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Circulating Irisin, Omentin- 1, and Lipoprotein Subparticles in Adults at Higher Cardiovascular Risk

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Abstract

Objective—Muscle and fat are now recognized as metabolism-regulating endocrine organs.

However, muscle and adipocyte-derived novel cytokines such as irisin and omentin-1 remain understudied in relation to metabolic biomarkers that are associated with cardiovascular risk.

Subjects and Methods—Thirty-nine subjects with mean ($\pm$ SD) BMI of 29.2 ± 5.4 kg/m² and either diabetes or two other cardiovascular risk factors were enrolled in a 6-month randomized trial of low-dose ethanol. We examined cross-sectional data at baseline, 3-month, and 6-month visits to assess (1) within-person stability of novel cytokines (irisin, omentin-1, visfatin, resistin, and soluble tumor necrosis factor receptor II) and (2) their associations with metabolic parameters, particularly lipoprotein subparticle profile.

Results—Repeated measures of irisin and omentin-1 were highly correlated, with intra-class correlations of 0.84 (95% CI: 0.74, 0.91; $P < 0.001$) and 0.81 (0.70, 0.89; $P < 0.001$), respectively.

Irisin was negatively correlated with omentin-1 (7.4% irisin decrease per a 1-SD increment in

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Conflict of Interest

The authors do not have any conflict of interest related to this manuscript.

Author Contribution

G.P. performed experiments, interpreted data, and drafted the manuscript. L.M. performed statistical analyses, interpreted data, and drafted the manuscript. B.N. collected data. K.J.M. designed the study and collected, analyzed, and interpreted data. C.S.M. designed these measurements and supervised their completion. All authors contributed in writing and critical revision of the manuscript and approved its final version.

omentin-1; 95% CI: 0.5%, 13.9%; $P=0.04$). In models adjusted for age, sex, and race, irisin was negatively associated with HDL cholesterol (7.3% decrease per a 10 mg/dL increment; 1.0%, 13.3%; $P=0.02$) and large HDL particles (15.5% decrease per a 1-SD or 3.5- μ mol/L increment; 5.2%, 24.7%; $P=0.005$). Omentin-1 was positively associated with mean VLDL size (3.8% increase per a 1-SD increment; 0.06%, 7.8%; $P=0.05$). Adjustment for alcohol intervention, BMI, and other cytokines did not materially affect these associations.

Conclusions—Irisin and omentin-1 are stable within-person, inversely associated with each other, and closely related to lipoprotein profile. These molecules may be promising markers for cardiovascular risk.

Keywords

Fibronectin type III domain containing 5; myokine; atherosclerosis; metabolic syndrome; longitudinal biomarker

INTRODUCTION

Obesity is a major cardiovascular risk factor [1], but the mechanisms by which adiposity exerts its influence continue to be elucidated. Many adipocyte-secreted cytokines have been proposed to mediate adipose tissue-cardiovascular cross-talk [2]. Of these, visfatin, resistin, and soluble tumor necrosis factor receptor II (sTNFR_{II}) may mark inflammation-related atherosclerosis and cardiovascular disease [3–6].

In contrast, omentin-1, an adipokine primarily secreted by omental adipose tissue [7] and originally described as the intestinal Paneth-cell derived molecule intelectin [8], is decreased in obesity [9] and type 2 diabetes [10, 11]. Its levels have been inversely associated with various body composition parameters and adipokines, such as leptin [9]. Omentin-1 is proposed as a beneficial adipokine, having insulin-sensitizing [7], anti-inflammatory [12], vasodilative [13], and cardioprotective [14] effects, similar to adiponectin. In fact, previous studies have shown its positive association with adiponectin and high-density lipoprotein (HDL) cholesterol [9, 15] and its increase following a weight loss program associated with improvement in the glycemic profile [16]. Therefore, it has been suggested that omentin-1 concentrations may signal metabolic impairment [17].

More recently, investigators have recognized that myocytes produce and secrete several molecules that regulate body metabolism and energy homeostasis [18]. Akin to adipokines, circulating muscle-derived molecules have been termed myokines [19]. Irisin, a recently identified myokine, acts as an exercise-induced, insulin-sensitizing hormone in mice [20]. Irisin is produced by the cleavage of fibronectin type III domain containing 5 (FNDC5) in a peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC1- α)-dependent manner [20]. Its proposed beneficial effects include browning of white adipose tissue and increase in energy expenditure leading to weight loss [20]. In recent studies, irisin mRNA expression and/or circulating levels have been associated with anthropometric and biochemical parameters [21–24], other hormones and adipokines [21], myokines [25] and obesity [22], insulin resistance [26] or type 2 diabetes [27, 28] and metabolic syndrome [29]. Despite growing interest in irisin and less-characterized adipokines, little is known about

