesser extent in the oral hypoglycemic metformin treated group[24]. CRP decreased by 33% in the lifestyle group and by 7% decrease in the metformin group, whereas there was a 5% increase in the placebo treated group. The coagulation factor fibrinogen showed a more modest change in lifestyle weight loss group compared to the usual care control group. We observed no difference in CRP between groups at 1-year. We selected PAI-1 as the biomarker for blood coagulation, instead of fibrinogen as seen by DPP, based on work that showed progression of PAI-1 levels, but not fibrinogen, over 5 years of follow-up, as well as high baseline levels was associated with the development of diabetes[46]. For PAI-1, we found an approximately 30% lower value for LWL vs. UC at 1-year. The higher adiponectin levels in LWL as compared to UC is consistent with changes previously observed for adiponectin by altering lifestyle factors. Adiponectin has a clear role in reducing obesity comorbidities, including insulin sensitivity[47].

In prospective studies, MetS has a relative risk of ~5 for developing T2DM [17], 1.65 for developing CVD and 1.27 for all-cause mortality[10]. In HELP PD, approximately 70% of their cohort had MetS. Although this study was unable to monitor the impact of modification of ATGMCVR on primary outcomes such as development of diabetes or CVD, we noted significant associations between these mediators and components of MetS. Adiponectin, the only marker reduced with increasing fat mass, correlated with blood lipids and blood pressure such that individuals with lower adiponectin had higher HDL-C, and lower plasma triglycerides, plasma glucose, and diastolic blood pressure. Consistent with this, adiponectin was negatively correlated with the summary score developed for MetS as this biomarker has been demonstrated to have anti-inflammatory activity. In the opposite direction, a number of the pro-inflammatory biomarkers targeted had positive correlations with the MetS summary score at baseline, suggesting their supportive nature to worsen CVD risk. In fact, consistent with the emerging concepts that cytokines contribute to hypertension, the one-year change in TNFα correlated with the diastolic blood pressure. The one-year change in adiponectin as well as the other ATGMCVR had limited correlations with changes in components for MetS. The lack of significance may be related to the small sample size as there were an encouraging number of strong trends ($p<0.10$) towards significance between the variables.

Several studies have shown the reduction in proinflammatory cytokines, part of the ATGMCVR profile of signaling molecules, in obese older adults undergoing an intentional weight loss intervention[48–51]. Leptin and IL-6 have been shown to be lower in a weight loss intervention as compared to physical activity alone, suggesting that weight loss rather than increased physical activity is responsible for improving the inflammatory profile in obesity[48]. Similarly Messier et al., found similar results in overweight and obese older adults with knee osteoarthritis undergoing a weight loss intervention[49]. Furthermore, substantial weight loss resulting from bariatric surgery is also known to reduce inflammation and other signaling molecules[52–54]. The individual contributions of the reductions in the proinflammatory cytokines and the correlation of the loss of weight with lower diastolic blood pressure cannot be distinguished in this study. However, since leptin and IL-6, as well as TNFα, have been suggested to elevate blood pressure, improvement in these biomarkers provides additional benefits apart from weight loss will require further investigation. Overall, the findings suggest that ATGMCVR can be improved with weight loss although further studies are needed to determine if metabolic dysfunction is also improved.

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Abbreviations

ATGMCVR	Adipose Tissue Generated Mediators of Cardiovascular Risk
CRP	C-reactive protein
IL-6	interleukin 6
TNFα	tumor necrosis factor alpha
PAI-1	plasminogen activator inhibitor 1
UC	usual care
LWL	lifestyle weight loss
CVD	cardiovascular disease
MetS	Metabolic Syndrome
T2DM	Type 2 Diabetes Mellitus
HELP PD	Healthy Living Partnerships to Prevent Diabetes

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Table 1

Baseline means (95%CI) for ATGMCVR comparing UC with LWL.

Variable	Usual Care	Lifestyle Weight Loss	p-value
Adiponectin (ng/ml)	7896.7 (6136.0, 10162.6)	8135.1 (6745.4, 9811.2)	0.8406
Leptin (ng/ml)	33.2 (25.2, 43.7)	27.4 (18.5, 40.6)	0.3997
CRP (mg/dl)	0.3 (0.2, 0.6)	0.3 (0.2, 0.4)	0.6046
TNFα (pg/ml)	12.8 (11.0, 14.9)	14.3 (11.4, 17.8)	0.4001
IL-6 (pg/ml)	0.3 (0.2, 0.6)	0.3 (0.2, 0.5)	0.9107
PAI-1 (pg/ml)	37.2 (29.1, 47.6)	49.2 (36.5, 66.3)	0.1311

Means calculated on log transformed variables and back transformed for ease of interpretation.

Table 2

One-year adjusted means (95% CI) for ATGMCVR from HELP PD comparing UC with LWL.

