

Effects of Pronounced Weight Loss on Adiponectin Oligomer Composition and Metabolic Parameters

Julia Engl,*|| Thomas Bobbert,†‡|| Christian Ciardi,*|| Markus Laimer,* Tobias Tatarczyk,* Susanne Kaser,* Helmut Weiss,§ Clemens Molnar,* Herbert Tilg,¶ Josef R. Patsch,* Joachim Spranger,†‡ and Christoph F. Ebenbichler*

Abstract

ENGL, JULIA, THOMAS BOBBERT, CHRISTIAN CIARDI, MARKUS LAIMER, TOBIAS TATARCZYK, SUSANNE KASER, HELMUT WEISS, CLEMENS MOLNAR, HERBERT TILG, JOSEF R. PATSCH, JOACHIM SPRANGER, AND CHRISTOPH F. EBENBICHLER. Effects of pronounced weight loss on adiponectin oligomer composition and metabolic parameters. *Obesity*. 2007;15:1172–1178.

Objective: Adiponectin is an adipocytokine secreted into circulation in three isoforms. The aim of the study was to investigate changes of adiponectin isoforms during profound weight loss and its relation to anthropomorphic and metabolic parameters.

Research Methods and Procedures: Thirteen severely obese female subjects were examined before and 1 year after surgical treatment. Total adiponectin was determined by radioimmunosorbent assay, and oligomer composition was detected by nondenaturing Western blot.

Results: BMI decreased substantially ($p < 0.001$), which was associated with an increase of total adiponectin from 12.9 ± 5.9 to $14.3 \pm 6.1 \mu\text{g/mL}$ ($p = 0.055$). Medium

molecular weight (MMW) adiponectin increased from 7.5 ± 3.6 to $9.1 \pm 4.1 \mu\text{g/mL}$ ($p = 0.009$), whereas high (HMW) and low molecular weight adiponectin remained unchanged. Δ values of total adiponectin correlated significantly with Δ values of anthropometric parameters. Similar correlations were found for Δ values of MMW (Δ weight: $r^2 = 0.4132$, $p = 0.0178$; Δ BMI: $r^2 = 0.3319$, $p = 0.0393$; Δ fat mass: $r^2 = 0.5202$, $p = 0.0054$).

Discussion: Thus, profound weight loss was associated with an increase in total adiponectin, which was mainly and consistently caused by increases in MMW adiponectin ($p = 0.009$). These changes result in a shift from low molecular weight to MMW and HMW adiponectin isoforms, which may be related to improvements in both anthropometric and metabolic parameters.

Key words: bariatric surgery, adiponectin, weight loss

Introduction

Excess body weight is among the most important risk factor contributing to the overall burden of disease worldwide (1). More than 1 billion adults and 10% of children are now classified as overweight or obese (2,3). As a consequence, average life expectancy is diminished in these subjects (4). Surgical intervention is generally considered an efficient method to reduce body weight in severely obese subjects and can be considered as a model to study the effects of pronounced weight loss on metabolism (5–9). In recent long-term studies, decreased mortality and morbidity (10), improved quality of life (11,12), and amelioration of most risk factors were reported (13,14).

Adiponectin, the most abundant adipocytokine, has been proposed to have a wide range of biological activities (15,16). Recently three major forms of circulating adiponectin have been separated (17,18), which were classified as

Received for review June 21, 2006.

Accepted in final form November 22, 2006.

The costs of publication of this article were defrayed, in part, by the payment of page charges. This article must, therefore, be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

*Department of Internal Medicine, Clinical Division of General Internal Medicine, Medical University Innsbruck, Innsbruck, Austria; †Department of Clinical Nutrition, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany; ‡Department of Endocrinology, Diabetes and Nutrition, Charité-Universitätsmedizin Berlin, Berlin, Germany; §Department of Surgery, Medical University Innsbruck, Innsbruck, Austria; and ¶Department of Medicine, Academic Teaching Hospital, Hall, Austria.

||These authors contributed equally to this work.

Address correspondence to C. F. Ebenbichler, Clinical Department of Internal Medicine, Clinical Division of General Internal Medicine, Medical University Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria.