their (1) within-person stability over time, (2) interrelationships, and (3) associations with novel biomarkers that relate to cardiovascular risk. In the current study, we aim to investigate these three areas of interest by conducting cross-sectional and longitudinal analyses among participants of a small clinical trial of adults at high cardiovascular risk. As part of that study, lipoprotein subparticle profile was evaluated given its potential to improve cardiovascular risk prediction and unique structural perspective on lipoprotein size and density [30, 31]. This, in turn, presents a unique opportunity for us to study novel cytokines in relation to specific lipoprotein subparticles and cardiovascular risk.

SUBJECTS AND METHODS

Study Participants

Participants aged 55 years and older with either diabetes or two other cardiovascular risk factors were recruited to participate in a parallel-design randomized trial conducted at Beth Israel Deaconess Medical Center (BIDMC) in Boston, MA that examined the effect of alcohol consumption on markers of cardiovascular risk. Inclusion criteria included either diabetes or two of the following cardiovascular risk factors: current smoking, hypertension, family history of heart disease, high low-density lipoprotein (LDL) cholesterol (>130 mg/dl), low HDL cholesterol (<40 mg/dl), body mass index (BMI) larger than 30 kg/m^2 , and waist circumference greater than 100 cm for men and 90 cm for women. Relevant exclusion criteria included intolerance or allergy to alcohol consumption, any severe illness expected to cause death or profound disability within 6 months, regular use of sedative/hypnotics, chronic liver disease, previous breast or gastrointestinal cancer, uncontrolled hypertension, chronic renal failure on dialysis, current use of metronidazole or warfarin, and psychiatric illness. From December 2008 to March 2011, we randomized eligible participants to consume either placebo or 150 mL 10% ethyl alcohol daily for 6 months; 39 participants completed the study. The Committee on Clinical Investigations at BIDMC approved our protocol, and all participants gave written informed consent. All participants in this randomized trial were included for analysis in this nested study.

Biochemical and Survey Assessments

At baseline, 3-month, and 6-month visits, we collected fasting blood samples to measure levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), glucose, and HDL; participants also completed the Center for Epidemiologic Studies Depression Scale (CES-D), Pittsburgh Sleep Quality Index (PSQI) [32, 33], and Yale Physical Activity Survey (YPAS) [34]. At baseline and 6-month visits, we measured hemoglobin A1c and nuclear magnetic resonance (NMR) lipoprotein profile (LipoScience, Inc., Raleigh, NC) [35]. In brief, lipoprotein subparticles of different sizes emit distinct lipid methyl group NMR signals, and the measured amplitudes of these signals are directly proportional to concentrations of lipoprotein subparticles, which are grouped into very low density lipoprotein (VLDL), LDL, and HDL. Mean lipoprotein subparticle sizes are then calculated from the diameter of each lipoprotein subparticle and its relative concentration.

Hormone Measurements

Circulating irisin levels were determined with commercially available ELISA (Aviscera Biosciences, Santa Clara, CA; sensitivity: 9.3 ng/mL; intra- and inter-assay coefficients of variation: <4–6% and <8–10%) [21]. Omentin-1 and visfatin were measured by using ELISA (Biovendor, Chandler, NC; omentin-1: 0.5 ng/mL, 3.7% and 4.6%; visfatin: 30 pg/mL, 2.31–9.11% and 4.66–7.24%). Resistin concentration was quantified with ELISA (Millipore Corporation, Billerica, MA; 0.02 ng/mL, 3.2–7.0% and 7.1–7.7%). sTNFRII was measured by ELISA (R&D Systems, Minneapolis, MN; 0.6 pg/mL, 2.6–4.8% and 3.5–5.1%).

Statistical Analysis

We collected data using the Research Electronic Data Capture (REDCap) platform [36] and conducted analysis using STATA 13.0 (College Station, TX, USA) and SAS version 9.3 (SAS Institute Inc, Cary, NC). We evaluated within-person stability of irisin and omentin-1 measurements using mixed-effect intraclass correlations (ICC) across all visits and examined associations between irisin, omentin-1, visfatin, resistin, and sTNFRII with Spearman correlations.

In addition, we assessed the cross-sectional relationships of these cytokines with other measured biomarkers including lipoprotein subparticles, depression, sleep quality, and physical activity. We logarithmically transformed outcomes to maximize normality and used mixed-effect models with a compound-symmetry covariance structure to account for repeated measures within-individual. We adjusted for age, sex, and race, and then additionally controlled for alcohol intervention and BMI. We assessed for linearity with tests of heterogeneity across quartiles of independent variables and found no significant departures.

