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Differential Effects of Insulin Sensitization and Insulin Provision Treatment Strategies on Concentrations of Circulating Adipokines in Patients with Diabetes and Coronary Artery Disease in the BARI 2D Trial

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Abstract

Aims—To determine the effects of insulin sensitization (IS) and insulin provision (IP) treatment strategies on adipokines associated with cardiovascular (CV) disease in patients with type 2 diabetes mellitus (DM2) and coronary artery disease (CAD) in the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial (BARI 2D).

Methods and results—Changes in adipokine levels were compared in patients with DM2 and CAD randomized to IS (n=1037) versus IP (n=1019) treatment strategies in BARI 2D. Circulating concentrations of leptin, adiponectin, monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor- α (TNF- α), interleukin 6 (IL-6) and C-reactive protein (CRP) were evaluated at baseline and 1 year. IS and IP treatment strategies exerted significant ($p<0.0001$) differential

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effects on: leptin (IS: 2% decrease, $p=0.21$; IP: 13% increase, $p<0.0001$); adiponectin (IS: 73% increase, $p<0.0001$; IP: no change, $p=0.53$); IL-6 (IS: 14% decrease, $p<0.0001$; IP: no change, $p=0.68$). Changes in MCP-1 and TNF- α were not statistically different between groups. CRP decreased but the effect was significantly greater in the IS group (-34% , $p<0.0001$) than in the IP group (-5% , $p=0.0005$).

Conclusion—The IS and IP treatment strategies exerted divergent effects on adipokine and inflammatory profile in patients with DM2 and CAD. The IS treatment strategy-induced changes may be more favorable than the IP treatment strategy regarding CV pathophysiology.

Keywords

Diabetes Mellitus; Coronary Disease; Risk Factors; Adipokines

INTRODUCTION

Insulin resistance (IR) is a common feature of type 2 diabetes (DM2) and obesity, and may underlie the clustering of cardiovascular risk factors ¹. For instance, the unfavorable metabolic (dyslipidemia, hyperglycemia) and cardiovascular (CV) (hypertension, endothelial dysfunction, coagulation abnormalities, impaired fibrinolysis, systemic inflammation) profile develops primarily in obese individuals who are also insulin resistant ², suggesting that IR is key in the development of vascular dysfunction. Indeed, IR has been associated with ultrasonographically or angiographically assessed atherosclerosis, even in the absence of other risk factors ³⁻⁵.

The pivotal role of IR in the pathophysiology and CV consequences of DM2 implies that therapeutic differences may exist between therapies for DM2 that improve insulin sensitivity versus those therapies that only increase insulin levels (without affecting insulin sensitivity), even when the same levels of glycemic control are achieved with both therapeutic approaches. For example, the analysis of the SYMPHONY and 2nd SYMPHONY trials showed that in patients with diabetes after acute coronary syndromes, hypoglycemic therapy including only insulin and/or sulfonylurea (insulin provision, IP) was associated with a higher 90-day rate of CV events compared with therapy that included only biguanide and/or thiazolidinedione (insulin sensitizing, IS)⁶. In the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial of patients with DM2 and clinically stable, angiographically documented coronary artery disease (CAD), the lowest rate of major CV events were in the group that underwent prompt revascularization plus IS treatment, with borderline statistical significance ($p=0.07$) ⁷. In another analysis of the BARI 2D trial, the IS (but not IP) strategy reduced the endpoints of myocardial infarction and cardiac death/myocardial infarction in patients with DM2 with more severe and extensive CAD⁸.

Whether IP and IS exert differential effects in patients with DM2 and CAD on specific metabolic pathways related to CV pathophysiology has not been determined. One attractive hypothesis is that such differential effects may be related to biologically active hormones released by adipose tissue (adipokines) ⁹. Studies suggest an important role for adipose tissue in the development of IR, DM2, and CV disease ^{9, 10}. IR is associated with chronic inflammation characterized by increases in pro-inflammatory adipokines (such as leptin,

tumor necrosis factor-alpha [TNF- α], monocyte chemoattractant protein-1 [MCP-1]) along with decreases in anti-inflammatory adipokines (such as adiponectin)¹¹. Many of the adipokines affect insulin sensitivity, while their secretion is also regulated by insulin. This includes leptin and adiponectin, which play a role in energy homeostasis. Thus, concentrations of adipokines may be affected by insulin levels and the magnitude of IR. In the present study we tested the hypothesis that IS and IP treatment strategies exert differential longitudinal effects on concentrations of selected adipokines in patients with DM2 and CAD.