E-mail: Christoph.Ebenbichler@uibk.ac.at

Copyright © 2007 NAASO

high (HMW),¹ medium (MMW), and low molecular weight (LMW) adiponectin. In obesity, plasma levels of adiponectin are decreased (19), and recent studies even show changes in adiponectin isoform composition (17). Reduced levels of HMW adiponectin are associated with upper body fat distribution, insulin resistance, impaired lipid oxidation, and dyslipidemia (20). The effect of moderate weight loss on adiponectin multimers resulted in a relative increase of HMW/MMW adiponectin ratio and a reduction of LMW adiponectin (17). Total adiponectin correlated significantly with high-density lipoprotein (HDL)-cholesterol after weight loss and was also found to be correlated between absolute HMW, MMW, and LMW adiponectin and HDL-cholesterol after weight reduction (17). In fact, the MMW and HMW isoforms seem to mediate most of the biological activities of total adiponectin (17,20,21).

The aim of this study was to analyze the effect of pronounced weight loss induced by restrictive, nonmalabsorptive bariatric surgery on adiponectin isoforms and to investigate relationships between adiponectin isoforms and anthropomorphic and metabolic parameters in a prospective study design.

Research Methods and Procedures

Subjects

A total of 13 women with a BMI >35 kg/m² with comorbidities or a BMI >40 kg/m² participated voluntarily in this prospective study. The patients were recruited consecutively since 2002. Exclusion criteria included secondary causes of obesity, pregnancy, and lipid-lowering or antipsychotic medication. Diabetic patients were also excluded because of the insulinotropic nature of many of the antidiabetic drugs, which would interfere with the homeostasis model assessment (HOMA) index (22). The study subjects were examined within a 2-month period before laparoscopic adjustable gastric banding (LAGB) and 1 year after LAGB. Because this study is prospective and restricted to women, only a limited number of patients undertook the examination after 1 year. For all of the patients, this was the first bariatric surgery, and none of them was reoperated. Informed consent was obtained from all subjects. All procedures were performed in accordance with institutional guidelines of the Clinical Division of General Internal Medicine at the Medical University Innsbruck, and the local ethical committee approved the study.

Surgical Procedure

The surgical procedures were performed at the Department of Surgery, Medical University Innsbruck, as previ-

ously described by Forsell (23). The Swedish Adjustable Gastric Band was inserted in all of the study patients (SAGB Obtech Medical AG, Zug, Switzerland) (24–26).

Body Composition

Body composition (lean mass, fat mass) was determined by impedance analysis using InBody 3.0 Body Composition Analyzer from Biospace Europe (Dietzenbach, Germany) with an integrated scale. Patient height was measured to the nearest 0.1 cm, and BMI was calculated as body weight in kilograms divided by height in meters squared using the software Lookin Body Version 1, Body Composition Analysis Data Management System. All measurements were taken in the morning in the fasting state by a medical doctor.

Analyses

Blood was drawn after an overnight fast from the antecubital vein into EDTA tubes (1.6 mg/mL) by a medical doctor. Plasma was separated from erythrocytes by centrifugation at 3000 rpm for 10 minutes at 4 °C immediately after collection. Plasma samples were stored at –80 °C until assayed.

Plasma triglycerides (TGs), total cholesterol, and HDL-cholesterol were quantified using a commercially available enzymatic kit (Roche Diagnostic Systems, Basel, Switzerland). Low-density lipoprotein-cholesterol was calculated using the Friedewald formula (27). Plasma glucose was measured by the hexokinase method on a Cobas, MIRA analyzer (Hoffmann-La Roche, Basel, Switzerland). Plasma insulin was measured by a microparticle enzyme immunoassay from Abbott (Wiesbaden, Germany). Total adiponectin levels were determined by a radioimmunoassay (Linco Research, St. Charles, MO). Serum insulin resistance was calculated by the HOMA index as follows: HOMA-IR = fasting insulin × plasma glucose/22.5 (22).

