Diabetes & Metabolic Syndrome: Clinical Research & Reviews 8 (2014) 205–211

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

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

Gary D. Miller [a,*], Scott Isom [b], Timothy M. Morgan [b], Mara Z. Vitolins [b], Caroline Blackwell [b], K. Bridget Brosnihan [c], Debra I. Diz [c], Jeff Katula [a], David Goff [d]

[a] Department of Health and Exercise Science, and Translational Science Center, Wake Forest University, United States
[b] Department of Public Health Sciences, Wake Forest School of Medicine, United States
[c] Department of General Surgery and The Hypertension and Vascular Research Center, Wake Forest School of Medicine, United States
[d] Colorado School of Public Health, United States

ARTICLE INFO

Keywords:
Obesity
Diabetes
Metabolic syndrome
Prediabetes
Adipose tissue
Weight loss

SUMMARY

Aims: 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.
Materials and 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-year were compared between groups by analysis of covariance; baseline value of the mediator was the covariate. Baseline means for ATGMCVR were compared between those with ($n = 21$) and without ($n = 9$) metabolic syndrome (MetS).
Results: At baseline, subjects were 58 ± 9 (SD) years, 70% female, with a BMI of 34 ± 4 kg/m^2. One-year weight loss (%) was 7.8 ± 6.0% for LWL and 1.7 ± 4.5% for UC. Group differences at 1-year were noted (adjusted means [95%CI] for UC and LWL, respectively) for adiponectin (8526.3 [7397.7, 9827]; 10,870.9 [9432.0, 12,529.3] 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.
Conclusion: 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.

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

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.

* Corresponding author at: Department Health and Exercise Science, Wake Forest University, Box 7868, Reynolda Station, Winston-Salem, NC 27109-7868, United States. Tel.: +1 336 758 1901; fax: +1 336 758 4680.
E-mail address: millergd@wfu.edu (G.D. Miller).

http://dx.doi.org/10.1016/j.dsx.2014.09.003
1871-4021/

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 = 25–40 kg/m^2); blood glucose of 95 mg/dl $\leq$125 mg/dl following at least an 8-h fast; and $\geq$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 (758C 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-h 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 $\leq$3.9%, and total coefficient of variation are $\leq$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-min 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.