RESULTS

Table 1 shows the baseline characteristics of study participants; there was no systemic difference in demographic or clinical characteristics between the two randomized groups. Repeated measures of irisin and omentin-1 were highly correlated, with ICCs of 0.84 (95% CI: 0.74, 0.91; $P<0.001$) and 0.81 (0.70, 0.89; $P<0.001$), respectively. Table 2 reports Spearman correlations (1) between levels of irisin, omentin-1, visfatin, resistin, and sTNFRII and (2) between levels at baseline and 6-month visits for each individual hormone. Irisin and omentin-1 were negatively correlated with each other with a 7.4% irisin decrement (95% CI: 0.5%, 13.9%; $P=0.04$) per a 1-SD omentin-1 increment; further adjustment for potential covariates did not alter this relationship appreciably.

We next evaluated relationships of irisin and omentin-1 with lipoprotein subparticle levels. In models adjusted for age, sex, and race, irisin was negatively associated with HDL (7.3% decrease per a 10-mg/dL increment in HDL cholesterol; 95% CI: 1.0%, 13.3%; $P=0.02$); in particular, a 1-SD or 3.5- μ mol/L increment in large HDL particles was associated with 15.5% decrease (5.2%, 24.7%; $P=0.005$) in irisin levels. In addition, irisin was positively, although marginally, associated with large VLDL particles (Table 3). Omentin-1 was

positively associated with mean VLDL size (3.8% increase per a 1-SD increment; 0.06%, 7.8%; $P=0.05$) and negatively associated with small VLDL particles (Table 4). Additional adjustment for alcohol group and BMI did not materially affect these associations, nor did mutual adjustment for all five hormones.

Lastly, we evaluated associations of irisin and omentin-1 with other metabolic parameters. In age, sex, and race adjusted models, omentin-1 was positively associated with GGT (5.7% increase per a 1-SD or 12-IU/L increment; 0.6%, 11.1%; $P=0.03$). We did not find associations of irisin or omentin-1 with AST, ALT, glucose, hemoglobin A1c, blood pressure, BMI, alcohol group, statin use, depression, sleep quality, or physical activity.

DISCUSSION

The present study is the first to explore associations between irisin, omentin-1, and lipoprotein subparticles in adults. Irisin was negatively associated with serum omentin-1, independently of various confounders including age and BMI. Moreover, irisin levels were also inversely associated with both HDL cholesterol and specifically with large HDL particle concentration. Both markers showed strong within-person correlations over 6 months, suggesting high long-term reliability, which is important for markers in longitudinal studies. Irisin was initially proposed to mediate the beneficial effects of exercise in adipose tissue metabolism [20, 37]. In previous cross-sectional studies, we observed negative correlations of irisin with adiponectin and HDL cholesterol, suggesting a compensatory mechanism or resistance in states of impaired metabolism [21, 38, 39]. In addition, accumulating data support the production of irisin by adipocytes, suggesting its dual role as a myokine and adipokine [22, 40]. Interestingly, two recent reports challenged the putative presence of irisin in human plasma [41, 42]. In this study, we selected a previously validated ELISA kit that was commercially available [21, 29, 38, 43], and our results corroborated the existence of irisin in human circulation. The high Spearman and intra-class correlations reported in this study further strengthen the validity of this finding.

A growing body of evidence suggests that irisin may influence lipid levels. Park et al. showed that circulating irisin levels were negatively associated with HDL cholesterol and positively associated with metabolic syndrome [29]. Plasma irisin concentrations have also been correlated with LDL receptor mRNA expression and overall cholesterol homeostasis [44], and decrease in circulating irisin has been associated with improvement in apolipoprotein B levels [45]. We expand these findings by showing that irisin is associated with lipoprotein subparticle profile, primarily large HDL and VLDL particle concentrations. Unfavorable changes in these particles, particularly large HDL particles, appear to be atherogenic and increase cardiovascular risk [30]. In addition, since the discovery of irisin, its levels have been associated with both cholesterol and steroid hormones, such as estradiol [21], which leads us to believe that it might be involved in the process of steroidogenesis. The mechanisms by which irisin may exert its effects on lipid synthesis, especially HDL cholesterol, will require in vitro and/or interventional studies, but low HDL cholesterol levels may signal a direct feedback loop on myocytes [46], thereby triggering the secretion of irisin to restore altered metabolism.