Determination of Adiponectin Oligomers

Samples were analyzed in a randomized and blinded fashion in the laboratory of the Department of Clinical Nutrition, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis, immunoblotting, densitometry analyses of adiponectin oligomers, and calculations of the relative distributions were performed as described previously (17,18).

Statistical Analyses

Data are expressed as mean ± SD. The Shapiro-Wilk test was used to determine normal distribution of the data. Because most data were not normally distributed, the Wilcoxon test for paired samples was used to determine significant changes before and after LAGB. To assess correlations between data, the Spearman ρ correlation coefficient was

¹ Nonstandard abbreviations: HMW, high molecular weight; MMW, medium molecular weight; LMW, low molecular weight; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; TG, triglyceride; LAGB, laparoscopic adjustable gastric banding.

Table 1. Body composition, glucose, and lipid parameters of the study population*

	Pre-LAGB (n = 13)	Post-LAGB (n = 13)	p†
Age (years)	38.2 ± 13.7		
Height (cm)	165.5 ± 0.1		
Weight (kg)	112.7 ± 12.8	95.0 ± 16.4	<0.001
BMI (kg/m ²)	41.2 ± 2.9	34.4 ± 4.8	<0.001
Fat mass (kg)	53.3 ± 8.6	38.2 ± 9.9	<0.001
Lean mass (kg)	59.4 ± 5.2	56.8 ± 7.7	0.050
Systolic blood pressure (mm HG)	129.1 ± 17.6	122.1 ± 22.1	0.854
Diastolic blood pressure (mm HG)	80.1 ± 11	82.3 ± 11	0.144
Creatinine (mg/dL)	0.81 ± 0.21	0.76 ± 0.15	0.221
Glucose (mg/dL)	99.1 ± 28.5	92.5 ± 9.4	0.875
Insulin (μU/mL)	20.0 ± 20.3	9.7 ± 6.3	0.026
HOMA-IR	5.1 ± 6.0	2.1 ± 1.4	0.033
TGs (mg/dL)	176.6 ± 167.7	102.8 ± 48.3	0.039
Total cholesterol (mg/dL)	213.7 ± 53.4	186.6 ± 18.2	0.033
LDL-cholesterol (mg/dL)	119.2 ± 23.6	110.2 ± 13.9	0.386
HDL-cholesterol (mg/dL)	54.7 ± 10.9	55.8 ± 10.0	0.727

LAGB, laparoscopic adjustable gastric banding; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

* Data are expressed as means ± standard deviation.

† *p* Values were determined by Wilcoxon signed ranks test.

used. Additionally, linear regression analyses were performed where applicable. A two sided *p* value ≤ 0.05 was considered statistically significant. All analyses were performed using SPSS 11.5 for Windows (SPSS, Chicago, IL).

Power analysis was performed using Statistica 6.0 (StatSoft, Tulsa, OK). With *n* = 13, the observed correlation coefficients, and α values, power analysis of regression analyses revealed a power of 60.5% for the correlation between Δ MMW with Δ weight, 59.19% between Δ MMW and Δ BMI, and 62.28% between Δ MMW and Δ fat mass. Power analysis of correlations showed a power of 69.52%, 89.68%, and 73.84% between the HOMA index and total adiponectin, HMW, and MMW before weight loss and a power of 71.46% and 74.86% between the HOMA index and HMW and MMW after weight loss, respectively.

Results

One year after LAGB, mean weight loss was 17.7 kg (*p* < 0.001), and the mean BMI decreased by 6.7 kg/m² (*p* < 0.001). Weight loss was mainly caused by a decrease in fat mass (15.1 kg, *p* < 0.001; Table 1). Total adiponectin levels increased from 12.9 ± 5.9 to 14.3 ± 6.1 μg/mL (*p* = 0.055), and absolute MMW adiponectin increased significantly from 7.5 ± 3.6 to 9.1 ± 4.1 μg/mL (*p* = 0.009). In

parallel, absolute HMW adiponectin tended to increase and absolute LMW adiponectin decreased, without reaching statistical significance (Figure 1). The relative amount of LMW adiponectin decreased from 0.29 ± 0.10 to 0.23 ± 0.08 (*p* = 0.003) and MMW adiponectin increased from 0.58 ± 0.06 to 0.63 ± 0.07 (*p* = 0.002; Table 2).

