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# Changes in Inflammation, Oxidative Stress, and Adipokines Following Bariatric Surgery among Adolescents with Severe Obesity

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## Abstract

**Background/Objectives—**Inflammation, oxidative stress, and dysregulation of adipokines are thought to be pathophysiological mechanisms linking obesity to the development of insulin resistance and atherosclerosis. In adults, bariatric surgery reduces inflammation and oxidative stress, and beneficially changes levels of several adipokines, but little is known about post-surgical changes among adolescents.

**Subjects/Methods—**In two separate longitudinal cohorts we evaluated change from baseline of interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), monocyte chemo-attractant protein-1 (MCP-1), oxidized LDL cholesterol (oxLDL), adiponectin, leptin, and resistin up to 12 months following elective laparoscopic roux en Y gastric bypass (RYGB) or vertical sleeve gastrectomy (VSG) surgery in adolescents with severe obesity.

**Results—**In cohort 1, which consisted of 39 adolescents (mean age 16.5±1.6; 29 females) undergoing either RYGB or VSG, IL-6 (baseline: 2.3±3.4 pg/mL vs. 12 months: 0.8±0.6 pg/mL, $p<0.01$), leptin (baseline: 178±224 ng/mL vs. 12 months: 41.4±31.9 ng/mL, $p<0.001$), and oxLDL (baseline: 41.6±11.6 U/L vs. 12 months: 35.5±11.1 U/L, $p=0.001$) significantly decreased and adiponectin significantly increased (baseline: 5.4±2.4 μg/mL vs. 12 months: 13.5±8.9 μg/mL,

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**Author Disclosures**

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p<0.001). In cohort 2, which consisted of 13 adolescents (mean age 16.5±1.6 years; 10 females) undergoing RYGB, results were similar: IL-6 (baseline: 1.7±0.9 pg/mL vs. 12 months: 0.4±0.9 pg/mL, p<0.05) and leptin (baseline: 92.9±31.3 ng/mL vs. 12 months: 37.3±33.4 ng/mL, p<0.001) significantly decreased and adiponectin significantly increased (baseline: 6.1±2.9 μg/mL vs. 12 months: 15.4±8.0 μg/mL, p<0.001). When the cohorts were combined to evaluate changes at 12 months, oxLDL also significantly decreased (baseline: 39.8±16.7 U/L vs. 12 months: 32.7±11.9 U/L, p=0.03).

**Conclusions—**Bariatric surgery produced robust improvements in markers of inflammation, oxidative stress, and several adipokines among adolescents with severe obesity, suggesting potential reductions in risk for type 2 diabetes and cardiovascular disease.

### Keywords

Adolescent; Bariatric Surgery; Inflammation; Oxidative Stress; Adipokines

## Introduction

Pediatric severe obesity is characterized by elevated levels of inflammation and oxidative stress and adverse levels of various adipokines, all of which are associated with increased risk of cardiovascular disease and type 2 diabetes.[1–5] Bariatric surgery is an effective treatment option for adolescents with severe obesity for whom conventional approaches to weight loss, such as lifestyle modification and/or pharmacotherapy, are frequently inadequate.[4;6–8] Among adults, a number of studies have demonstrated that bariatric surgery reduces levels of inflammation and oxidative stress and improves the levels of various adipokines.[9–15] However, to our knowledge, pediatric data in this area are limited to one small study (N = 11) that reported significant improvements in adiponectin, leptin, and C-reactive protein among adolescents 12 months following roux en Y gastric bypass (RYGB).[16] Therefore, the primary objective of this study was to evaluate post-surgical changes in serum biomarkers of inflammation, oxidative stress and adipokines among a relatively large number of adolescents with severe obesity that had undergone elective bariatric surgery. We hypothesized that interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), monocyte chemo-attractant protein-1 (MCP-1), oxidized LDL cholesterol (oxLDL), leptin, and resistin would be reduced, and adiponectin increased, following bariatric surgery. These biomarkers were chosen since each represents a distinct domain related to inflammation, oxidative stress, and fat cell function within the context of obesity[17] and owing to the fact that many of the same biomarkers have been reported in studies of adult bariatric surgery, potentially allowing us to draw comparisons to adult outcomes.

