Changes of Adiponectin Oligomer Composition by Moderate Weight Reduction

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Adiponectin affects lipid metabolism and insulin sensitivity. However, adiponectin circulates in three different oligomers that may also have distinct biological functions. We aimed to analyze the role of these oligomers in obesity and lipid metabolism after weight reduction. A total of 17 obese volunteers (15 women and 2 men) participated in a weight reduction program. Individuals were characterized before and after 6 months of a balanced diet. Adiponectin was determined by enzyme-linked immunosorbent assay, and oligomers were detected by nondenaturating Western blot. BMI decreased (35.1 ± 1.2 to 32.8 ± 1.1 kg/m², P < 0.001), which was associated with an improved metabolite profile. Total adiponectin increased from 5.3 ± 0.5 to 6.1 ± 0.6 μg/ml (P = 0.076). High (HMW) and medium molecular weight (MMW) adiponectin oligomers significantly increased during weight reduction (HMW: 0.37 ± 0.07 to 0.4 ± 0.08 μg/ml, P = 0.042; MMW: 2.3 ± 0.2 to 2.9 ± 0.3 μg/ml, P = 0.007), while low molecular weight (LMW) did not significantly change. Body weight inversely correlated with HMW (r = −0.695, P = 0.002) and positively with LMW (r = 0.579, P = 0.015). Interestingly, HDL cholesterol and HMW were strongly correlated (r = 0.665, P = 0.007). Indeed, HMW and free fatty acids before weight reduction predicted ~60% of HDL changes during intervention. In conclusion, weight reduction results in a relative increase of HMW/MMW adiponectin and a reduction of LMW adiponectin. Total adiponectin and especially HMW adiponectin are related to circulating HDL cholesterol. Diabetes 54: 2712–2719, 2005

Original Article

Obesity is associated with dyslipidemia, hypertension, type 2 diabetes, and atherosclerotic cardiovascular disease (1,2). Adipose tissue was believed to be a fat-storage organ, but it is now acknowledged to be an active participant in energy homeostasis and other physiological functions. Adipose tissue is known to express and secrete a variety of novel adipocytokines that have been implicated in the development of insulin resistance and atherosclerosis (3,4). Dysregulation of adipocytokine production is directly involved in the pathophysiology of the metabolic syndrome, and normalization or elevation of plasma concentrations of some adipocytokines reverses the phenotype of the metabolic syndrome (5,6). Adipocytes secrete a variety of polypeptides, such as leptin, resistin, and adiponectin. Adiponectin, the gene product of the adipose tissue’s most abundant gene transcript (7), may be a link between obesity and the development of insulin resistance. Especially in the regulation of the glucose and lipid metabolism, adiponectin has been shown to play an important role (8–10). In contrast to other adipose-derived proteins, plasma levels of adiponectin have been found to be decreased in a number of impaired metabolic states, including obesity (11), dyslipidemia (12), type 2 diabetes, or insulin resistance (9,13,14). Previous studies (14,15) have demonstrated that reduced circulating adiponectin levels are partially reversible by weight reduction in obese and in insulin-resistant subjects. Apart from the link to obesity or diabetes, further parameters like age, sex hormones, or glucocorticoids are likely to play a role in the regulation of adiponectin levels (16,17).

Adiponectin is composed of a carboxyl-terminal globular domain and an amino-terminal collagenous domain (18,19). Adiponectin belongs to the soluble collagen superfamily and has structural homology with collagen VIII and X, complement factor C1q (13), and the tumor necrosis factor family (7,18). This kind of structure is known to form characteristic multimers (20,21). Gel filtration and velocity gradient sedimentation studies revealed adiponectin circulating in serum to form several different molecular weight species; the largest species was more than several hundred kilodaltons in size (8,10,11). Scherer et al. (8) described that adiponectin from 3T3-L1 adipocytes forms trimers, hexamers, and larger multimers. Tsao et al. (22) and Arita et al. (11) analyzed multimer formation of...
adiponectin in serum by gel filtration chromatography and showed adiponectin to be separable into three species. Waki et al. (23) showed a new method of evaluating the multimer formation of adiponectin. With an SDS-PAGE under nonreducing and nonheat-denaturing conditions, they separated multimers of adiponectin from various sources into three species: low molecular weight (LMW) trimers, middle molecular weight (MMW) multimers, and high molecular weight (HMW) multimers. The biological activities of these different multimers are discussed controversially. HMW multimer levels appear to be higher in women compared with men (23). Further on, adiponectin exerts multiple metabolic actions at multiple tissue sites. The isolated globular domain of adiponectin stimulates fatty acid oxidation in skeletal muscle, whereas full-length adiponectin synergizes with insulin to inhibit hepatic glucose production (13,24,25). In mice, disruption of the adiponectin locus leading to its ablation resulted in impaired fatty acid clearance, increased tumor necrosis factor-α levels, and aggravated insulin resistance in animals fed a high-fat diet (26,27). The HMW and hexameric adiponectin can activate the transcription factor nuclear factor-κB in undifferentiated or differentiated C2C12 cells, but trimeric adiponectin or the isolated globular domain of adiponectin cannot. The isolated globular domain of adiponectin, but not full-length adiponectin hexamer, enhances muscle fatty acid oxidation by inactivating acetyl-CoA carboxylase following stimulation of AMP-activated protein kinase (28,29). Waki et al. (23) have reported that the HMW isoform, specifically, promotes AMP-activated protein kinase in hepatocytes. In contrast, Tsao et al. (30) recently reported that only trimers activate AMPK in muscle, whereas hexamers and HMW forms activated nuclear factor-κB. Differences in the tissue-specific expression patterns of two adiponectin receptors may contribute to these divergent activities (31). There are first hints that weight reduction influences not only total adiponectin but also adiponectin oligomers. In six individuals, significantly increased levels of HMW adiponectin and decreased levels of the hexamer and trimer structure of adiponectin were found after 3 months of weight reduction (32).

The precise interplay between adiponectin oligomers and anthropometry, lipid, and glucose metabolism in humans has not yet been investigated. We therefore investigated within this study the relationship between anthropometry, metabolism, and adiponectin oligomers before and after moderate weight loss.

**RESEARCH DESIGN AND METHODS**

A total of 17 volunteers (15 women and 2 men) participated in a weight reduction program for 6 months. Mean age was 51.8 ± 3.1 years. Mean starting weight was 96.2 ± 3.1 kg and BMI was 35.1 ± 1.2 kg/m². All participants were screened for serious health problems and the intake of medication and were excluded if vascular diseases or hepatic or renal diseases were found. Individuals with insulin-dependent diabetes were excluded. One woman who had impaired fasting glucose was treated by diet. Two patients with type 2 diabetes (one man and one woman) were treated with oral antidiabetes medication. One patient was treated with repaglinide and metformin, and the other patient was treated with sulfonylureas. No thiazolidinediones were used. Further characteristics of the participants are provided in Table 1. The experimental protocol was approved by the institutional review board, and all subjects gave written informed consent.

**Dietary intervention.** All volunteers documented their eating behavior for 3 days before intervention. Basal metabolic rate was measured with indirect calorimetry, which was 1,537 ± 60 kcal in average. Based on eating protocols, an individual consultation was performed, with the recommendation of a daily calorie intake of 100–600 kcal less than the total energy expenditure. The diet was composed according to the guidelines of the German Association of Nutrition, with the following distribution of macronutrients: carbohydrates 50%, fat 30%, and protein 20% of the daily energy intake. Meetings for all volunteers took place once a week over the 6 months. In the first 90 min at the first 10 dates, nutrition consultants accomplished group workshops with practical cooking exercises. At nine dates, the workshop was done by a psychologist with relaxation exercises. One workshop was done by a medical doctor with medical hints and advice. At all dates, moderate exercise with gymnastics or aqua fitness was performed during the last 60 min.

**Measurement and laboratory parameters.** The following measurements and laboratory parameters were determined in all participants before the dietary intervention and at the end of 6 months. Anthropometry was performed as previously described (33,34). Bioelectric impedance measurement was performed on resting participants. After attaching the electrodes to the right hand and the right food, three measurements were conducted and the mean value was calculated. Basal metabolic rate (MVmax29; Sensor Medicis) was determined after a 20-min rest. During steady state, basal metabolic rate was measured for 5–10 min. Hyperinsulinemic-euglycemic clamp was performed for at least 2 h using 40 mIU · m⁻² · min⁻¹ human insulin (Actrapid; Novo Nordisk, Bagsvaerd, Denmark) and a variable infusion of 10% glucose (Serag Wiesner, Nails, Germany). The priming dose of insulin was calculated as previously described (35). Capillary glucose concentration was monitored every 5 min and was maintained between 4.0 and 4.9 mmol/l. Blood samples were collected before the test and at least 2 h after starting the clamp during steady-state conditions. All infusions were administered into an antecubital vein, while blood samples were drawn from the antecubital vein at the contralateral arm. Blood samples were taken at baseline and during steady state of the euglycemic-hyperinsulinemic clamp. Blood potassium concentrations were controlled before and during clamp procedure to avoid insulin-induced hypokalemia. Potassium substitution was not required within this study.

**TABLE 1**

<table>
<thead>
<tr>
<th>Baseline characteristics of the participants</th>
<th>Before weight reduction</th>
<th>After weight reduction</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.8 ± 2.8</td>
<td>51.0 ± 2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>15/2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>96.2 ± 3.1</td>
<td>90.0 ± 2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>35.1 ± 1.2</td>
<td>32.8 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.94 ± 0.02</td>
<td>0.92 ± 0.02</td>
<td>0.442</td>
</tr>
<tr>
<td>BIA BCM</td>
<td>31.7 ± 0.6</td>
<td>33.6 ± 0.9</td>
<td>0.010</td>
</tr>
<tr>
<td>BIA FM</td>
<td>39.6 ± 1.8</td>
<td>34.3 ± 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BIA FA</td>
<td>39.5 ± 0.8</td>
<td>37.3 ± 1.0</td>
<td>0.005</td>
</tr>
<tr>
<td>RQ</td>
<td>0.87 ± 0.01</td>
<td>0.86 ± 0.01</td>
<td>0.497</td>
</tr>
<tr>
<td>Basal metabolic rate (kcal)</td>
<td>1,537 ± 60</td>
<td>1,391 ± 43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>5.3 ± 0.5</td>
<td>6.1 ± 0.6</td>
<td>0.076</td>
</tr>
<tr>
<td>HMW (µg/ml)</td>
<td>0.37 ± 0.07</td>
<td>0.49 ± 0.08</td>
<td>0.042</td>
</tr>
<tr>
<td>MMW (µg/ml)</td>
<td>2.3 ± 0.2</td>
<td>2.9 ± 0.3</td>
<td>0.007</td>
</tr>
<tr>
<td>LMW (µg/ml)</td>
<td>2.6 ± 0.1</td>
<td>2.7 ± 0.2</td>
<td>0.609</td>
</tr>
<tr>
<td>HMW (%)</td>
<td>6.7 ± 0.9</td>
<td>7.9 ± 0.7</td>
<td>0.100</td>
</tr>
<tr>
<td>MMW (%)</td>
<td>43.1 ± 1.4</td>
<td>46.1 ± 1.5</td>
<td>0.070</td>
</tr>
<tr>
<td>LMW (%)</td>
<td>50.0 ± 1.8</td>
<td>45.8 ± 1.7</td>
<td>0.055</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.7 ± 0.2</td>
<td>5.9 ± 0.2</td>
<td>0.305</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.7 ± 0.1</td>
<td>3.8 ± 0.1</td>
<td>0.693</td>
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<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.28 ± 0.06</td>
<td>1.36 ± 0.06</td>
<td>0.029</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.6 ± 0.1</td>
<td>1.6 ± 0.2</td>
<td>0.699</td>
</tr>
<tr>
<td>FFAs (mmol/l)</td>
<td>0.74 ± 0.05</td>
<td>0.63 ± 0.06</td>
<td>0.121</td>
</tr>
<tr>
<td>M value</td>
<td>2.9 ± 0.3</td>
<td>3.2 ± 0.2</td>
<td>0.320</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>5.5 ± 0.1</td>
<td>5.6 ± 0.2</td>
<td>0.802</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>5.4 ± 0.1</td>
<td>5.4 ± 1.0</td>
<td>1.000</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>4.5 ± 0.8</td>
<td>4.5 ± 0.8</td>
<td>0.991</td>
</tr>
</tbody>
</table>

Data are means ± SE. BCM, body cell mass; BIA, bioelectric impedance measurement; FA, fat allotment; FM, fat mass; RQ, respiratory quotient.
FIG. 1. Adiponectin oligomers under nonreducing and nonheat-denaturating conditions. Specificity of reaction is shown by competition (M, marker; S, sample; C, competition). Specific adiponectin oligomers were found at ~70 kDa (**), which represents the LMW trimmer, two bands at ~140 and ~180 kDa (**), which represent the MMW hexamers, and the HMW complex at >300 kDa (*), as described previously (23).

Laboratory parameters. After sampling in EDTA or serum tubes, blood was immediately chilled on ice and centrifuged, and aliquots were immediately frozen at ~20°C until assayed. Blood samples were analyzed for glucose, insulin, C-reactive protein, free fatty acids (FFAs), cholesterol, LDL and HDL cholesterol, and triglycerides with COBAS MIRA from Roche (Lorriach, Germany) (intra-assay coefficient of variation [CV]: glucose, 5.5%; insulin, 6.0%; C-reactive protein, 10.0%; FFAs, 10.5%; cholesterol, 5.1%; HDL cholesterol, 5.4%; and triglycerides, 5.1%). Adiponectin concentrations were measured by immunosorbent assay (ELISA; Biovendor, Nashvile, TN) (intra-assay CV, 14.7%; inter assay CV, 7.3%).

Determination of adiponectin oligomers SDS-PAGE and immunoblotting. SDS-PAGE was performed according to the standard Laemmli’s method (36). Sample buffer for nonreducing, nonheat-denaturating conditions contained 3% SDS; 50 mmol/l Tris-HCl, pH 6.8; and the standard Laemmli’s method (36). Sample buffer for nonreducing, nonheat-denaturating conditions contained 3% SDS; 50 mmol/l Tris-HCl, pH 6.8; and the standard Laemmli’s method (36). Sample buffer for nonreducing, nonheat-denaturating conditions contained 3% SDS; 50 mmol/l Tris-HCl, pH 6.8; and the standard Laemmli’s method (36).

Percentage of adiponectin oligomers were multiplied with total adiponectin levels to calculate absolute oligomer values. Density. Percentage of adiponectin oligomers were calculated by dividing band density through total density. Percentage of adiponectin oligomers were multiplied with total adiponectin levels to calculate absolute oligomer values.

Statistics. Statistical calculations were performed with SPSS 11.5 (SPSS, Chicago, IL).

All values are given as means ± SE. Paired t test was applied if parameters were normally distributed; otherwise, Wilcoxon test was used. Correlations between variables were investigated by Pearson’s coefficient of correlation. Multivariate linear regression was calculated to analyze the factors independently affecting specific variants. An α-error <5% was considered statistically significant.

RESULTS

After 6 months of a low-caloric diet, body weight and BMI decreased significantly from 96.2 ± 3.1 to 90.0 ± 2.6 kg (P < 0.001) and from 35.1 ± 1.2 to 32.8 ± 1.1 kg/m² (P < 0.001) (Table 1), respectively. Parameters of body composition, like bioelectrical impedance measurement or basal metabolic rate, changed significantly (Table 1). Total adiponectin increased from 5.3 ± 0.5 to 6.1 ± 0.6 μg/ml, which closely failed to be significant (P = 0.076). While relative proportion of HMW and MMW increased, the relative amount of LMW decreased correspondingly (HMW: 6.7 ± 0.9 to 7.9 ± 0.7%, P = 0.1; MMW: 43.1 ± 1.4 to 46.1 ± 1.5%, P = 0.070; and LMW: 50.0 ± 1.8 to 45.8 ± 1.7%, P = 0.055). Comparably, absolute levels of HMW, MMW, and LMW changed substantially (HMW: 0.37 ± 0.07 to 0.49 ± 0.08 μg/ml, P = 0.042; MMW: 2.3 ± 0.2 to 2.9 ± 0.3 μg/ml, P = 0.007; LMW: 2.6 ± 0.1 to 2.7 ± 0.2 μg/ml, P = 0.609).

As expected, parameters of fat and glucose metabolism were only slightly changed by the presented moderate weight reduction here. Only HDL cholesterol increased significantly from 1.28 ± 0.06 to 1.36 ± 0.06 mmol/l (P = 0.029). FFAs were also altered (0.74 ± 0.05 to 0.63 ± 0.06 mmol/l, P = 0.121), which also closely failed significance. Total cholesterol (5.7 ± 0.2 to 5.9 ± 0.2 mmol/l, P = 0.305), LDL cholesterol (3.7 ± 0.1 to 3.8 ± 0.1 mmol/l, P = 0.693), and triglycerides (1.6 ± 0.1 to 1.6 ± 0.2 mmol/l, P = 0.699) remained nearly unchanged. Also, parameters for glucose metabolism were almost unaltered, like fasting glucose (5.5 ± 0.1 to 5.6 ± 0.2 mmol/l, P = 0.502), HbA1c (A1C) (5.4 ± 0.1 to 5.4 ± 0.1%, P = 1.0), and M value (2.9 ± 0.3 to 3.2 ± 0.2, P = 0.320).

No significant correlation was found between total adiponectin and body weight before and after weight reduction, but there was a trend for an inverse relationship between these two parameters (Fig. 2A). Adiponectin oligomers in percent showed no correlation to body weight before weight reduction (Fig. 2B). However, after weight reduction, the negative correlation between HMW in percent and body weight was highly significant (r = −0.685, P = 0.002). In contrast, LMW in percent positively correlated with body weight (r = 0.579, P = 0.015). Although MMW in percent and body weight negatively correlated, this correlation failed to be statistically significant (r = −0.352, P = 0.165).

We also questioned whether the anthropometric changes induced by weight reduction (in percent of the basal value) correlated with the relative changes of oligomers (again in percent of basal values). Indeed, the correlations of MMW and LMW in percent with percentage changes of weight were considerable but closely failed significance (HMW: r = −0.17, P = 0.951; MMW: r = −0.444, P = 0.098; and LMW: r = 0.454, P = 0.089). The absolute levels of adiponectin oligomers showed no correlation to body weight both before or after weight reduction (Fig. 2C).

Next, we analyzed the relationship between adiponectin oligomers and obesity-associated metabolic changes. Surprisingly, no correlation was found between insulin sensitivity (M value) and total adiponectin before (r = 0.365, P = 0.181) and after (r = 0.020, P = 0.944) weight reduction. Also, no correlation between insulin sensitivity and relative amounts of adiponectin oligomers could be observed before (HMW: r = 0.145, P = 0.591; MMW: r = −0.147, P = 0.587; and LMW: r = 0.071, P = 0.795) and after (HMW: r = 0.033, P = 0.904; MMW: r = −0.189, P = 0.484; and LMW: r = 0.128, P = 0.637) weight reduction.
Further on, no correlation between absolute adiponectin oligomers and insulin sensitivity was found before (HMW: $r = 0.252, P = 0.365$; MMW: $r = 0.229, P = 0.411$; and LMW: $r = 0.432, P = 0.107$) and after weight reduction (HMW: $r = 0.052, P = 0.854$; MMW: $r = 0.013, P = 0.962$; and LMW: $r = 0.013, P = 0.963$) weight reduction.

In contrast, a positive correlation between total adiponectin and HDL cholesterol was observed before weight reduction ($r = 0.346, P = 0.206$), which was even stronger after weight reduction ($r = 0.61, P = 0.016$). Adiponectin oligomers in percent showed a correlation pattern to HDL cholesterol, which was comparable to that of body weight (Fig. 3B). HMW and MMW adiponectin in percent positively correlated with HDL cholesterol, whereas LMW in percent negatively correlated with HDL. All correlations failed to be statistically significant before weight reduction, while the correlations were again stronger after weight reduction, and the correlations from HDL cholesterol to HMW and LMW were especially of borderline significance ($r = 0.479, P = 0.052$ and $r = -0.445, P = 0.073$, respectively).

Absolute adiponectin oligomers positively correlated before and after weight reduction with HDL cholesterol (Fig. 3C). After weight reduction, the correlations between HDL cholesterol and absolute HMW ($r = 0.665, P = 0.007$), MMW ($r = 0.604, P = 0.017$), and LMW ($r = 0.536, P = 0.039$) adiponectin were statistically significant.

Including only women into the analyses yielded comparable results as including all individuals. If women were divided into pre-, peri-, and postmenopausal groups, trends of results were comparable to those in the whole group, although results usually failed to be significant due to the low number of individuals in the respective groups. We also found no significant differences in the mean values of adiponectin oligomers between pre-, peri-, and postmenopausal women, but again, groups were too small to investigate this question in detail. In addition, all calculations were done without those individuals with impaired glucose metabolism. Again, results did not considerably change.

In consideration of the effects of the weight reduction on the parameters of fat metabolism, we calculated a multivariate linear regression model aiming to predict changes in HDL by weight reduction. Our correlation data suggested that the effects on HDL cholesterol seemed to be affected quite strongly by HMW adiponectin rather than...
Indeed, we found that absolute HMW oligomers and FFAs (both before weight reduction) had a considerable impact on subsequent changes of HDL cholesterol (Table 2 and Fig. 4). Absolute HMW and FFAs before weight reduction explained $\frac{60}{100}$ of the variability of subsequent changes of HDL cholesterol. The precise relationship is depicted in Fig. 4, showing that lower levels of absolute HMW and FFAs before weight reduction were associated with higher HDL changes. A multivariate linear regression was also calculated with total adiponectin instead of absolute HMW adiponectin (Table 2). With total adiponectin and FFAs, only $\frac{40}{100}$ of the variability of HDL cholesterol changes could be explained.

### DISCUSSION

This study investigated the effects of moderate weight reduction by a lifestyle intervention on adiponectin oligomer composition and its relation to glucose and fat metabolism. While HMW and MMW adiponectin increased, a decreased amount of LMW adiponectin was found after weight reduction.
found only slight nonsignificant improvement of insulin sensitivity after moderate weight loss, which is in agreement with various previous studies (40,41). While insulin sensitivity was determined by euglycemic-hyperinsulinemic clamp, we did not analyze endogenous glucose production as a measure of hepatic insulin sensitivity. Possibly, HMW adiponectin is primarily associated with hepatic rather than total insulin sensitivity. Clearly, future studies addressing this important aspect are desirable. In addition, our patients were not treated with thiazolidinediones, which might have considerable impact on the results, as the effects of weight reduction and PPAR-\(\gamma\) agonists certainly differ not only in terms of insulin sensitivity.

Many studies have demonstrated a correlation between total adiponectin and HDL cholesterol, and most of these studies suggested that hypoadiponectinemia is more closely related to adiposity and dyslipidemia rather than insulin sensitivity, which is in agreement with our results at oligomer levels (42). Indeed, we found a strong correlation between HMW adiponectin and HDL cholesterol, which suggests that the relationship between total adiponectin and HDL cholesterol is primarily driven by HMW adiponectin rather than total adiponectin. HDL cholesterol is basically generated from lipid-free apolipoprotein A-I or lipid-poor pre–\(\beta\)-1-HDL as precursors. These precursors are partially produced by the liver, and it is well known that adiponectin oligomers specifically affect liver metabolism (22). However, to our knowledge, no studies investigated the effects of adiponectin oligomers on pathways involved in the generation of HDL cholesterol, such as adenosine triphosphate–binding cassette transporter A1, lecithin: cholesterol acyltransferase, or choleseryl ester transfer protein, which appears to be mandatory given the amount of data showing a relation between HDL cholesterol and adiponectin. Especially, the consideration of adiponectin oligomers may be important, which is supported by our multivariate analyses that revealed that HMW adiponectin explained \(\sim 30\%\) of the variability of HDL cholesterol. Actually, these results confirm those of Baratta et al. (43), who demonstrated that adiponectin is correlated with serum lipid improvement independently of insulin sensitivity changes after weight loss. We also found this correlation but extend the picture by showing that HMW adiponectin is the key for this relationship. Definitely, different adiponectin oligomers and the varying appearance of the two adiponectin receptors AdipoR1 and AdipoR2 may be responsible for the different actions of adiponectin oligomers on fat or glucose metabolism. However, the precise molecular mechanism for the oligomer-specific effect is yet unclear.

In summary, this study demonstrated changes of adiponectin oligomer composition and fat metabolism by moderate weight reduction. While HMW and MMW adiponectin increased during weight loss, a corresponding reduction of LMW adiponectin was found. Specifically, HMW adiponectin was closely related to HDL cholesterol. Multivariate linear regression demonstrated that HMW and FFAs predicted \(\sim 60\%\) of HDL cholesterol changes during weight loss. Our data suggest that adiponectin is associated with dyslipidemia rather than insulin sensitivity. Beneficial effects of moderate weight loss may be medi-
ated by changes of the adiponectin oligomer composition. In more general terms, we show that adiponectin oligomers might have specific biological functions in vivo in humans, especially with respect to lipid metabolism.

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