The linear regression analyses showed a pronounced reduction in weight, BMI, and fat mass associated with distinct changes in total adiponectin and MMW adiponectin. Δ values of total adiponectin correlated significantly with Δ values of anthropometric parameters (Δ weight: $r^2 = 0.3876$, *p* = 0.023; Δ BMI: $r^2 = 0.367$, *p* = 0.0282; Δ fat mass: $r^2 = 0.4368$, *p* = 0.0139), and even stronger correlations were found for Δ values of MMW adiponectin (Δ weight: $r^2 = 0.4132$, *p* = 0.0178; Δ BMI: $r^2 = 0.3319$, *p* = 0.0393; Δ fat mass: $r^2 = 0.5202$, *p* = 0.0054; Figure 2).

The study subjects achieved improvements in parameters of glucose and lipid metabolism (Table 1). Parameters of glucose metabolism ameliorated 1 year after the surgical procedure. Insulin levels decreased significantly from 20.0 ± 20.3 to 9.7 ± 6.3 μU/mL (*p* = 0.026). Insulin sensitivity as estimated by HOMA index improved significantly from 5.1 ± 6.9 to 2.1 ± 1.4 mM/mU/L² (*p* = 0.033).

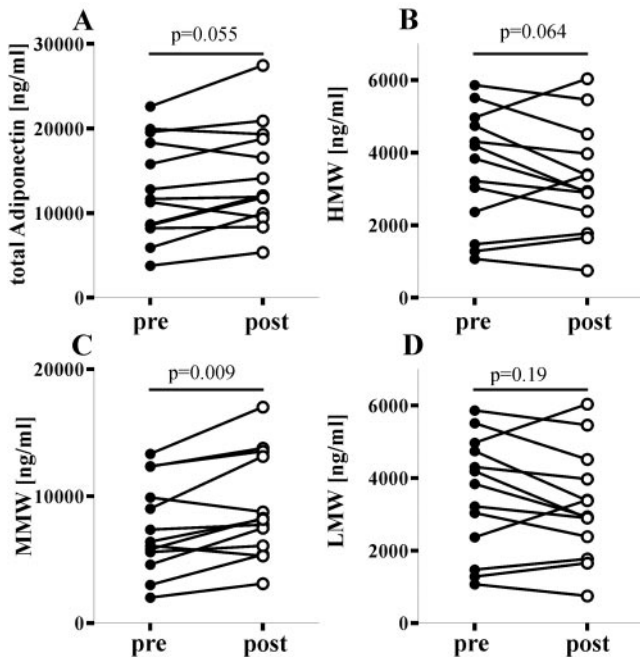


Figure 1: Changes in total adiponectin and oligomers after weight loss. Total adiponectin (A), HMW adiponectin (B), MMW adiponectin (C), and LMW adiponectin (D) before and after weight loss.

Analyzing the relationship between adiponectin oligomers and the HOMA index before and after weight loss, we found significant correlations for the three different adiponectin isoforms. HOMA index before weight loss correlated negatively with total adiponectin ($r = -0.873, p < 0.001$), HMW adiponectin ($r = -0.918, p < 0.001$), and MMW adiponectin ($r = -0.882, p < 0.001$). After weight

loss, this negative correlation remained significant for HMW adiponectin ($r = -0.765, p = 0.006$) and MMW adiponectin ($r = -0.836, p = 0.001$). The relative amounts of the adiponectin isoforms correlated with HOMA index before (HMW adiponectin: $r = -0.764, p = 0.013$; MMW adiponectin: $r = -0.691, p = 0.019$; LMW adiponectin: $r = 0.691, p = 0.019$) but not after weight loss.

TGs decreased by 42% and total cholesterol by 12.7%, whereas no significant changes were found for low-density lipoprotein-cholesterol and HDL-cholesterol. Before weight loss, the correlations between HDL-cholesterol and HMW adiponectin and LMW adiponectin failed statistical significance (HMW adiponectin absolute: $r = 0.493, p = 0.087$; LMW adiponectin absolute: $r = 0.507, p = 0.077$). After weight loss, we found positive correlations between HDL-cholesterol and total adiponectin ($r = 0.726, p = 0.005$) and for the different isoforms (HMW adiponectin absolute: $r = 0.564, p = 0.045$; MMW adiponectin absolute: $r = 0.611, p = 0.027$; LMW adiponectin absolute: $r = 0.657, p = 0.015$).

Discussion

Generally, adiponectin functions as an insulin-sensitizing and antiatherogenic, anti-inflammatory adipocytokine (28,29) and thereby plays a protective role in the pathogenesis of type 2 diabetes (30,31). Recent studies found three adiponectin isoforms and allocated these biological activities differentially to each of these three species (32). In fact, the MMW and HMW isoforms seem to mediate most of the biological activities of total adiponectin (17,20,21).

In this study, we investigated the effects of pronounced weight loss induced by bariatric surgery on adiponectin oligomer composition. In our study, population total adi-

Table 2. Total adiponectin and adiponectin oligomer composition*

	Pre-LAGB (n = 13)	Post-LAGB (n = 13)	p†
Adiponectin (µg/mL)	12.9 ± 5.9	14.3 ± 6.1	0.055
HMW (µg/mL)	1.8 ± 1.2	2.0 ± 1.0	0.064
MMW (µg/mL)	7.5 ± 3.6	9.1 ± 4.1	0.009
LMW (µg/mL)	3.5 ± 1.6	3.2 ± 1.5	0.19
HMW (%)	0.13 ± 0.04	0.14 ± 0.02	0.345
MMW (%)	0.58 ± 0.06	0.63 ± 0.07	0.002
LMW (%)	0.29 ± 0.10	0.23 ± 0.08	0.003

LAGB, laparoscopic adjustable gastric banding; HMW, high molecular weight; MMW, medium molecular weight; LMW, low molecular weight.

* Data are expressed as means ± standard deviation.

† p Values were determined by Wilcoxon signed ranks test.

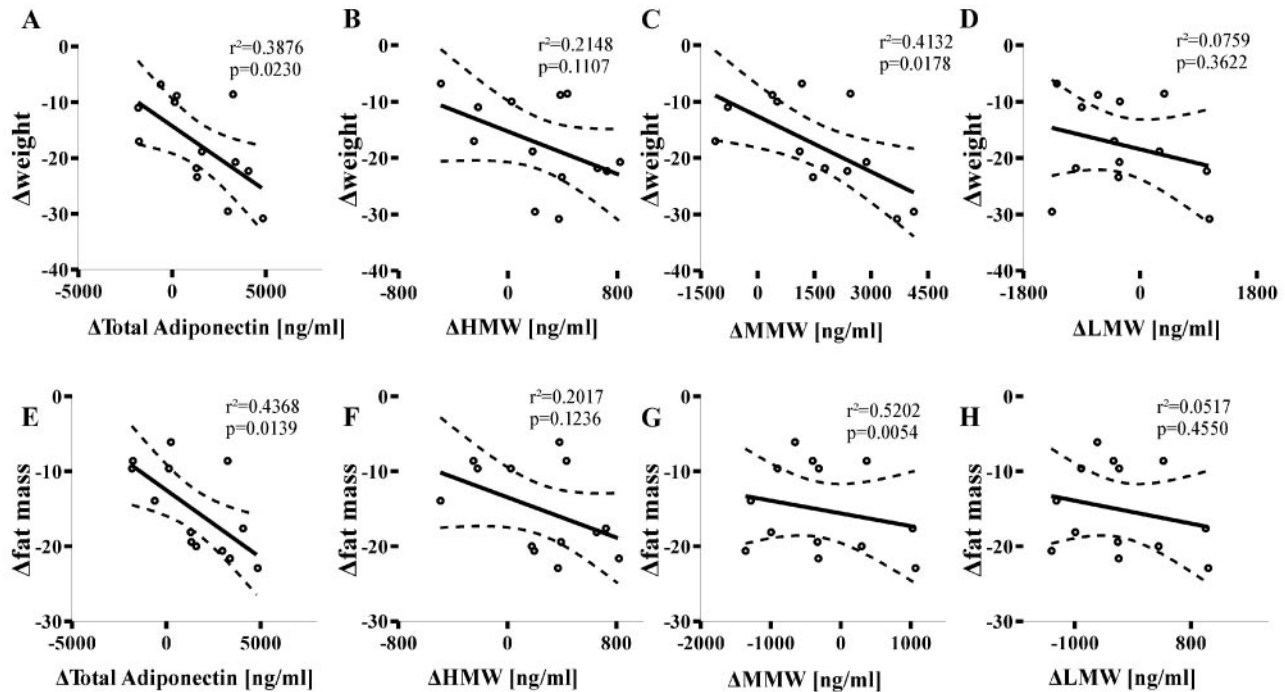


Figure 2: Correlations between Δ values of weight with Δ total adiponectin (A), Δ HMW adiponectin (B), Δ MMW adiponectin (C), and Δ LMW adiponectin (D). Correlations between Δ values of fat mass with Δ total adiponectin (E), Δ HMW adiponectin (F), Δ MMW adiponectin (G), and Δ LMW adiponectin (H).

adiponectin levels were elevated after substantial weight loss, which confirms previous studies in obese subjects (33). Furthermore, we observed significant changes in adiponectin oligomer composition induced by profound weight loss with a shift from LMW adiponectin to MMW adiponectin and HMW adiponectin. These results are similar to that seen after moderate weight reduction, where the increment of total MMW adiponectin was more pronounced than the increment of total HMW adiponectin (17). In a recent report, Swarbrick et al. (34) studied circulating concentrations of HMW after pronounced weight loss. After recruiting Roux-en-Y gastric bypass surgery patients and using an enzyme-linked immunosorbent assay system to determine adiponectin isoforms, the results confirmed that, after 12 months, the increase of total adiponectin levels was caused by an increase of HMW and MMW adiponectin isoforms (34).

In addition, we found strong relationships between Δ values of anthropometric parameters and adiponectin. Δ values of total adiponectin correlated significantly with Δ weight, Δ BMI, and Δ fat mass, and similar correlations were found for Δ values of MMW adiponectin. The association of MMW adiponectin isoform was even stronger with anthropometric parameters than the association of total adiponectin. Regression analyses revealed that 43% of the

change in total adiponectin is explainable by changes in fat mass, whereas for MMW adiponectin this percentage increases to 52%.

It is well established that weight loss improves parameters of glucose and lipid metabolism. In our study, insulin levels decreased significantly, and, in parallel, the HOMA index diminished on average 3 mM/mU/L² ($p = 0.033$). These results confirmed previous studies showing that adiponectin is involved in the regulation of muscle glucose use (35) and that plasma adiponectin concentrations predict insulin sensitivity (36). Baseline HOMA index before weight loss correlated negatively with total adiponectin, HMW adiponectin, and MMW adiponectin, and after weight loss, this negative correlation persisted for both the HMW and MMW isoforms. These findings are novel and could suggest that mainly the HMW and MMW isoforms predict insulin sensitivity and that the improvements in insulin sensitivity are paralleled with an increase in HMW and MMW adiponectin isoforms. In states of hypoadiponectinemia, a significant decrease in HMW adiponectin was observed, and these changes were related to decreased insulin sensitivity (37).

TGs and total cholesterol decreased significantly after weight loss. HDL-cholesterol was positively correlated with total adiponectin and absolute HMW, MMW, and LMW concentrations, which confirmed the results obtained after a

moderate weight reduction (17). In addition, in this study, MMW adiponectin correlated to a higher degree with HDL-cholesterol than HMW adiponectin.

The strengths of this study are the prospective study design and the blinded fashion of adiponectin isoform determination. Furthermore, this is the first study analyzing adiponectin isoforms after pronounced weight loss caused by gastric banding, the most common bariatric surgery procedure in Europe (38). Our findings confirm the results obtained by other groups after moderate diet-induced weight loss (17) and after gastric bypass (34).