Variable	Usual Care N=15	Lifestyle Weight Loss N=15	p-value
Adiponectin (ng/ml)	8526.3 (7397.7, 9827)	10870.9 (9432, 12529.3)	0.0196
Leptin (pg/ml)	30.4 (26.1, 35.4)	23.7 (20.3, 27.5)	0.0239
CRP (mg/dl)	0.2 (0.2, 0.3)	0.2 (0.1, 0.2)	0.1729
TNFα (pg/ml)	10.6 (8.7, 12.8)	13.5 (11.1, 16.3)	0.0834
IL-6 (pg/ml)	0.4 (0.3, 0.5)	0.2 (0.1, 0.2)	0.0013
PAI-1 (pg/ml)	50 (42.7, 58.7)	36.2 (30.8, 42.4)	0.0071

Means calculated on log transformed variables and back transformed for ease of interpretation.

Table 3

Baseline means (95%CI) for ATGMCVR comparing participants with and without metabolic syndrome.

Variable	No MetS	MetS	p-value
Adiponectin (ng/ml)	9538.3 (6692.5, 13594.3)	7439.1 (6348.8, 8716.7)	0.12
Leptin (pg/ml)	27.3 (17.7, 42.2)	31.5 (23.5, 42.0)	0.57
CRP (mg/dl)	0.2 (0.1, 0.4)	0.3 (0.2, 0.5)	0.57
TNFα (pg/ml)	12.6 (10.1, 15.7)	13.9 (11.8, 16.4)	0.46
IL-6 (pg/ml)	0.2 (0.1, 0.3)	0.4 (0.2, 0.7)	0.07
PAI-1 (ng/ml)	34.0 (20.9, 55.3)	47.2 (39.0, 57.2)	0.22

Means calculated on log transformed variables and back transformed for ease of interpretation.

Table 4

Spearman correlations (p value) between criteria measures of MetS, ATGMCVR, body weight, and BMI at baseline.

	Adiponectin	Leptin	CRP	TNFα	IL-6	PAI-1	ATGMCVR Summary
Waist Circumference	−0.18 (0.34)	−0.13 (0.5)	0.28 (0.13)	0.17 (0.38)	0.48 (<0.01)	0.39 (0.03)	0.23 (0.23)
HDL-C	0.35 (0.06)	0.27 (0.15)	0.00 (0.99)	−0.14 (0.46)	−0.23 (0.22)	−0.28 (0.13)	0.12 (0.51)
Triglycerides	−0.34 (0.07)	−0.20 (0.28)	0.15 (0.42)	0.25 (0.18)	0.27 (0.15)	0.75 (<0.01)	0.16 (0.39)
Glucose	−0.48 (<0.01)	−0.44 (0.01)	−0.17 (0.36)	0.18 (0.33)	−0.26 (0.16)	0.13 (0.49)	−0.53 (<0.01)
Systolic BP	−0.24 (0.2)	0.30 (0.11)	0.03 (0.88)	0.30 (0.11)	0.15 (0.44)	0.24 (0.21)	0.18 (0.35)
Diastolic BP	−0.49 (<0.01)	−0.16 (0.38)	0.21 (0.27)	0.28 (0.14)	0.05 (0.78)	0.40 (0.03)	0.01 (0.96)
MetS-Sum	−0.38 (0.04)	0.00 (0.99)	0.12 (0.53)	0.42 (0.02)	0.37 (0.04)	0.40 (0.03)	0.10 (0.6)
Weight	−0.11 (0.56)	−0.02 (0.93)	0.11 (0.56)	0.01 (0.97)	0.41 (0.03)	0.14 (0.45)	0.22 (0.24)
BMI	−0.10 (0.61)	0.35 (0.06)	0.47 (<0.01)	−0.13 (0.5)	0.41 (0.03)	0.26 (0.16)	0.48 (<0.01)

MetS-Sum is the number of components (range 0–5) meeting the MetS criteria (NCEP updated ATPIII definition)

The summary measure is calculated by summing the standardized value of each of the six ATGMCVR measures.

Table 5

Spearman correlations (p value) between 1 year changes in criteria measures of MetS and ATGMCVR.

	ΔAdiponectin	**ΔLeptin**	**ΔCRP**	**ΔATNFα**	**ΔIL-6**	**ΔPAI-1**
ΔWaist Circumference	−0.49 (<0.01)	0.33 (0.08)	0.16 (0.39)	−0.14 (0.47)	0.22 (0.24)	0.36 (0.05)
ΔHDL-C	0.31 (0.09)	−0.11 (0.55)	−0.3 (0.10)	−0.18 (0.34)	−0.15 (0.42)	−0.34 (0.07)
ΔTriglycerides	−0.3 (0.11)	0.24 (0.21)	0.15 (0.43)	−0.21 (0.27)	−0.05 (0.8)	0.47 (<0.01)
ΔGlucose	−0.08 (0.66)	0.12 (0.53)	−0.24 (0.21)	−0.28 (0.14)	−0.11 (0.55)	0.29 (0.13)
ΔSystolic BP	−0.06 (0.74)	−0.11 (0.55)	−0.23 (0.23)	−0.19 (0.31)	−0.19 (0.31)	−0.25 (0.19)
ΔDiastolic BP	0.06 (0.74)	0.08 (0.68)	−0.12 (0.52)	−0.33 (0.07)	−0.21 (0.27)	−0.06 (0.76)