Decreased levels of omentin-1 have been associated with cardiovascular diseases, such as endothelial dysfunction [47], coronary artery disease [15], and nascent metabolic syndrome [48, 49]. In particular, omentin-1 levels are associated with arterial stiffness [50] and carotid artery intima-media thickness [51], perhaps by inhibiting TNF-induced endothelial dysfunction in human endothelial cells [52]. However, to the best of our knowledge, no prior studies have investigated its associations with markers of cardiovascular risk, such as lipoprotein subparticle distribution. We observed an association between serum omentin-1 and small VLDL particle size, after adjusting for potential covariates. In addition, although there have been studies exploring associations between omentin-1 and other adipokines [9, 11, 15, 53], our study is the first to relate omentin-1 to lower levels of irisin, independently of various confounders. Due to the cross-sectional design of our study, we cannot prove any causal relationship between these two molecular entities. Therefore, interventional studies are needed to explore whether there is a direct interplay or any underlying linking mechanism between these two bioactive molecules. For example, given that omentin-1 and adiponectin share similar expression and regulation patterns, follow-up studies exploring adiponectin's role in this association seem warranted.

In this study, we did not find associations of irisin or omentin-1 with some known markers of insulin resistance, diabetes, and cardiovascular diseases such as glucose, hemoglobin A1c, blood pressure, and BMI. While this lack of association is largely consistent with two recent studies in obese children and adults [54, 55], it may also be result of the small sample size and limited heterogeneity of our studied population, which were composed of older adults at higher cardiovascular risk. In addition, the size and characteristics of our studied population may also limit the generalizability of our findings in healthy populations. The strengths of our study, however, include multiple measurements of novel markers within-individual over a period of six months and recruitment of free-living men and women without substantial cardiovascular disease.

Understanding the connections between irisin, omentin-1, and lipoprotein subparticles has important ramifications. Given their proposed role in metabolism, our results support a notion of irisin resistance in patients in risk for or with metabolic syndrome, similar to insulin or leptin resistance, as already suggested by Bostrom et al. [38]. Also, our findings implicate irisin in pro-inflammatory and atherogenic pathways, delineate the muscle-adipo-cardiovascular axis, and thus point to the potential of irisin-sensitizers, possibly omentin-1, in the fight against obesity-associated co-morbidities. However, future mechanistic studies are necessary to confirm this hypothesis.

In conclusion, our study demonstrated strong within-person correlations of irisin and omentin-1 measures across six months and found their significant inverse association in serum. Further, it suggests that irisin and omentin-1 may be closely involved in lipoprotein subparticle regulation and lipid metabolism. Large observational and interventional studies are needed to further examine these molecules as diagnostic markers and intervention targets for nascent atherosclerosis, metabolic syndrome, and cardiovascular disease.

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List of Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BIDMC	Beth Israel Deaconess Medical Center
BMI	body mass index
CES-D	Center for Epidemiologic Studies Depression Scale
FNDC5	fibronectin type III domain containing 5
GGT	gamma-glutamyltransferase
HDL	high-density lipoprotein
LDL	low-density lipoprotein
PGC1-α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PSQI	Pittsburgh Sleep Quality Index
sTNFRII	soluble tumor necrosis factor receptor type II
VLDL	very low density lipoprotein
YPAS	Yale Physical Activity Survey

References

1. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation*. 1983; 67:968–77. [PubMed: 6219830]
2. Van de Voorde J, Pauwels B, Boydens C, Decaluwe K. Adipocytokines in relation to cardiovascular disease. *Metabolism: clinical and experimental*. 2013; 62:1513–21. [PubMed: 23866981]
3. Kadooglou NP, Sailer N, Moutzouoglou A, Kapelouzou A, Tsanikidis H, Vitta I, et al. Visfatin (nampt) and ghrelin as novel markers of carotid atherosclerosis in patients with type 2 diabetes. *Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association*. 2010; 118:75–80.
4. Dahl TB, Yndestad A, Skjelland M, Oie E, Dahl A, Michelsen A, et al. Increased expression of visfatin in macrophages of human unstable carotid and coronary atherosclerosis: possible role in inflammation and plaque destabilization. *Circulation*. 2007; 115:972–80. [PubMed: 17283255]
5. Chen C, Jiang J, Lu JM, Chai H, Wang X, Lin PH, et al. Resistin decreases expression of endothelial nitric oxide synthase through oxidative stress in human coronary artery endothelial cells. *American journal of physiology Heart and circulatory physiology*. 2010; 299:H193–201. [PubMed: 20435848]