## Subjects and Methods

### Study Cohorts and Measurement Time-Points

Specimens and data from two independent cohorts were analyzed in this study. Cohort 1 was comprised of a subset of participants (N = 39) from the “Teen-Longitudinal Assessment of Bariatric Surgery” (Teen-LABS; U01DK072493) study enrolled at the Cincinnati Children’s

Hospital Medical Center. In brief, Teen-LABS is an ongoing, prospective, longitudinal, multicenter study of adolescent bariatric surgery outcomes funded by the National Institute of Diabetes and Digestive and Kidney Diseases.[18] Eligibility criteria included age 19 years old or younger and scheduled for elective bariatric surgery. Blood samples from baseline, 6 months, and 12 months after either the RYGB (N = 19) or the vertical sleeve gastrectomy (VSG; N = 20) operation were obtained from the Pediatric Obesity Tissue Repository at Cincinnati Children's Hospital Medical Center. Samples were selected to represent the overall sex distribution of the entire Teen-LABS study cohort (approximately 75% female) and achieve an approximately equal distribution of RYGB and VSG procedures. Cohort 2 was comprised of adolescents (N = 13) who were prospectively enrolled in the "Adolescent Gastric Bypass and Diabetic Precursors Study" (RO3DK068228) and underwent elective laparoscopic RYGB at Cincinnati Children's Hospital Medical Center as previously described.[19] Eligibility criteria included age 14 to 20 years old and scheduled for elective RYGB surgery. Blood samples from baseline, 3 months, and 12 months post-surgery were obtained from the Pediatric Obesity Tissue Repository at Cincinnati Children's Hospital Medical Center. In both of the studies, consent from participants ≥18 years old or parental consent and participant assent in those <18 years old were obtained. Both study protocols were approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board.

## Clinical Measures and Blood Assay Procedures

Participant demographics, research data, and specimens were collected prospectively. Data and specimens were obtained for the current analyses from the respective study databases and specimen repositories. In both studies, height and weight were measured on a wall-mounted stadiometer and weight on an electronic scale (Scale-Tronix 5200, Scale Tronix, White Plains, NY, USA or Tanita TBF310, Arlington Heights, Illinois, USA) and BMI was calculated. Glucose and insulin were determined using standard procedures and the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as previously described.[20] Blood samples were stored at −80 C and batched for analysis in the Cytokine Reference Laboratory (Clinical Laboratory Improvement Amendments licensed) at the University of Minnesota. IL-6 and TNF-α were measured together by multiplex (R&D Systems, Minneapolis, MN); MCP-1, leptin, and resistin were measured together by multiplex (R&D Systems, Minneapolis, MN) (all analyzed on a Luminex 200, with Bio-Plex Manager Software 5.1); OxLDL was measured by ELISA (Mercodia, Uppsala, Sweden); and adiponectin was measured by ELISA (R&D Systems, Minneapolis, MN). For cohort 1, the intra- and inter-assay coefficients of variation were as follows: IL-6: 5.8% and 7.3%; TNF-α: 4.7% and 6.2%; leptin: 4.2% and 10.6%; MCP-1: 4.4% and 5.0%; resistin: 4.1% and 4.8%; OxLDL: 5.0% and 5.1%; adiponectin: 7.9% and 8.1%. For cohort 2, the intra-assay coefficients of variation (small sample size precluded calculation of inter-assay coefficient of variation) were as follows: IL-6: 7.3%; TNF-α: 6.3%; leptin: 5.5%; MCP-1: 6.2%; resistin: 7.6%; OxLDL: 6.1%; adiponectin: 3.2%.

## Statistical Analysis

Data are expressed as mean ± standard deviation (SD). Change from baseline was calculated at 6 months and 12 months for cohort 1, and 3 months and 12 months for cohort 2. A

generalized linear mixed model with random effect for individual participant was used to assess paired differences across visits within each cohort and between baseline and 12 months for the cohorts combined. Analysis was conducted using SPSS version 22.0 (IBM, Armonk, NY, USA). A p-value <0.05 signified statistical significance.