METHODS

BARI 2D Trial

The BARI 2D protocol and 5-year results were previously published^{7, 12}. The study complied with the Declaration of Helsinki. The protocol was approved by the institutional ethics committee of all participating sites and all subjects provided informed consent. BARI 2D had a 2×2 factorial design to simultaneously randomize patients into a cardiac treatment strategy (comparing prompt revascularization and aggressive medical therapy vs. aggressive medical therapy alone with deferred revascularization as needed) AND a diabetes treatment strategy (comparing primarily IS vs. IP therapy). The goal was for participants to have an HbA1c <7.0%. If this was not possible using only the drugs within the assigned randomization group, drugs from the alternate group could be used only after maximizing the drugs in the participants' randomized group. The randomization was not blinded, as participants and physicians would know if they received CABG or PCI, or if they used injectable insulin. For more details, see the Methods section of the Supplementary Appendix. It took approximately six months for the participants to stabilize their treatment strategies. The primary paper reported no difference between the IS and IP groups with respect to the primary outcome (death) or the principal secondary outcome (the composite of death/myocardial infarction/stroke).

This ancillary study to BARI 2D was performed to analyze a subset of existing blood samples for selected adipokine and cytokine levels, specifically leptin, adiponectin, MCP-1, TNF- α , interleukin 6 (IL-6) and C-reactive protein (CRP). These adipokines/cytokines were selected because of their relationship to both insulin resistance and CV disease.

Sample collection was coordinated by the BARI 2D Fibrinolysis and Coagulation Systems Core Laboratory at the University of Vermont (B. Sobel, PI). All samples were analyzed in the Laboratory of Clinical Biochemistry Research at the University of Vermont. IL-6, leptin, TNF- α and MCP-1 were analyzed using a bead-based multiplex assay system (Millipore Adipokine Panel B). Insulin was assayed using a solid phase two-site enzyme immunoassay (ALPCO). Total adiponectin was measured by a validated enzyme-linked immunoassay (R&D Systems) and high sensitivity CRP by Nephelometry (Siemens). The interassay coefficients of variation were between 5.0% and 8.5%. Additional information regarding the sample preservation is in the Supplementary Methods and Supplementary Table 1S of the on-line appendix.

Statistical analysis

This study compared IS vs. IP randomized treatment groups from the BARI 2D trial. Continuous and categorical variables at baseline were tested using t-tests and chi-square tests, respectively. The adipokine and cytokine measures were skewed, non-parametric tests such as Kruskal-Wallis or signed tests were used on non-transformed data. Log transformations were used to obtain approximately normal distributions of the skewed variables. The adipokine and cytokine variables were standardized based on the sex-specific log baseline mean and standard deviation (SD). Of the 6590 laboratory values, there were 26 values that were more than 5 standard deviations away from the mean on the sex-standardized log scale (12 for leptin, 4 for MCP-1, 9 for TNF- α , 1 for IL-6) and were considered missing. The number of outliers removed values that were >5 SD below the mean was 12 for leptin, 2 for MCP-1, 1 for TNF- α and 1 for IL-6, with the remaining outliers being >5 SD above the mean. Two patients with extreme values on blood insulin were also considered missing. A sex-standardized log transformation was used to determine interaction effects and/or mediation effects within linear models. The mediation analysis includes only the adjustment of the mediating variable. Heat maps of the adipokine values were produced using the R function heatmap.3.

The p-values reported are nominal and not adjusted for multiple comparisons.

RESULTS

Of 2368 patients enrolled in BARI 2D, 2056 (87%) contributed a baseline and a year 1 sample. The baseline demographics, medical history and drug usage were balanced between groups (Table 1). Supplementary Table 2S contains the baseline values of the adipokine, lipid, insulin and body weight measures at baseline, stratified by sex. Statistically significant differences between men and women were present for all measures except MCP-1.