6. Shai I, Schulze MB, Manson JE, Rexrode KM, Stampfer MJ, Mantzoros C, et al. A prospective study of soluble tumor necrosis factor- α receptor II (sTNF-RII) and risk of coronary heart disease among women with type 2 diabetes. *Diabetes care*. 2005; 28:1376–82. [PubMed: 15920055]
7. Yang RZ, Lee MJ, Hu H, Pray J, Wu HB, Hansen BC, et al. Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action. *American journal of physiology Endocrinology and metabolism*. 2006; 290:E1253–61. [PubMed: 16531507]
8. Komiya T, Tanigawa Y, Hirohashi S. Cloning of the novel gene intelectin, which is expressed in intestinal paneth cells in mice. *Biochemical and biophysical research communications*. 1998; 251:759–62. [PubMed: 9790983]
9. de Souza Batista CM, Yang RZ, Lee MJ, Glynn NM, Yu DZ, Pray J, et al. Omentin plasma levels and gene expression are decreased in obesity. *Diabetes*. 2007; 56:1655–61. [PubMed: 17329619]
10. Pan HY, Guo L, Li Q. Changes of serum omentin-1 levels in normal subjects and in patients with impaired glucose regulation and with newly diagnosed and untreated type 2 diabetes. *Diabetes research and clinical practice*. 2010; 88:29–33. [PubMed: 20129687]
11. Yan P, Liu D, Long M, Ren Y, Pang J, Li R. Changes of serum omentin levels and relationship between omentin and adiponectin concentrations in type 2 diabetes mellitus. *Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association*. 2011; 119:257–63.
12. Kazama K, Usui T, Okada M, Hara Y, Yamawaki H. Omentin plays an anti-inflammatory role through inhibition of TNF- α -induced superoxide production in vascular smooth muscle cells. *European journal of pharmacology*. 2012; 686:116–23. [PubMed: 22554771]
13. Yamawaki H, Tsubaki N, Mukohda M, Okada M, Hara Y. Omentin, a novel adipokine, induces vasodilation in rat isolated blood vessels. *Biochemical and biophysical research communications*. 2010; 393:668–72. [PubMed: 20170632]
14. Greulich S, Chen WJ, Maxhera B, Rijzewijk LJ, van der Meer RW, Jonker JT, et al. Cardioprotective properties of omentin-1 in type 2 diabetes: evidence from clinical and in vitro studies. *PloS one*. 2013; 8:e59697. [PubMed: 23555749]
15. Shibata R, Ouchi N, Kikuchi R, Takahashi R, Takeshita K, Kataoka Y, et al. Circulating omentin is associated with coronary artery disease in men. *Atherosclerosis*. 2011; 219:811–4. [PubMed: 21925659]
16. Moreno-Navarrete JM, Catalan V, Ortega F, Gomez-Ambrosi J, Ricart W, Fruhbeck G, et al. Circulating omentin concentration increases after weight loss. *Nutrition & metabolism*. 2010; 7:27. [PubMed: 20380714]
17. Prats-Puig A, Bassols J, Bargallo E, Mas-Parareda M, Ribot R, Soriano-Rodriguez P, et al. Toward an early marker of metabolic dysfunction: omentin-1 in prepubertal children. *Obesity*. 2011; 19:1905–7. [PubMed: 21720428]
18. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nature reviews Endocrinology*. 2012; 8:457–65.
19. Pedersen BK, Steensberg A, Fischer C, Keller C, Keller P, Plomgaard P, et al. Searching for the exercise factor: is IL-6 a candidate? *Journal of muscle research and cell motility*. 2003; 24:113–9. [PubMed: 14609022]
20. Bostrom P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, et al. A PGC1- α -dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*. 2012; 481:463–8. [PubMed: 22237023]
21. Huh JY, Panagiotou G, Mougios V, Brinkoetter M, Vamvini MT, Schneider BE, et al. FND5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II. mRNA expression and circulating concentrations in response to weight loss and exercise. *Metabolism: clinical and experimental*. 2012; 61:1725–38. [PubMed: 23018146]
22. Moreno-Navarrete JM, Ortega F, Serrano M, Guerra E, Pardo G, Tinahones F, et al. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. *The Journal of clinical endocrinology and metabolism*. 2013; 98:E769–78. [PubMed: 23436919]