## Results

Baseline demographics for the study cohorts separately and combined are presented in Table 1. The mean age of participants in each cohort was identical (16.5±1.6 years old) and both cohorts included over 70% girls and were predominately white. The majority of participants in both cohorts had a clinical diagnosis of sleep apnea and dyslipidemia. Participants in cohort 1 underwent either RYGB or VSG whereas participants in cohort 2 received RYGB.

### Cohort 1

Cohort 1 consisted of 39 adolescents (mean age 16.5±1.6; 29 females). Mean BMI at baseline, 51.0±9.6 kg/m$^2$, was reduced to 37.4±8.1 kg/m$^2$ (−26.7%) and 34.7±7.7 kg/m$^2$ (−32.0%) at 6- and 12 months, respectively. Baseline, 6-, and 12-month levels of biomarkers of inflammation, oxidative stress, and adipokines from cohort 1 are presented in Table 2 and Figure 1. Significant reductions were observed for IL-6 (baseline: 2.3±3.4 pg/mL vs. 6 months: 1.1±1.0 pg/mL, p<0.05 and vs. 12 months: 0.8±0.6 pg/mL, p<0.01) and leptin (baseline: 178±224 ng/mL vs. 6 months: 44.0±33.1 ng/mL, p<0.001 and vs. 12 months: 41.4±31.9 ng/mL, p<0.001) and adiponectin was significantly increased (baseline: 5.4±2.4 μg/mL vs. 6 months: 10.2±6.0 μg/mL, p<0.001 and vs. 12 months: 13.5±8.9 μg/mL, p<0.001). At 12 months, oxLDL was significantly reduced (baseline: 41.6±11.6 U/L vs. 12 months: 35.5±11.1 U/L, p=0.001). No statistically significant differences were observed for TNF-α, MCP-1, or resistin. Changes in inflammation, oxidative stress, and levels of adipokines did not significantly differ by type of surgical procedure (RYGB vs. VSG).

### Cohort 2

Cohort 2 consisted of 13 adolescents (mean age 16.5±1.6 years; 10 females). Mean BMI at baseline, 58.7±6.8 kg/m$^2$, was reduced to 46.8±5.4 (−21.4%) and 36.8±6.5 (−37.4%) at 3- and 12 months, respectively. Baseline, 3-, and 12-month levels of biomarkers of inflammation, oxidative stress, and adipokines from cohort 2 are presented in Table 3 and Figure 1. Significant reductions were observed for IL-6 (baseline: 1.7±0.9 pg/mL vs. 3 months: 0.8±1.1 pg/mL, p=0.05 and vs. 12 months: 0.4±0.9 pg/mL, p<0.05) and leptin (baseline: 92.9±31.3 ng/mL vs. 3 months: 59.2±52.4 ng/mL, p<0.01 and vs. 12 months: 37.3±33.4 ng/mL, p<0.001) and adiponectin was significantly increased (baseline: 6.1±2.9 μg/mL vs. 3 months: 12.7±7.7 μg/mL, p<0.01 and vs. 12 months: 15.4±8.0 μg/mL, p<0.001). A trend toward reduced MCP-1 was observed at 12-months. No significant differences were observed for TNF-α, resistin, or oxLDL.

### Combined Cohort

When data from both cohorts were combined (N = 52), significant reductions were observed for IL-6 (baseline: 2.1±3.1 pg/mL vs. 12 months: 0.7±0.7 pg/mL, p<0.001), oxLDL (baseline: 39.8±16.7 U/L vs. 12-months: 32.7±11.9 U/L, p=0.03), and leptin (baseline:

158±199 ng/mL vs. 12 months: 40.5±31.9 ng/mL, p<0.001) and adiponectin was significantly increased (baseline: 5.4±2.4 μg/mL vs. 12 months: 14.0±8.7 μg/mL, p<0.001) (Figure 1). No significant differences were observed for TNF-α, MCP-1, or resistin. Changes in inflammation, oxidative stress, and levels of adipokines did not meaningfully differ by type of surgical procedure (RYGB vs. VSG). No statistically significant or meaningful correlations were observed between percent change in BMI and percent change in any of the biomarkers at 12 months in the combined cohort.