A major limitation of this study is the restriction to women and the limited number of subjects. The latter could explain that, although we found an increase in total adiponectin levels, these differences were not significant in the respective statistical tests.

Although our results can be considered as preliminary work, larger numbers of patients, including both sexes, need to be studied in a prospective, randomized controlled trial. Even considering these strengths and limitations, the findings are consistent and both confirm and extend our current knowledge on the effects of weight changes on total adiponectin and adiponectin oligomer composition. Profound weight loss increased total adiponectin, and this increase was mainly and consistently mediated by an increase in the MMW adiponectin isoform. The clinical implications at this time are very limited, because the methods involved in determination of the isoforms are performed on few places in the world. Because there is now a commercially available enzyme-linked immunosorbent assay on the market, larger number of patients in different clinical conditions could be studied.

We conclude that weight loss caused by gastric banding results in a shift from LMW adiponectin to MMW adiponectin and HMW adiponectin isoforms and that these changes are associated with improvements in various anthropometric and metabolic parameters.

Acknowledgment

There was no funding/outside support for this study.

References

1. **Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ.** Selected major risk factors and global and regional burden of disease. *Lancet*. 2002;360:1347–60.
2. **Haslam DW, James WP.** *Obesity Lancet*. 2005;366:1197–209.
3. **Freedman DS, Khan LK, Serdula MK, Ogden CL, Dietz WH.** Racial and ethnic differences in secular trends for childhood BMI, weight, and height. *Obesity (Silver Spring)*. 2006; 14:301–8.
4. **Peeters A, Barendregt JJ, Willekens F, Mackenbach JP, Al Mamun A, Bonneux L.** Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Ann Intern Med*. 2003;138:24–32.
5. **Ebenbichler CF, Laimer M, Kaser S, et al.** Relationship between cholesteryl ester transfer protein and atherogenic lipoprotein profile in morbidly obese women. *Arterioscler Thromb Vasc Biol*. 2002;22:1465–9.
6. **Kaser S, Sandhofer A, Foger B, et al.** Influence of obesity and insulin sensitivity on phospholipid transfer protein activity. *Diabetologia*. 2001;44:1111–7.
7. **Laimer M, Ebenbichler CF, Kaser S, et al.** Weight loss increases soluble leptin receptor levels and the soluble receptor bound fraction of leptin. *Obes Res*. 2002;10:597–601.
8. **Laimer M, Ebenbichler CF, Kaser S, et al.** Markers of chronic inflammation and obesity: a prospective study on the reversibility of this association in middle-aged women undergoing weight loss by surgical intervention. *Int J Obes Relat Metab Disord*. 2002;26:659–62.
9. **Laimer M, Kaser S, Kranebitter M, et al.** Effect of pronounced weight loss on the nontraditional cardiovascular risk marker matrix metalloproteinase-9 in middle-aged morbidly obese women. *Int J Obes (Lond)*. 2005;29:498–501.
10. **Christou NV, Sampalis JS, Liberman M, et al.** Surgery decreases long-term mortality, morbidity, and health care use in morbidly obese patients. *Ann Surg*. 2004;240:416–23.
11. **Nguyen NT, Goldman C, Rosenquist CJ, et al.** Laparoscopic versus open gastric bypass: a randomized study of outcomes, quality of life, and costs. *Ann Surg*. 2001;234:279–89.
12. **Dixon JB, O'Brien PE.** Changes in comorbidities and improvements in quality of life after LAP-BAND placement. *Am J Surg* 2002;184:51S–4S.
13. **Sjöström L, Lindroos AK, Peltonen M, et al.** Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med*. 2004;351:2683–93.
14. **Buchwald H, Avidor Y, Braunwald E, et al.** Bariatric surgery: a systematic review and meta-analysis. *JAMA*. 2004; 292:1724–37.
15. **Meier U, Gressner AM.** Endocrine regulation of energy metabolism: review of pathobiochemical and clinical chemical aspects of leptin, ghrelin, adiponectin, and resistin. *Clin Chem*. 2004;50:1511–25.
16. **Tilg H, Moschen AR.** Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol*. 2006;6:772–83.
17. **Bobbert T, Rochlitz H, Wegewitz U, et al.** Changes of adiponectin oligomer composition by moderate weight reduction. *Diabetes*. 2005;54:2712–9.
18. **Waki H, Yamauchi T, Kamon J, et al.** Impaired multimerization of human adiponectin mutants associated with diabetes. Molecular structure and multimer formation of adiponectin. *J Biol Chem*. 2003;278:40352–63.
19. **Arita Y, Kihara S, Ouchi N, et al.** Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun*. 1999;257:79–83.
20. **Lara-Castro C, Luo N, Wallace P, Klein RL, Garvey WT.** Adiponectin multimeric complexes and the metabolic syndrome trait cluster. *Diabetes*. 2006;55:249–59.
21. **Kobayashi H, Ouchi N, Kihara S, et al.** Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. *Circ Res*. 2004;94:e27–31.

22. **Wallace TM, Levy JC, Matthews DR.** Use and abuse of HOMA modeling. *Diabetes Care.* 2004;27:1487–95.
23. **Forsell P, Hallberg D, Hellers G.** Gastric banding for morbid obesity: initial experience with a new adjustable band. *Obes Surg.* 1993;3:369–74.
24. **Mittermair RP, Weiss H, Nehoda H, Kirchmayr W, Aigner F.** Laparoscopic Swedish adjustable gastric banding: 6-year follow-up and comparison to other laparoscopic bariatric procedures. *Obes Surg.* 2003;13:412–7.
25. **Mittermair RP, Aigner F, Nehoda H.** Results and complications after laparoscopic adjustable gastric banding in super-obese patients, using the Swedish band. *Obes Surg.* 2004;14:1327–30.
26. **Nehoda H, Weiss H, Labeck B, et al.** Results and complications after adjustable gastric banding in a series of 250 patients. *Am J Surg.* 2001;181:12–5.
27. **Friedewald WT, Levy RI, Fredrickson DS.** Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972;18:499–502.
28. **Okamoto Y, Kihara S, Funahashi T, Matsuzawa Y, Libby P.** Adiponectin: a key adipocytokine in metabolic syndrome. *Clin Sci (Lond).* 2006;110:267–78.
29. **Ahima RS.** Metabolic actions of adipocyte hormones: focus on adiponectin. *Obesity (Silver Spring)* 2006;14(Suppl 1):9S–15S.
30. **Spranger J, Kroke A, Mohlig M, et al.** Adiponectin and protection against type 2 diabetes mellitus. *Lancet.* 2003;361:226–8.
31. **Kantartzis K, Fritsche A, Tschritter O, et al.** The association between plasma adiponectin and insulin sensitivity in humans depends on obesity. *Obes Res.* 2005;13:1683–91.
32. **Wang Y, Lam KS, Xu JY, et al.** Adiponectin inhibits cell proliferation by interacting with several growth factors in an oligomerization-dependent manner. *J Biol Chem.* 2005;280:18341–7.
33. **Yang WS, Lee WJ, Funahashi T, et al.** Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. *J Clin Endocrinol Metab.* 2001;86:3815–9.
34. **Swarbrick MM, Austrheim-Smith IT, Stanhope KL, et al.** Circulating concentrations of high-molecular-weight adiponectin are increased following Roux-en-Y gastric bypass surgery. *Diabetologia.* 2006;49:2552–8.
35. **Yamauchi T, Kamon J, Minokoshi Y, et al.** Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med.* 2002;8:1288–95.
36. **Tschritter O, Fritsche A, Thamer C, et al.** Plasma adiponectin concentrations predict insulin sensitivity of both glucose and lipid metabolism. *Diabetes.* 2003;52:239–43.
37. **Catalano PM, Hoegh M, Minium J, et al.** Adiponectin in human pregnancy: implications for regulation of glucose and lipid metabolism. *Diabetologia.* 2006;49:1677–85.
38. **Buchwald H, Williams SE.** Bariatric surgery worldwide 2003. *Obes Surg.* 2004;14:1157–64.