23. Stengel A, Hofmann T, Goebel-Stengel M, Elbelt U, Kobelt P, Klapp BF. Circulating levels of irisin in patients with anorexia nervosa and different stages of obesity—correlation with body mass index. *Peptides*. 2013; 39:125–30. [PubMed: 23219488]
24. Park KH, Zaichenko L, Peter P, Davis CR, Crowell JA, Mantzoros CS. Diet quality is associated with circulating C-reactive protein but not irisin levels in humans. *Metabolism: clinical and experimental*. 2014; 63:233–41. [PubMed: 24315778]
25. Vamvini MT, Aronis KN, Panagiotou G, Huh JY, Chamberland JP, Brinkoetter MT, et al. Irisin mRNA and circulating levels in relation to other myokines in healthy and morbidly obese humans. *European journal of endocrinology / European Federation of Endocrine Societies*. 2013; 169:829–34. [PubMed: 24062354]
26. Crujeiras AB, Zulet MA, Lopez-Legarrea P, de la Iglesia R, Pardo M, Carreira MC, et al. Association between circulating irisin levels and the promotion of insulin resistance during the weight maintenance period after a dietary weight-lowering program in obese patients. *Metabolism: clinical and experimental*. 2013
27. Choi YK, Kim MK, Bae KH, Seo HA, Jeong JY, Lee WK, et al. Serum irisin levels in new-onset type 2 diabetes. *Diabetes research and clinical practice*. 2013; 100:96–101. [PubMed: 23369227]
28. Liu JJ, Wong MD, Toy WC, Tan CS, Liu S, Ng XW, et al. Lower circulating irisin is associated with type 2 diabetes mellitus. *Journal of diabetes and its complications*. 2013; 27:365–9. [PubMed: 23619195]
29. Park KH, Zaichenko L, Brinkoetter M, Thakkar B, Sahin-Efe A, Joung KE, et al. Circulating irisin in relation to insulin resistance and the metabolic syndrome. *The Journal of clinical endocrinology and metabolism*. 2013; 98:4899–907. [PubMed: 24057291]
30. Mora S, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. *Circulation*. 2009; 119:931–9. [PubMed: 19204302]
31. Krauss RM. Lipoprotein subfractions and cardiovascular disease risk. *Current opinion in lipidology*. 2010; 21:305–11. [PubMed: 20531184]
32. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research*. 1989; 28:193–213. [PubMed: 2748771]
33. Carpenter JS, Andrykowski MA. Psychometric evaluation of the Pittsburgh Sleep Quality Index. *Journal of psychosomatic research*. 1998; 45:5–13. [PubMed: 9720850]
34. Dipietro L, Caspersen CJ, Ostfeld AM, Nadel ER. A survey for assessing physical activity among older adults. *Medicine and science in sports and exercise*. 1993; 25:628–42. [PubMed: 8492692]
35. Jeyarajah EJ, Cromwell WC, Otvos JD. Lipoprotein particle analysis by nuclear magnetic resonance spectroscopy. *Clinics in laboratory medicine*. 2006; 26:847–70. [PubMed: 17110242]
36. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of biomedical informatics*. 2009; 42:377–81. [PubMed: 18929686]
37. Huh JY, Mougios V, Skraparlis A, Kabasakalis A, Mantzoros CS. Irisin in response to acute and chronic whole-body vibration exercise in humans. *Metabolism: clinical and experimental*. 2014
38. Bostrom PA, Fernandez-Real JM. *Metabolism: Irisin, the metabolic syndrome and follistatin in humans. Nature reviews Endocrinology*. 2014; 10:11–2.
39. Polyzos SA, Kountouras J, Shields K, Mantzoros CS. Irisin: a renaissance in metabolism? *Metabolism: clinical and experimental*. 2013; 62:1037–44. [PubMed: 23664085]
40. Roca-Rivada A, Castelao C, Senin LL, Landrove MO, Baltar J, Belen Crujeiras A, et al. FNDC5/irisin is not only a myokine but also an adipokine. *Plos One*. 2013; 8:e60563. [PubMed: 23593248]
41. Erickson HP. Irisin and FNDC5 in retrospect: An exercise hormone or a transmembrane receptor? *Adipocyte*. 2013; 2:289–93. [PubMed: 24052909]
42. Raschke S, Elsen M, Gassenhuber H, Sommerfeld M, Schwahn U, Brockmann B, et al. Evidence against a beneficial effect of irisin in humans. *Plos One*. 2013; 8:e73680. [PubMed: 24040023]