## Discussion

Findings from this study, which included two independent cohorts of youth with severe obesity, indicate that bariatric surgery significantly reduced levels of IL-6, oxLDL, and leptin, and significantly increased levels of adiponectin. Despite improvements in these biomarkers, statistically significant changes in average levels of TNF-α, MCP-1, and resistin were not observed. Our results are in agreement with another small study of adolescents who underwent RYGB (N = 11) reporting improvements in adiponectin and leptin 12 months post-surgery.[16] The lowering of IL-6 in our study suggests a potential reduction in future risk of cardiovascular disease since inflammation has been implicated as an independent contributor to the atherosclerotic process and predicts adverse cardiovascular events in adults.[21;22] Moreover, since inflammation is involved in the pathogenesis of insulin resistance and predicts the development of type 2 diabetes,[23;24] our results indicate that bariatric surgery may reduce the risk of type 2 diabetes in youth with severe obesity. Our findings demonstrating reductions in fasting glucose, insulin, and HOMA-IR further substantiate this contention, albeit these measures are only surrogates of insulin resistance. The decrease in oxLDL suggests reductions in risk of cardiovascular disease and potentially type 2 diabetes, as this biomarker is pro-atherogenic[25;26] and independently associated with insulin resistance in youth.[27] The large magnitude of improvement in levels of adiponectin in our study provides additional evidence that bariatric surgery may increase insulin sensitivity[28] and potentially slow the atherosclerotic process.[29;30] Taken together, these results demonstrate that bariatric surgery favorably changes multiple biomarkers of type 2 diabetes and cardiovascular risk among adolescents.

The large magnitude of reduction in levels of IL-6 and leptin and increase in adiponectin was roughly equivalent to reports from adult bariatric surgery studies.[9;11–13;31] Our findings regarding TNF-α are consistent with adult studies, which have reported either very modest or no change in levels of this inflammatory cytokine following bariatric surgery.[11–13] Improvements in levels of IL-6, oxLDL, leptin, and adiponectin with bariatric surgery in the current study compare favorably to results of lifestyle modification interventions among children and adolescents.[32–39] However, it should be noted that weight loss and/or BMI reduction per se are not necessarily obligatory to elicit improvements in some of these biomarkers. Indeed, some evidence suggests that lifestyle modification, even without concomitant weight loss or BMI reduction, can improve markers of inflammation among youth with obesity as long as body fat mass is decreased and/or redistributed.[38;40] Interestingly, in our study, improvements in biomarkers were not associated with reduction in BMI. This somewhat surprising finding warrants further investigation and suggests that RYGB and/or VSG may act through non-weight loss

pathways to elicit changes in inflammation, oxidative stress, and adipokines. Nevertheless, although long-term weight loss outcomes appear to be far superior with bariatric surgery as compared to lifestyle modification therapy,[7;41] future studies will need to elucidate the mechanisms of improvement and determine whether changes in inflammation and adipokines following surgery persist beyond 12 months.

Strengths of this study include the robust nature of the findings within two independent adolescent cohorts that underwent bariatric surgery (i.e., results were consistent between the samples), the inclusion of more than one type of bariatric surgical procedure (RYGB and VSG), and the high level of internal validity of the assays (i.e., blood samples were batched and assayed simultaneously on the same plates). The study was limited by the fact that no control groups were used. However, inclusion of controls is often not feasible in studies of pediatric bariatric surgery owing to ethical concerns of withholding treatment. Additionally, the studies may have been underpowered to detect significant differences for some of the biomarkers. Also, our panel of biomarkers was not exhaustive and many other potentially important adipokines and biomarkers of inflammation and oxidative stress were not measured. Finally, we were unable to account for the potential influence of diet and physical activity levels on changes in biomarkers.

In conclusion, our results demonstrate significant reductions in inflammation and oxidative stress as well as marked improvements in levels of adipokines following bariatric surgery in adolescents with severe obesity. The striking degree of improvement in many of these biomarkers suggests that adolescents undergoing bariatric surgery potentially experience a clinically-meaningful reduction in risk of developing type 2 diabetes and cardiovascular disease. Future studies should evaluate whether changes in these biomarkers are durable beyond one year and ultimately result in long-term chronic disease reduction. In addition, it would be informative to assess changes in other non-invasive vascular outcomes such as endothelial function, vascular stiffness, and arterial thickness following bariatric surgery in adolescents.

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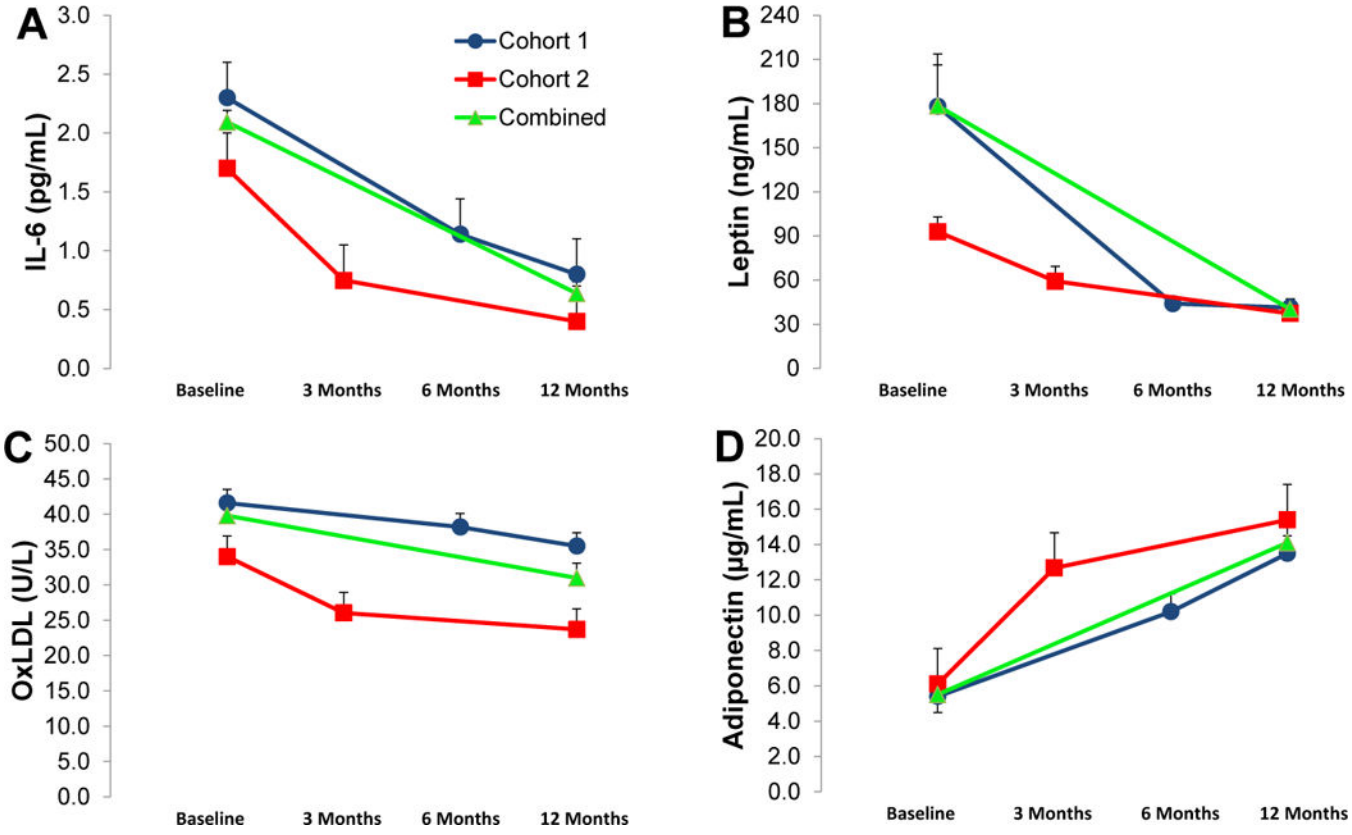


**Figure 1.**

Longitudinal changes from baseline in IL-6 (A), leptin (B), oxLDL (C), and adiponectin (D) in cohort 1, cohort 2, and the cohorts combined.