The baseline and first year change are reported in Table 2 with sex-stratified results in Supplementary Tables 3AS and 3BS. At baseline, the IS and IP groups had no significant differences. At one year, insulin levels were reduced in the IS group. The amount and direction of change varied significantly between IS and IP treatment strategies for all measures except for MCP-1 and TNF- α . Leptin levels did not change meaningfully in the IS group, but increased by 13% (13.32 to 15.1 ng/ml) in the IP group; adiponectin increased in the IS group by 73% (4.47 to 8.32 μ g/ml) and did not change in the IP group; IL-6 decreased in the IS group by 14% (2.31 to 1.98 pg/) and did not change in the IP group. The decrease in CRP was significantly greater in the IS group (34%, 2.31 to 1.98 pg/ml) than in the IP group (5%, 2.23 to 2.12 μ g/ml), which is consistent with what was reported previously in BARI 2D¹³. These changes are visualized in the heatmaps in Supplementary Figure 1S. In Figure 1, the mean and 95% confidence interval of the IS treatment strategy effect (compared to the IP treatment strategy effect) on the first year change in the sex-standardized log values is graphed separately for men and women. The post-hoc interaction p-value, testing if the effect of the IS strategy is the same in men as in women, is reported. The MCP-1 and TNF- α confidence intervals cross the zero line, indicating were no differential effect between IS and IP treatment strategies in either sex. The remaining measures, except for adiponectin, show patients in the IP treatment strategy had a larger

increases in the adipokine levels after one year than patients in the IS treatment strategy. For adiponectin, patients in the IS treatment strategy had a larger increase than patients in the IP treatment strategy. The only adipokine where the IS treatment strategy had a statistically different effect in men and women is leptin ($p=0.04$).

The percent of the IS treatment strategy effect mediated by the changes in waist circumference and BMI is in Table 3. For mediation, the IS treatment strategy effect on the adipokine measure should be significant, as measured in the “IS Alone” column. The effect of the waist circumference (or BMI) should also be significant when the IS treatment strategy is in the model, as it is for leptin, the leptin/adiponectin ratio, and the leptin/BMI ratio (not shown). As shown, 15% of the effect of the IS treatment strategy on the first year change in leptin, 2.6% of the effect on the first year change in the leptin/adiponectin ratio, and 30% of the effect on the first year change in the leptin/BMI ratio are due to the first year changes in waist circumference. Similarly, 39% of the effect of the IS treatment strategy on the first year change in leptin, 7.5% of the effect on the first year change in the leptin/adiponectin ratio, and 92% of the effect on the change in the leptin/BMI ratio are due to the first year changes in BMI.

DISCUSSION

Adipose tissue is an endocrine organ capable of releasing biologically active hormones (adipokines)⁹, which have significant effects on CV status and regulation of systemic metabolism⁹. In this study we investigated leptin, adiponectin, IL-6, TNF- α , and MCP-1. These adipokines have been implicated in the pathogenesis of CV disease, and changes in the blood concentrations of these adipokines may influence therapeutic interventions with CV outcome. We demonstrated that, in patients with DM2 and CAD, two therapeutic strategies, IS vs. IP, exert differential effects on the adipokine profile after 1 year of therapy.

Although pathophysiological mechanisms accounting for the observed effects cannot be directly determined based on results in a clinical trial, mechanistic insights can be inferred. The IS and IP treatment strategies exerted differential effects on body weight (a decrease in weight and BMI in the IS group and an increase in the IP group) and body fat distribution (a decrease in waist circumference in the IS group, suggesting a decrease in abdominal fat). Leptin and IL-6 are elevated in the bloodstream in amounts related to the degree of obesity, while adiponectin is paradoxically lower in obesity^{9, 10}. The differential effects of the IS and IP strategies and these adipokines may be related to the differential effects on body fat. In the present study, 39% of the effect of the IS treatment strategy on leptin was mediated by body weight/BMI and 15% was mediated by waist circumference, suggesting that part of the observed effects was related to changes in body fat and fat distribution. No such mediation was seen for adiponectin and IL-6 suggesting those effects and the remainder of the effect on leptin, should be ascribed to the specific actions of the IS and IP interventions on concentrations of plasma adipokines. This is consistent with several experimental studies demonstrating direct effects of IS and IP on adipokines¹⁴⁻¹⁸.

The differential effect of the two therapeutic strategies on adipokine expression may be partly explained by the interactions between insulin and leptin signaling. At cellular level,

insulin and leptin signaling pathways cross-talk, and the proteins which contribute to impaired insulin signaling also cause impaired leptin signaling^{19, 20}. Therefore, therapeutic strategies that improve insulin sensitivity are likely to improve leptin cellular signaling as well. Considering the role of leptin in energy homeostasis, this may be the underlying mechanism responsible for the observed differential effects between IS and IP on weight. Improvement in leptin sensitivity may also explain the decreases in insulin for the IS strategy, as leptin has been shown to regulate insulin expression. Furthermore, changes in leptin sensitivity may explain the increases in adiponectin with IS strategy, as a recent study showed that leptin increases adiponectin expression and impaired leptin signaling may contribute to paradoxically low adiponectin levels in human obesity²¹. On the other hand, IP strategy provides additional insulin required to maintain optimal levels of glucose, but does not improve leptin sensitivity.

Regardless of the underlying mechanism, the differential effects of IS and IP treatment strategies on leptin, adiponectin, IL-6 and CRP may have potential implications for CV disease²²⁻²⁹. Some biological properties of these adipokines with respect to CV effects and CV outcomes are summarized in Supplementary Table 4S. The effects of the IS and IP treatment strategies on the adipokine profile and CRP levels are consistent with the notion that IS may exert beneficial effects on CV pathophysiology, in contrast to IP. This is also supported by the recent report that, in contrast to the IP strategy, the IS strategy leads to lower plasminogen activator inhibitor type 1 antigen and activity, lower tissue plasminogen activator antigen, and lower fibrinogen, suggesting that IS also exerts profibrinolytic and antithrombotic effects¹³. One potential implication is for the clinical management of patients with DM2 with CAD. The paradigm of using early and aggressive insulin therapy in patient with DM2 has developed³⁰. The rationale for this is based on evidence that early insulin therapy may improve glycemic control and prolong beta cell lifespan and function, as well as improve microvascular endpoints. The benefits on macrovascular endpoints have not been demonstrated in all studies, but overall there is evidence to support the link between tight glycemic control and improved macrovascular CV outcomes. Our results suggest potential additional CV benefits of IS therapies beyond glycemic control, which can conceivably be achieved with administration of IS agents. These potential benefits need to be considered in the context of specific recognized side effects associated with some IS agents³¹. Additional clinical studies, focusing on the role of early IS based therapies in the management of patients with DM2 and CAD, are therefore warranted. Furthermore, future studies should also evaluate if there are any relevant differences between specific IS interventions (e.g., thiazolidinediones vs. metformin) or IP interventions (e.g., insulin vs. sulfonylureas).

In conclusion, the present study demonstrated that the IS and IP treatment strategies exert divergent effects on the adipokine profile in DM2 patients with CAD. The IS treatment strategy-induced changes in circulating adipokines appear to be more favorable than the IP treatment strategy from the perspective of attenuating the pathogenesis of CV disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Haffner S, Taegtmeyer H. Epidemic obesity and the metabolic syndrome. *Circulation*. 2003; 108(13):1541–5. [PubMed: 14517149]
2. Reaven G. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. *Endocrinol Metab Clin North Am*. 2004; 33(2):283–303. [PubMed: 15158520]
3. Agewall S, Fagerberg B, Attvall S, Wendelhag I, Urbanavicius V, Wikstrand J. Carotid artery wall intima-media thickness is associated with insulin-mediated glucose disposal in men at high and low coronary risk. *Stroke*. 1995; 26(6):956–60. [PubMed: 7762045]
4. Bressler P, Bailey SR, Matsuda M, DeFronzo RA. Insulin resistance and coronary artery disease. *Diabetologia*. 1996; 39(11):1345–50. [PubMed: 8933003]
5. Howard G, O'Leary DH, Zaccaro D, Haffner S, Rewers M, Hamman R, Selby JV, Saad MF, Savage P, Bergman R, The Insulin Resistance Atherosclerosis Study (IRAS) Investigators. Insulin sensitivity and atherosclerosis. *Circulation*. 1996; 93(10):1809–17. [PubMed: 8635260]
6. McGuire DK, Newby LK, Bhapkar MV, Moliterno DJ, Hochman JS, Klein WW, Weaver WD, Pfisterer M, Corbalan R, Dellborg M, Granger CB, Van De Werf F, Topol EJ, Califf RM. Association of diabetes mellitus and glycemic control strategies with clinical outcomes after acute coronary syndromes. *Am Heart J*. 2004; 147(2):246–52. [PubMed: 14760321]
7. Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, Orchard TJ, Chaitman BR, Genuth SM, Goldberg SH, Hlatky MA, Jones TL, Molitch ME, Nesto RW, Sako EY, Sobel BE. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009; 360(24):2503–15. [PubMed: 19502645]
8. Chaitman BR, Hardison RM, Adler D, Gebhart S, Grogan M, Ocampo S, Sopko G, Ramires JA, Schneider D, Frye RL. The Bypass Angioplasty Revascularization Investigation 2 Diabetes randomized trial of different treatment strategies in type 2 diabetes mellitus with stable ischemic heart disease: impact of treatment strategy on cardiac mortality and myocardial infarction. *Circulation*. 2009; 120(25):2529–40. [PubMed: 19920001]
9. Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. *Mol Cell Endocrinol*. 2010; 316(2):129–39. [PubMed: 19723556]
10. Antuna-Puente B, Feve B, Fellahi S, Bastard JP. Adipokines: the missing link between insulin resistance and obesity. *Diabetes Metab*. 2008; 34(1):2–11. [PubMed: 18093861]
11. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest*. 2003; 112(12):1821–30. [PubMed: 14679177]
12. Brooks MM, Frye RL, Genuth S, Detre KM, Nesto R, Sobel BE, Kelsey SF, Orchard TJ. Hypotheses, design, and methods for the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. *Am J Cardiol*. 2006; 97(12A):9G–19G.
13. Sobel BE, Hardison RM, Genuth S, Brooks MM, McBane RD 3rd, Schneider DJ, Pratley RE, Huber K, Wolk R, Krishnaswami A, Frye RL. Profibrinolytic, antithrombotic, and antiinflammatory effects of an insulin-sensitizing strategy in patients in the Bypass Angioplasty

- Revascularization Investigation 2 Diabetes (BARI 2D) trial. *Circulation*. 2011; 124(6):695–703. [PubMed: 21768545]
14. Yang WS, Jeng CY, Wu TJ, Tanaka S, Funahashi T, Matsuzawa Y, Wang JP, Chen CL, Tai TY, Chuang LM. Synthetic peroxisome proliferator-activated receptor-gamma agonist, rosiglitazone, increases plasma levels of adiponectin in type 2 diabetic patients. *Diabetes Care*. 2002; 25(2):376–80. [PubMed: 11815513]
 15. Yu JG, Javorschi S, Hevener AL, Kruszynska YT, Norman RA, Sinha M, Olefsky JM. The effect of thiazolidinediones on plasma adiponectin levels in normal, obese, and type 2 diabetic subjects. *Diabetes*. 2002; 51(10):2968–74. [PubMed: 12351435]
 16. Patel NG, Holder JC, Smith SA, Kumar S, Eggo MC. Differential regulation of lipogenesis and leptin production by independent signaling pathways and rosiglitazone during human adipocyte differentiation. *Diabetes*. 2003; 52(1):43–50. [PubMed: 12502492]
 17. Kolaczynski JW, Nyce MR, Considine RV, Boden G, Nolan JJ, Henry R, Mudaliar SR, Olefsky J, Caro JF. Acute and chronic effects of insulin on leptin production in humans: Studies in vivo and in vitro. *Diabetes*. 1996; 45(5):699–701. [PubMed: 8621027]
 18. Motoshima H, Wu X, Sinha MK, Hardy VE, Rosato EL, Barbot DJ, Rosato FE, Goldstein BJ. Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. *J Clin Endocrinol Metab*. 2002; 87(12):5662–7. [PubMed: 12466369]
 19. Niswender KD, Schwartz MW. Insulin and leptin revisited: adiposity signals with overlapping physiological and intracellular signaling capabilities. *Front Neuroendocrinol*. 2003; 24(1):1–10. [PubMed: 12609497]
 20. Kahn BB, Flier JS. Obesity and insulin resistance. *J Clin Invest*. 2000; 106(4):473–81. [PubMed: 10953022]
 21. Singh P, Sahakyan KR, Sert-Kuniyoshi FH, Romero-Corral A, Delacroix S, Davison DE, Jensen MD, Somers VK. Leptin induces adiponectin expression: Implications in obesity. *The FASEB Journal*. 2013; 27:1192.7. 1_MeetingAbstracts.
 22. Wolk R, Somers VK. Leptin and vascular function: Friend or foe? *Eur Heart J*. 2006; 27(19):2263–5. [PubMed: 16966346]
 23. Wallace AM, McMahon AD, Packard CJ, Kelly A, Shepherd J, Gaw A, Sattar N. Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS). *Circulation*. 2001; 104(25):3052–6. [PubMed: 11748099]
 24. Wolk R, Berger P, Lennon RJ, Brilakis ES, Johnson BD, Somers VK. Plasma leptin and prognosis in patients with established coronary atherosclerosis. *J Am Coll Cardiol*. 2004; 44(9):1819–24. [PubMed: 15519013]
 25. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. *Jama*. 2004; 291(14):1730–7. [PubMed: 15082700]
 26. Wolk R, Berger P, Lennon RJ, Brilakis ES, Davison DE, Somers VK. Association between plasma adiponectin levels and unstable coronary syndromes. *Eur Heart J*. 2007; 28(3):292–8. [PubMed: 17090613]
 27. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation*. 2000; 101(15):1767–72. [PubMed: 10769275]
 28. Lindmark E, Diderholm E, Wallentin L, Siegbahn A. Relationship between interleukin 6 and mortality in patients with unstable coronary artery disease: effects of an early invasive or noninvasive strategy. *Jama*. 2001; 286(17):2107–13. [PubMed: 11694151]
 29. Verma S, Szmitko PE, Ridker PM. C-reactive protein comes of age. *Nat Clin Pract Cardiovasc Med*. 2005; 2(1):29–36. quiz 58. [PubMed: 16265340]
 30. Niswender K. Early and Aggressive Initiation of Insulin Therapy for Type 2 Diabetes: What Is the Evidence? *Clinical Diabetes*. 2009; 27(2):60–68.
 31. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European

Association for the Study of Diabetes (EASD). Diabetes Care. 2012; 35(6):1364–79. [PubMed: 22517736]

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Randomized Treatment Comparison of One-Year Change of Adipokines by Sex

Figure 1.

First year change in adipokines by sex, logged then standardized based on baseline sex (mean and SD).

Table 1

Baseline characteristics.

	Total (N=2056)	IP (N=1019)	IS (N=1037)
Demographics and Clinical Characteristics			
Male, %	70.3	70.3	70.3
Age, mean (SD)	62.3 (8.8)	62.2 (8.5)	62.3 (9.1)
Race/Ethnicity, %			
White non-Hispanic	66.2	66.3	66.1
Black non-Hispanic	16.3	16.4	16.2
Hispanic	12.5	12.8	12.2
Other non-Hispanic	5.0	4.5	5.5
BMI, mean (SD)	31.8 (5.9)	31.8 (5.9)	31.7 (5.9)
Current cigarette smoker, %	11.8	11.2	12.3
Systolic BP, mean (SD)	131.6 (20.1)	131.6 (20.3)	131.7 (19.9)
Diastolic BP, mean (SD)	74.6 (11.3)	74.6 (11.2)	74.6 (11.3)
HbA1c %, mean (SD)	7.7 (1.6)	7.7 (1.6)	7.6 (1.6)
Insulin micro IU/ml, mean (SD)	14.0 (13.7)	13.9 (13.1)	14.0 (14.2)
Total cholesterol mg/dl, mean (SD)	169.4 (41.0)	170.6 (40.2)	168.2 (41.7)
LDL mg/dl, mean (SD)	96.4 (33.5)	97.4 (33.1)	95.3 (33.8)
HDL mg/dl, mean (SD)	38.2 (10.1)	38.5 (10.3)	38.0 (9.9)
Triglycerides mg/dl, mean (SD)	179.8 (133.1)	181.8 (141.8)	177.9 (124.0)
Medical History			
Prior Revascularization, %	23.3	24.3	22.3
History of MI, %	31.6	31.2	32.1
History of CHF req tx, %	6.1	6.5	5.6
Hypertension req tx, %	81.8	83.2	80.4
Hypercholesterolemia req tx, %	81.7	83.2	80.2
Drug Usage			
Beta blocker, %	72.5	70.9	74.1
ACEi or ARB, %	77.1	77.5	76.7
Statin, %	75.0	74.9	75.1
Aspirin, %	88.2	88.0	88.5
Biguanide, %	54.9	54.7	55.1
TZD, %	18.9	18.1	19.8
Sulfonylurea, %	54.4	54.3	54.5
Currently taking insulin, %	27.2	28.0	26.3

SD – standard deviation; BMI – body mass index; BP - blood pressure; LDL – low density lipoprotein; HDL – high density lipoprotein; MI – myocardial infarction; CHF – congestive heart failure; req tx – requiring treatment; ACEi – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; TZD - thiazolidinedione

Table 2

Baseline and first year changes in adipokine and other measures.

	Baseline (N=2056)			IP (N=1019)			IS (N=1037)			1st Year Change (N=2056)			IS (N=1037)			1st Year Change IS vs. IP		
	Median	(Q1, Q3)	Median	Median	(Q1, Q3)	p-value *	Median	(Q1, Q3)	p-value †	Median	(Q1, Q3)	p-value ‡	Median	(Q1, Q3)	p-value §	p-value ¶	p-value ¶	p-value ¶
Leptin ng/ml	18.74	(8.74, 34.87)	17.73	(8.85, 33.01)	0.57	2.35	(-2.75, 9.30)	<0.0001	<0.0001	-0.29	(-6.63, 6.13)	0.0102	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Adiponectin µg/ml	4.54	(3.04, 7.46)	4.81	(2.95, 7.79)	0.62	0.05	(-1.12, 1.14)	0.52	0.52	3.51	(0.63, 9.96)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
MCP-1 pg/ml	192.20	(147.33, 238.98)	199.29	(152.09, 250.31)	0.02	6.45	(-23.88, 40.92)	0.0005	0.0005	3.56	(-32.72, 38.88)	0.05	0.13	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Leptin / Adiponectin Ratio [‡]	3.69	(1.78, 7.72)	3.64	(1.58, 7.65)	0.36	0.48	(-0.94, 2.72)	0.0006	0.0006	-1.24	(-3.89, 0.00)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Leptin / BMI Ratio	0.57	(0.31, 1.01)	0.56	(0.30, 0.99)	0.66	-0.00	(-0.02, 0.01)	0.0001	0.0001	0.00	(-0.01, 0.03)	0.0033	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
TNF-α pg/ml	4.82	(3.63, 6.47)	4.86	(3.63, 6.55)	0.75	0.12	(-0.81, 1.17)	0.06	0.06	0.05	(-0.88, 1.03)	0.20	0.35	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
IL-6 pg/ml	2.20	(1.22, 3.81)	2.31	(1.33, 4.01)	0.29	0.00	(-1.16, 1.01)	0.68	0.68	-0.33	(-1.52, 0.54)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CRP µg/ml	2.23	(0.92, 5.17)	2.01	(0.87, 5.65)	0.89	-0.11	(-1.51, 0.89)	0.0005	0.0005	-0.64	(-2.81, 0.01)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Insulin micro IU/ml	9.70	(5.90, 17.00)	9.70	(5.60, 17.00)	0.44	0.00	(-4.00, 6.10)	0.59	0.59	-2.80	(-8.20, 1.00)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
BMI kg m ²	30.86	(27.48, 34.96)	30.99	(27.57, 34.67)	0.84	0.38	(-0.73, 1.49)	<0.0001	<0.0001	-0.15	(-1.42, 0.96)	0.0037	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Weight kg	88.12	(74.14, 101.56)	87.11	(75.50, 101.59)	0.79	1.03	(-2.00, 4.15)	<0.0001	<0.0001	-0.40	(-4.06, 2.73)	0.0027	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Waist Circumference cm	106.00	(97.50, 116.00)	106.19	(98.50, 115.65)	0.48	0.00	(-3.27, 3.70)	0.74	0.74	-0.99	(-4.90, 2.46)	0.0237	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
LDL mg/dl	93.00	73.00 116.00	91.00	72.00 113.00	0.12	-9.00	(-32.00, 9.00)	<0.0001	<0.0001	-6.00	(-31.00, 14.00)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
HDL mg/dl	37.00	32.00 43.00	36.00	31.00 43.00	0.25	2.00	(-3.00, 6.00)	<0.0001	<0.0001	3.00	(-1.00, 8.00)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Triglycerides mg/dl	148.00	107.00 217.00	148.00	102.00 221.00	0.65	-11.00	(-60.00, 30.00)	<0.0001	<0.0001	-11.00	(-64.00, 36.00)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Total cholesterol mg/dl	166.00	143.00 192.00	163.00	140.00 191.00	0.11	-10.00	(-40.00, 12.00)	<0.0001	<0.0001	-6.00	(-35.00, 18.00)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

* Based on Wilcoxon Rank Sum test;

† Based on Signed test.

‡ Leptin is reported in pg/ml and adiponectin is reported in µg/ml, so their ratio is a multiple of 1000.

Table 3

Mediation of IS effect on first year change of gender standardized log Adipokines by Waist Circumference and BMI

a) waist circumference					
	IS Alone		IS effect adjusted for Waist Circumference		% of IS effect that is mediated
	IS vs. IP*	p-value	IS vs. IP*	p-value	
Leptin ng/ml	-0.1939	<0.0001	-0.1645	<0.0001	15%
Adiponectin ug/ml	0.9652	<0.0001	0.9718	<0.0001	-0.68%
MCP-1 pg/ml	-0.0435	0.22	-0.0403	0.28	7.4%
Leptin / Adiponectin Ratio [†]	-0.6756	<0.0001	-0.6579	<0.0001	2.6%
Leptin / BMI Ratio	0.0230	<0.0001	0.0161	<0.0001	30%
TNF-α pg/ml	-0.0292	0.42	-0.0483	0.19	- 65%
IL-6 pg/ml	-0.2092	<0.0001	-0.2124	<0.0001	-1.5%
CRP ug/ml	-0.4127	<0.0001	-0.4182	<0.0001	-1.3%

b) BMI					
	IS Alone		IS effect adjusted for BMI		% of IS effect that is mediated
	IS vs. IP*	p-value	IS vs. IP*	p-value	
Leptin ng/ml	-0.1939	<0.0001	-0.1179	0.0013	39%
Adiponectin ug/ml	0.9652	<0.0001	0.9792	<0.0001	-1.4%
MCP-1 pg/ml	-0.0435	0.23	-0.0419	0.26	3.8%
Leptin / Adiponectin Ratio [†]	-0.6756	<0.0001	-0.6252	<0.0001	7.5%
Leptin / BMI Ratio	0.0230	<0.0001	0.0019	0.0059	92%
TNF-α pg/ml	-0.0292	0.42	-0.0479	0.19	- 64%
IL-6 pg/ml	-0.2092	<0.0001	-0.1988	<0.0001	5.0%
CRP ug/ml	-0.4127	<0.0001	-0.4140	<0.0001	-0.33%

* Beta coefficients from a linear regression model

[†] Leptin is reported in pg/ml and adiponectin is reported in µg/ml, so their ratio is a multiple of 1000.