43. Bostrom PA, Fernandez-Real JM, Mantzoros C. Irisin in humans: recent advances and questions for future research. *Metabolism: clinical and experimental*. 2014; 63:178–80. [PubMed: 24342075]
44. Gouni-Berthold I, Berthold HK, Huh JY, Berman R, Spenrath N, Krone W, et al. Effects of lipid-lowering drugs on irisin in human subjects in vivo and in human skeletal muscle cells ex vivo. *Plos One*. 2013; 8:e72858. [PubMed: 24023786]
45. de la Iglesia R, Lopez-Legarrea P, Crujeiras AB, Pardo M, Casanueva FF, Zulet MA, et al. Plasma irisin depletion under energy restriction is associated with improvements in lipid profile in metabolic syndrome patients. *Clinical endocrinology*. 2013
46. Lehti M, Donelan E, Abplanalp W, Al-Massadi O, Habegger KM, Weber J, et al. High-density lipoprotein maintains skeletal muscle function by modulating cellular respiration in mice. *Circulation*. 2013; 128:2364–71. [PubMed: 24170386]
47. Moreno-Navarrete JM, Ortega F, Castro A, Sabater M, Ricart W, Fernandez-Real JM. Circulating omentin as a novel biomarker of endothelial dysfunction. *Obesity*. 2011; 19:1552–9. [PubMed: 21293447]
48. Bremer AA, Jialal I. Adipose tissue dysfunction in nascent metabolic syndrome. *Journal of obesity*. 2013; 2013:393192. [PubMed: 23653857]
49. Jialal I, Devaraj S, Kaur H, Adams-Huet B, Bremer AA. Increased chemerin and decreased omentin-1 in both adipose tissue and plasma in nascent metabolic syndrome. *The Journal of clinical endocrinology and metabolism*. 2013; 98:E514–7. [PubMed: 23303213]
50. Yoo HJ, Hwang SY, Hong HC, Choi HY, Yang SJ, Lee KW, et al. Implication of circulating omentin-1 level on the arterial stiffening in type 2 diabetes mellitus. *Endocrine*. 2013; 44:680–7. [PubMed: 23532633]
51. Shibata R, Takahashi R, Kataoka Y, Ohashi K, Ikeda N, Kihara S, et al. Association of a fat-derived plasma protein omentin with carotid artery intima-media thickness in apparently healthy men. *Hypertension research : official journal of the Japanese Society of Hypertension*. 2011; 34:1309–12. [PubMed: 21814208]
52. Yamawaki H, Kuramoto J, Kameshima S, Usui T, Okada M, Hara Y. Omentin, a novel adipocytokine inhibits TNF-induced vascular inflammation in human endothelial cells. *Biochemical and biophysical research communications*. 2011; 408:339–43. [PubMed: 21514279]
53. Auguet T, Quintero Y, Riesco D, Morancho B, Terra X, Crescenti A, et al. New adipokines vaspin and omentin. Circulating levels and gene expression in adipose tissue from morbidly obese women. *BMC medical genetics*. 2011; 12:60. [PubMed: 21526992]
54. Bluher S, Panagiotou G, Petroff D, Markert J, Wagner A, Klemm T, et al. Effects of a 1-year exercise and lifestyle intervention on irisin, adipokines, and inflammatory markers in obese children. *Obesity*. 2014
55. Yan B, Shi X, Zhang H, Pan L, Ma Z, Liu S, et al. Association of serum irisin with metabolic syndrome in obese Chinese adults. *Plos One*. 2014; 9:e94235. [PubMed: 24709991]

Table 1Baseline Characteristics of Participants (N=39)^a

Demographics	
Age (years)	64 ± 6
Female	14 (36%)
Smoking Status	
Former	14 (36%)
Current	5 (13%)
BMI (kg/m ²)	29.2 ± 5.4
Overweight (25–30 kg/m ²)	15 (38%)
Obese (>30 kg/m ²)	15 (38%)
Blood Pressure (mm Hg)	130 ± 19 / 75 ± 11
Hypertension	25 (64%)
Diabetes	6 (15%)
Myocardial Infarction	1 (3%)
Stroke	1 (3%)
Medication Use	
Statin	16 (41%)
Blood Pressure	22 (56%)
Diabetes	4 (10%)
Laboratories	
High-Density Lipoprotein Cholesterol, HDL (mg/dL) ^b	50 ± 13
Hemoglobin A1c (%)	6.0 ± 0.6
Aspartate Aminotransferase, AST (IU/L)	23 ± 7
Alanine Aminotransferase, ALT (IU/L)	24 ± 9
Gamma Glutamyltransferase, GGT (IU/L)	25 ± 15
Glucose (mg/dL) ^c	99 ± 24
Questionnaires	
Center for Epidemiologic Studies Depression Scale, CES-D	2.5 ± 3.4
Pittsburgh Sleep Quality Index, PSQI	8.6 ± 6.4
Yale Physical Activity Survey, YPAS, Total Activity Time (hours/week)	29 ± 19
Yale Physical Activity Survey, YPAS, Energy Expenditure (kcal/week)	6502 ± 4547

^aData are means ± SD or number (%).^bN=38.^cN=37.