## Table 1

Baseline Characteristics of Study Cohorts

| Variable | Cohort 1 (N = 39) | Cohort 2 (N = 13) | Combined (N=52) |
|---|---|---|---|
| Age (years) | 16.5 ± 1.6 | 16.5 ± 1.6 | 16.5 ± 1.6 |
| Sex (M/F) | 10 (26%)/29 (74%) | 3 (23%)/10 (77%) | 13 (25%)/39 (75%) |
| Race | | | |
| White | 28 (72%) | 11 (85%) | 39 (75%) |
| Other | 11 (28%) | 2 (15%) | 13 (25%) |
| Height (cm) | 168.7 ± 11.6 | 168.3 ± 7.3 | 168.6 ± 10.6 |
| Weight (kg) | 146.4 ± 35.8 | 168.7 ± 22.9 | 151.7 ± 34.4 |
| BMI (kg/m$^2$) | 51.0 ± 9.6 | 58.7 ± 6.8 | 52.8 ± 9.6 |
| Co-morbidities | | | |
| Sleep Apnea | 22 (56%) | 9 (69%) | 31 (60%) |
| Hypertension | 16 (41%) | 3 (23%) | 19 (37%) |
| Type 2 Diabetes | 5 (13%) | 1 (8%) | 6 (12%) |
| Polycystic Ovary | 6 (15%) | 3 (23%) | 9 (17%) |
| Syndrome | | | |
| Dyslipidemia | 33 (85%) | 8 (62%) | 41 (79%) |
| Surgery Type | | | |
| RYGB | 19 (49%) | 13 (100%) | 32 (62%) |
| VSG | 20 (51%) | 0 (0%) | 20 (38%) |
| Glucose (mg/dL) | 74.6 ± 10.9 | 94.0 ± 8.3 | 79.2 ± 13.2 |
| Insulin (μU/mL) | 21.3 ± 8.5 | 15.2 ± 11.5 | 21.3 ± 9.5 |
| HOMA-IR | 4.0 ± 1.8 | 4.9 ± 2.8 | 4.2 ± 2.1 |
| IL-6 (pg/mL) | 2.3 ± 3.4 | 1.7 ± 0.9 | 2.1 ± 1.6 |
| TNF-α (pg/mL) | 3.1 ± 1.3 | 1.3 ± 0.9 | 2.7 ± 1.5 |
| Leptin (ng/mL) | 178 ± 224 | 93 ± 31 | 158 ± 199 |
| MCP-1 (pg/mL) | 198.1 ± 88.6 | 216.8 ± 103.4 | 201.7 ± 92.3 |
| Resistin ng/mL) | 7.0 ± 2.6 | 7.8 ± 3.4 | 7.2 ± 2.8 |
| OxLDL (U/L) | 41.6 ± 11.6 | 34.0 ± 26.3 | 39.8 ± 16.7 |
| Adiponectin (μg/mL) | 5.4 ± 2.4 | 6.1 ± 2.9 | 5.4 ± 2.3 |

Data are presented as mean ± standard deviation or number and percent. RYGB = laparoscopic roux en Y gastric bypass; VSG = vertical sleeve gastrectomy

## Table 2

Percent change from baseline at 6 and 12 months in clinical characteristics and levels of adipokines and biomarkers of inflammation and oxidative stress from cohort 1 (N = 39)

| | 6 months Mean % change (95%CI) | 12 months Mean % change (95%CI) | Baseline vs. 6 months p-value | Baseline vs. 12 months p-value |
|---|---|---|---|---|
| Weight (kg) | −27.3% (−26.0 to 28.6%) | −32.4% (−30.5 to −34.4%) | p<0.001 | p<0.001 |
| BMI (kg/m$^2$) | −27.3% (−25.9 to −28.7%) | −32.6% (−30.8 to −34.7%) | p<0.001 | p<0.001 |
| Glucose (mg/dL) | −5.4% (11.4 to −13.8%) | −9.3% (−5.0 to −13.4%) | p=0.233 | p<0.001 |
| Insulin (μU/mL) | −57.7% (−49.0 to −65.5%) | −66.4% (−59.8 to −71.6%) | p<0.001 | p<0.001 |
| HOMA-IR | −61.1% (−52.8 to −68.1%) | −68.8% (−62.2 to −74.2%) | p<0.001 | p<0.001 |
| IL-6 (pg/mL) | −16.7% (16.2 to −39.9%) | −43.1% (−15.6 to −61.8%) | p=0.045 | p=0.008 |
| TNF-α (pg/mL) | 19.4% (59.1 to −4.4%) | 7.5% (−44.2 to 15.5%) | p=0.751 | p=0.213 |
| Leptin (ng/mL) | −57.6% (−39.6 to −70.9%) | −60.6% (−45.5% to −73.2%) | p=0.001 | p=0.001 |
| MCP-1 (pg/mL) | −3.7% (6.5 to −13.9% | −11.8% (3.7 to −19.9%) | p=0.221 | p=0.160 |
| Resistin ng/mL) | 6.1% (17.5 to −4.7%) | 3.4% (12.9 to −5.3%) | p=0.983 | p=0.599 |
| OxLDL (U/L) | −5.1% (3.4 to −13.8%) | −12.5% (−6.4 to −18.5%) | p=0.072 | p=0.001 |
| Adiponectin (μg/mL) | 107.6% (159.8 to 70.1%) | 153.7% (198.0 to 115.3%) | p<0.001 | p<0.001 |

Data are presented as mean ± standard deviation. IL-6 = interleukin-6; TNF-α = tumor necrosis factor-alpha; MCP-1 = monocyte chemo-attractant protein-1; OxLDL = oxidized LDL cholesterol

## Table 3

Percent change from baseline at 3 and 12 months in clinical characteristics and levels of adipokines and biomarkers of inflammation and oxidative stress from cohort 2 (N = 13)

| | **3 months Mean % change (95%CI)** | **12 months Mean % change (95%CI)** | **Baseline vs. 3 months p-value** | **Baseline vs. 12 months p-value** |
|---|---|---|---|---|
| Weight (kg) | −21.4% (−19.4 to −23.6%) | −35.5% (−29.9 to −41.0%) | p<0.001 | p<0.001 |
| BMI (kg/m$^2$) | −21.2% (−19.2 to −23.5%) | −35.6% (−30.0 to −41.0%) | p<0.001 | p<0.001 |
| Glucose (mg/dL) | −11.5% (−5.9 to −17.0%) | −10.3% (−5.5 to 15.3%) | p=0.002 | p=0.001 |
| Insulin (μU/mL) | −57.9% (−50.4 to −66.3%) | −62.5% (−55.6 to 68.8%) | p=0.004 | p=0.001 |
| HOMA-IR | −62.3% (−54.4 to −71.1%) | −66.6% (−60.4 to −71.9%) | p=0.002 | p<0.001 |
| IL-6 (pg/mL) | −54.6% (−118.7 to 9.5%) | −74.4% (−115.7 to −33.2%) | p<0.05 | p<0.05 |
| TNF-α (pg/mL) | 40.1% (−59.0 to 139.1%) | −4.2% (−65.6 to 57.2%) | p=0.321 | p=0.303 |
| Leptin (ng/mL) | −41.7% (−62.7 to 20.7%) | −61.9% (−77.7 to 46.2%) | p<0.01 | p<0.001 |
| MCP-1 (pg/mL) | 26.3% (−34.6 to 87.1%) | −14.5% (−41.3 to 12.3%) | p=0.591 | p=0.075 |
| Resistin ng/mL) | −10.4% (−27.9 to 7.1%) | −6.3% (−24.9 to 12.3%) | p=0.170 | p=0.257 |
| OxLDL (U/L) | −5.4% (−25.8 to 15.0%) | −16.5% (−32.9 to 0.1%) | p=0.366 | p=0.188 |
| Adiponectin (μg/mL) | 116.6% (59.2 to 174.1%) | 194.2% (110.5 to 277.9%) | p<0.01 | p<0.001 |

Data are presented as mean ± standard deviation. IL-6 = interleukin-6; TNF-α = tumor necrosis factor-alpha; MCP-1 = monocyte chemo-attractant protein-1; OxLDL = oxidized LDL cholesterol