Table 2

Spearman Correlations between Hormone Measurements^a

		Baseline Measurements, Mean (SD)				
		Irisin	Omentin-1	Visfatin	Resistin	sTNFRII
		546 (265)	550 (167)	1,04 (0.98)	13.1 (8.1)	2754 (950)
	Irisin	0.83 ^b (<0.001)				
	526 (279)					
	Omentin-1	-0.16 (0.09)	0.82 ^b (<0.001)			
	520 (151)					
	Visfatin	0.18 (0.16)	-0.10 (0.41)	0.42 ^b (0.02)		
	0.82 (0.48)					
	Resistin	0.11 (0.28)	-0.07 (0.47)	0.27 (0.04)	0.75 ^b (<0.001)	
	13.0 (6.9)					
	sTNFRII	0.18 (0.05)	0.14 (0.12)	-0.12 (0.36)	0.31 (0.002)	0.81 ^b (<0.001)
	2659 (788)					

^aData are presented as correlation coefficients (P values).^bThese correlations were obtained by comparing levels at baseline and 6-month visits.

Abbreviations: soluble tumor necrosis factor receptor type II (sTNFRII)

Table 3

Associations of Irisin Levels with Lipoprotein Subparticles

	Unadjusted			Age, sex, race adjusted			Age, sex, race, cytokines adjusted		
	% Change (95% CI)	P		% Change (95% CI)	P		% Change (95% CI)	P	
VLDL particle (nmol/L)									
Large ^a	6.7 (−0.7, 14.7)	0.08		6.4 (−1.1, 14.5)	0.09		6.0 (−1.8, 14.5)	0.13	
Medium ^a	−1.8 (−12.1, 9.7)	0.74		−1.1 (−11.8, 10.9)	0.84		−0.8 (−11.7, 11.5)	0.89	
Small ^a	2.3 (−6.2, 11.5)	0.60		2.4 (−6.2, 11.8)	0.59		0.7 (−8.9, 11.3)	0.89	
LDL particle (nmol/L)									
Large ^a	−2.5 (−13.0, 9.2)	0.65		−5.2 (−16.3, 7.3)	0.39		−5.7 (−17.8, 8.2)	0.38	
Small ^a	3.9 (−6.6, 15.6)	0.47		2.9 (−7.8, 14.7)	0.60		−3.7 (−14.9, 9.0)	0.54	
HDL particle (μmol/L)									
Large ^a	−12.1 (−20.9, −2.2)	0.02		−15.5 (−24.7, −5.2)	0.005		−12.8 (−22.8, −1.5)	0.03	
Medium ^a	−1.2 (−7.6, 5.6)	0.71		−1.5 (−7.9, 5.3)	0.64		0.7 (−6.9, 8.8)	0.86	
Small ^a	2.5 (−5.0, 10.6)	0.52		2.5 (−5.0, 10.5)	0.52		−1.1 (−9.2, 7.7)	0.78	

^a Particle concentrations of different sizes were mutually adjusted.

Abbreviations: very low density lipoprotein (VLDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL).

Table 4

Associations of Omentin-1 Levels with Lipoprotein Subparticles

	Unadjusted			Age, sex, race adjusted			Age, sex, race, cytokines adjusted		
	% Change (95% CI)	P		% Change (95% CI)	P		% Change (95% CI)	P	
VLDL particle (nmol/L)									
Large ^a	0.3 (-4.8, 5.5)	0.92		0.4 (-4.7, 5.7)	0.88		0.6 (-5.7, 7.4)	0.84	
Medium ^a	2.9 (-4.7, 11.0)	0.46		3.6 (-4.1, 11.9)	0.36		3.1 (-6.2, 13.4)	0.51	
Small ^a	-6.5 (-12.0, -0.6)	0.03		-5.4 (-11, 0.6)	0.07		-5.3 (-12.6, 2.6)	0.17	
LDL particle (nmol/L)									
Large ^a	-1.2 (-8.9, 7.1)	0.76		-3.2 (-11.3, 5.5)	0.45		-6.6 (-15.7, 3.5)	0.18	
Small ^a	-0.9 (-8.2, 6.9)	0.81		-0.2 (-7.4, 7.6)	0.96		-1.4 (-10.2, 8.2)	0.75	
HDL particle (μmol/L)									
Large ^a	4.1 (-3.4, 12.3)	0.29		0.2 (-7.6, 8.7)	0.96		-5.6 (-14.5, 4.3)	0.24	
Medium ^a	-0.3 (-5.4, 5.0)	0.91		-0.1 (-5.2, 5.3)	0.97		-2.0 (-8.4, 4.8)	0.53	
Small ^a	0.3 (-5.3, 6.3)	0.91		0.3 (-5.3, 6.2)	0.91		-1.1 (-8.3, 6.6)	0.75	

^a Particle concentrations of different sizes were mutually adjusted.

Abbreviations: very low density lipoprotein (VLDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL).