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Total and High Molecular Weight But Not Trimeric or Hexameric Forms of Adiponectin Correlate with Markers of the Metabolic Syndrome and Liver Injury in Thai Subjects

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Context/Objective: Decreased total adiponectin has been associated with metabolic disorders, including obesity, diabetes, fatty liver, and the metabolic syndrome. Although circulating adiponectin is composed of trimers, hexamers, and high molecular weight (HMW) multimers, there has been limited study of the specific metabolic correlates of these isoforms in humans. Thus, our objective was to evaluate the associations of these adiponectin isoforms with metabolic and anthropometric parameters.

Design/Participants/Setting: A total of 53 diabetic and 68 nondiabetic subjects attending outpatient clinics underwent cross-sectional metabolic characterization. Circulating levels of HMW, hexameric, and trimeric adiponectin were measured using a multimeric adiponectin ELISA based upon selective protease-mediated digestion.

Results: On Spearman univariate analysis, both total and HMW adiponectin levels were inversely associated with body mass index, fasting glucose, homeostasis model of assessment of insulin resistance, triglycerides, and alanine aminotransferase (ALT) (all $|r| \geq 0.22$; $P < 0.05$), with the HMW isoform also positively correlated with high-density lipoprotein cholesterol ($r = 0.19$; $P = 0.036$). In contrast, hexameric and trimeric adiponectin were significantly associated with only body mass index ($r = -0.23$; $P = 0.0102$) and mid-upper arm circumference ($r = 0.21$; $P = 0.039$), respectively. On separate forward stepwise multiple linear regression analyses, fasting glucose and ALT emerged as independent, negative covariates of both total and HMW adiponectin, whereas no independent covariates of hexameric and trimeric adiponectin were identified. Furthermore, after adjustment for age, gender, and diabetes, mean ALT was highest in subjects in the lowest tertile of HMW adiponectin, followed in turn by the middle and highest tertiles, respectively (trend $P = 0.028$).

Conclusions: HMW adiponectin, but not hexameric or trimeric, tracks with the metabolic correlates of total adiponectin. Furthermore, an independent inverse association exists between ALT and HMW adiponectin. **(*J Clin Endocrinol Metab* 92: 4313–4318, 2007)**

ADIPONECTIN IS ONE of the most abundant plasma proteins and possesses antidiabetic properties due to insulin-mimetic and insulin-sensitizing actions (1–3). Whereas circulating levels of adipokines typically show a positive correlation with body mass index (BMI), decreased total adiponectin levels are observed in obesity and in metabolic disorders, including type 2 diabetes, nonalcoholic fatty liver disease, and the metabolic syndrome. Indeed, there is currently intense interest in the role of adiponectin in the pathophysiology of the metabolic syndrome and as a useful biomarker in this respect (3, 4). However, analysis of adiponectin function and regulation is complicated by the fact that the monomeric gene product is not found in the circulation. Instead, adiponectin undergoes extensive posttranslational modification (5, 6) and circulates in trimeric, hexameric, and oligomeric (18-mer) forms (5). Furthermore, basic research studies have shown that the various multimeric forms of adiponectin may mediate distinct physiological effects (1–3).

The vast majority of clinical studies published to date have evaluated correlations between total adiponectin levels and various markers of the metabolic syndrome. However, in the context of recent advances in our understanding of adiponectin structure and function, it has been suggested that assessment of total adiponectin may be insufficient and that analysis of the relative levels of the multimeric forms should be undertaken in relation to physiological parameters (7). However, to date, the metabolic correlates of oligomeric, hexameric, and trimeric adiponectin have not been extensively studied in humans. Indeed, establishing the specific clinical correlates of each multimer may be of particular value given the current need for more accurate risk assessment markers

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Abbreviations: ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model of assessment of insulin resistance; HMW, high molecular weight; LDL-C, low-density lipoprotein cholesterol; LMW, low molecular weight; MMW, middle molecular weight; TC, total cholesterol; TG, triglyceride.

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in the metabolic syndrome (8). Therefore, a particular strength of our current study is the detailed analysis of adiponectin multimer levels in circulation, and their correlation with metabolic and anthropometric measures.

We have used a recently developed ELISA, based upon selective protease-mediated digestion of adiponectin (9, 10), to undertake quantitative analysis of each multimeric form of adiponectin in human plasma. We determined the circulating levels of oligomeric [high molecular weight (HMW)], hexameric [middle molecular weight (MMW)], and trimeric [low molecular weight (LMW)] adiponectin in a cohort of Thai patients and evaluated the relationships among these isoforms and a variety of biochemical and anthropometric measures associated with the metabolic syndrome.

Subjects and Methods

A total of 121 individuals participated in this cross-sectional study. The participants were: 1) volunteers from a diabetes mellitus outpatient clinic of the Burapha University Health Center, Thailand; and 2) healthy volunteers from the villages around the health center, representing the same catchment area from which the diabetic subjects for this study were recruited. All diabetic participants had type 2 diabetes diagnosed by a physician, and confirmed at recruitment by biochemical testing and clinical examination by study physicians. Exclusion criteria included current use of insulin, thus excluding individuals with type 1 diabetes mellitus, and previous history of any chronic disease, including kidney, liver, and inflammatory disorders. None of the patients included in this study were being treated with a thiazolidinedione. The protocol was approved by the ethics committee of Burapha University, and all participants provided written informed consent.

Circulating total, HMW, MMW, and LMW adiponectin levels were determined using an ELISA from American Laboratory Products Company (ALPCO Diagnostics) (Salem, NH). This system is capable of quantifying HMW, MMW, LMW, and total adiponectin in a single ELISA, and is advantageous because previously, the various oligomeric forms of adiponectin were fractionated and quantified by laborious techniques, including velocity sedimentation in sucrose gradients, HPLC, fast protein liquid chromatography, and Western blot analyses. S_A was calculated as the ratio of HMW to total adiponectin, expressed as a percentage, as originally defined (7). RIA from LINCO Research (St. Charles, MO) was used to determine serum insulin and resistin levels. Plasma glucose was measured by the enzymatic colorimetric method by the method of Ware and Marbach (11). The homeostasis model of assessment of insulin resistance (HOMA-IR) score was calculated as fasting insulin (μU/ml) times fasting glucose (mM/liter) divided by 22.5. Fasting blood sugar and lipid profile determinations were done on the same day after blood collection, whereas plasma was stored at −70 C for insulin determination. Serum creatinine was determined by standard colorimetry, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were determined by enzymatic methods as previously described (12). Total cholesterol (TC) was determined by a colorimetric method. Triglyceride (TG) levels were determined by an enzymatic colorimetric test with lipid clearing factor (glycerol phosphate oxidase phenol 4-aminoantipyrine peroxidase method). Chylomicrons, very low-density lipoprotein cholesterol (LDL-C), and LDL-C were removed from blood plasma by a precipitation method in adding phosphotungstic acid and magnesium chloride to the plasma. After centrifugation of the remaining plasma, high-density lipoprotein cholesterol (HDL-C) concentrations in the supernatant fluid were measured. The determination was done in the same way as TC using the CHOD-PAP method. LDL-C was calculated according to the formula LDL-C = TC − HDL-C − (TG/5) mg/dl.

Weight, height, waist circumference, hip circumference, mid-upper arm circumference, and triceps skinfold thickness were assessed. The BMI and waist-hip ratio were graded and calculated according to the World Health Organization Expert Committee.

Statistical analysis

All statistical analyses were conducted using the Statistical Analysis System (version 9.1; SAS Institute Inc., Cary, NC). In Table 1 continuous variables are presented as mean followed by SD, and categorical variables are presented as percentages. The distributions of AST, ALT, TGs, fasting glucose, HOMA-IR, resistin, and total, HMW, MMW, and LMW adiponectin were skewed, and, thus, medians and interquartile ranges are presented for these variables in Table 1. The natural logarithmic transformations of these skewed variables (AST, ALT, TGs, fasting glucose, HOMA-IR, resistin, and total, HMW, MMW, and LMW adiponectin) were used in subsequent multivariate analyses, with back-transformed values presented where applicable. In Table 1, differences between the diabetic and nondiabetic groups were determined by the *t* and χ^2 tests for continuous and categorical variables, respectively. Spearman correlation analysis was used to assess the univariate associations of clinical and metabolic variables with total, HMW, MMW, and LMW adiponectin, respectively, in the full data set (Table 2). This approach enabled the assessment of associations of adiponectin multimeric forms across the spectrum of glucose tolerance, and provided maximum statistical power for subsequent multivariate adjustment. Forward stepwise multiple linear regression analysis was used to determine factors independently associated with total, HMW, MMW, and LMW adiponectin, respectively (Table 3). Covariates considered for selection in this analysis were chosen on the basis of either: 1) significant association with adiponectin (total, HMW, MMW, or LMW) in the univariate analysis (BMI, mid-upper arm circumference, fasting glucose, HOMA-IR, HDL, TGs, ALT); or 2) known/suspected clinical or biological relevance (age, gender). Analysis of covariance was used to assess differences in mean ALT between study participants stratified by tertiles of HMW adiponectin, after adjustment for age, gender, and diabetes (Fig. 1).

Results

Table 1 shows demographic, clinical, and metabolic characteristics of the 121 study participants stratified by the presence (n = 53) or absence (n = 68) of diabetes. Subjects with diabetes were older than their nondiabetic peers. As expected, the diabetic participants exhibited greater adiposity (BMI, waist circumference, waist to hip ratio, mid-upper arm circumference), higher fasting glucose, and greater insulin resistance (HOMA-IR). In addition, the diabetic group had higher serum creatinine, TGs, LDL, and TC. There were trends toward higher total and LMW adiponectin in the nondiabetic subjects, with no significant differences between the groups in S_A, HMW, and MMW adiponectin.

On Spearman univariate correlation analysis (Table 2), total adiponectin was inversely and significantly associated with BMI, fasting glucose, HOMA-IR, TGs, and ALT. HMW adiponectin showed similar inverse associations with each of these five variables, in addition to a positive correlation with HDL-C. In contrast, MMW adiponectin was only significantly associated with BMI, whereas LMW adiponectin was only related to mid-upper arm circumference. Similar relationships were generally noted upon adjustment for age, gender, and diabetes (data not shown).

Forward stepwise multiple linear regression analysis was performed to determine independent correlates of total, HMW, MMW, and LMW adiponectin. Covariates considered for selection in these models included age, gender, and the univariate correlates identified in Table 2 (BMI, mid-upper arm circumference, fasting glucose, HOMA-IR, HDL, TGs, and ALT). On this analysis, fasting glucose and ALT emerged as independent, negative covariates of dependent variable total adiponectin, whereas age was a positive determinant (Table 3). The same three covariates were identified as in-

TABLE 1. Demographic, clinical, and metabolic characteristics of participants stratified by presence or absence of diabetes

	No diabetes (n = 68)	Diabetes (n = 53)	*P* value
Demographics			
Age (yr)	50.6 (11.2)	57.2 (9.4)	0.0009
Gender (M/F)	25%/75%	13%/87%	0.1080
Anthropometry			
BMI (kg/m^2)	24.8(4.4)	26.9 (4.6)	0.0124
Waist (cm)	84.0 (10.5)	93.3 (8.9)	<0.0001
Waist to hip ratio	0.88 (0.05)	0.92 (0.06)	0.0001
Triceps skinfold (mm)	26.8 (10.1)	24.7 (6.2)	0.2320
Mid-upper arm circumference (cm)	29.9 (3.6)	32.0 (4.0)	0.0077
Liver/renal			
Creatinine (μmol/liter)	74.6 ([19.2)	94.7 (34.8)	<0.0001
AST (U/liter)	27.5 (23.0–36.5)	33.0 (26–39)	0.1055
ALT (U/liter)	23.5 (17.0–30.5)	24.5 (18–36)	0.2325
Traditional risk factors			
Systolic BP (mm Hg)	128.3 (27.9)	137.4 (17.1)	0.0543
Diastolic BP (mm Hg)	80.9 (16.1)	84.4 (11.0)	0.2173
TC (mmol/liter)	5.64 (1.27)	6.50 (1.83)	0.0026
LDL (mmol/liter)	3.77 (1.30)	4.42 (1.88)	0.0419
HDL (mmol/liter)	1.25 (0.33)	1.18 (0.24)	0.1734
TGs (mmol/liter)	1.32 (0.88–1.94)	1.88 (1.25–2.58)	0.0039
HOMA-IR	3.0 (2.1–3.9)	6.5 (3.9–10.4)	<0.0001
Fasting glucose (mmol/liter)	4.5 (4.2–5.3)	7.3 (6.0–11.6)	<0.0001
Nontraditional risk factors			
Resistin (ng/ml)	1.97 (1.30–3.42)	2.72 (1.86–4.63)	0.1845
Total adiponectin (μg/ml)	6.12 (4.82–8.33)	5.35 (4.48–6.23)	0.0728
HMW adiponectin (μg/ml)	3.82 (2.81–5.23)	3.16 (2.49–4.02)	0.1393
MMW adiponectin (μg/ml)	1.25 (0.71–1.52)	1.19 (0.72–1.59)	0.3892
LMW adiponectin (μg/ml)	1.19 (0.88–1.86)	0.98 (0.69–1.41)	0.0523
S_A (%)	60.6 (11.7)	60.0 (10.2)	0.7868

Data are presented as mean followed by SD in *parentheses* except for: 1) gender (presented as percentages); and 2) AST, ALT, TGs, HOMA-IR, fasting glucose, resistin, and total, HMW, MMW, and LMW adiponectin (presented as median followed by interquartile range in *parentheses*). *P* values refer to differences between groups as determined by *t* and χ^2 tests for continuous and categorical variables, respectively. F, Female; M, male.

dependently associated with HMW adiponectin. In contrast, no independent correlates were found for MMW and LMW adiponectin (data not shown).

Having noted that ALT was the strongest univariate correlate of HMW adiponectin (Table 2; r = −0.33; $P = 0.0002$) and an independent covariate of this multimeric form on multiple linear regression analysis (Table 3), we sought to evaluate further this relationship. Indeed, after adjustment for age, gender, and diabetes status, mean ALT was highest in subjects in the lowest tertile of HMW adiponectin (28), followed in turn by the middle tertile (24), and highest tertile (21), respectively (trend $P = 0.0283$) (Fig. 1).

Discussion

A multitude of previous studies have consistently characterized hypoadiponectinemia as an independent biomarker of the metabolic syndrome (13–22). These studies have exclusively measured total circulating adiponectin levels, yet it has become apparent that the multimeric forms of adiponectin in circulation require independent analysis (1). Accordingly, within the last year or so, several studies have begun to address the clinical significance of adiponectin multimers. A recent study based upon calculation of S_A values from Western blot analysis of serum has suggested that

TABLE 2. Spearman univariate correlations of total, HMW, MMW, and LMW adiponectin

	Total adiponectin		HMW adiponectin		MMW adiponectin		LMW adiponectin	
	r value	*P* value	r value	*P* value	r value	*P* value	r value	*P* value
BMI	**−0.28**	**0.0018**	**−0.29**	**0.0010**	**−0.23**	**0.0102**	0.12	0.2053
Waist-to-hip ratio	−0.15	0.1507	−0.18	0.0794	0.05	0.5962	−0.02	0.8768
Mid-upper arm circ	−0.12	0.2512	−0.16	0.1133	−0.13	0.1882	**0.21**	**0.0394**
ALT	**−0.24**	**0.0072**	**−0.33**	**0.0002**	0.12	0.2058	−0.07	0.4461
Systolic BP	−0.01	0.9098	−0.02	0.8579	−0.09	0.3817	0.05	0.6073
LDL	0.03	0.7992	0.01	0.9595	0.16	0.1052	−0.16	0.1139
HDL	0.15	0.1108	**0.19**	**0.0363**	0	0.9978	0.09	0.3531
TGs	**−0.22**	**0.0179**	**−0.24**	**0.0089**	0.03	0.7855	−0.04	0.6353
HOMA-IR	**−0.26**	**0.0068**	**−0.25**	**0.0093**	−0.13	0.1882	0	0.9833
Fasting glucose	**−0.29**	**0.0024**	**−0.26**	**0.0066**	−0.06	0.5632	−0.15	0.1198
Resistin	−0.11	0.2584	−0.16	0.0967	0.07	0.4881	−0.03	0.7279

Bold indicates $P < 0.05$. BP, Blood pressure; circ, circumference.

TABLE 3. Forward stepwise multiple linear regression models of dependent variable total and HMW adiponectin

Total adiponectin				HMW adiponectin			
Variable	Estimate	F	*P*	Variable	Estimate	F	*P*
Log fasting glucose	−0.27219	10.1	0,0020	Log fasting glucose	−0.32445	9.8	0.0023
Log ALT	−0.14723	5.1	0.0263	Log ALT	−0.20996	7.1	0.0092
Age	0.00785	4.6	0.0350	Age	0.01383	9.1	0.0032
Model r^2 = 16.1%				Model r^2 = 24.7%			

Covariates considered for selection in each model: age, gender, BMI, mid-upper arm circumference, fasting glucose, HOMA-IR, HDL, TGs, and ALT.

HMW is the active form (23). In a study of 298 Japanese patients, the ratio of plasma HMW to total adiponectin was found to be a stronger predictor of insulin resistance than total adiponectin (9). More recently, it was suggested that the quantity of HMW, rather than total adiponectin or S_A, correlated best with lipoprotein alterations characteristic of the metabolic syndrome (24). The current study is among the first to use accurate quantitative analysis of adiponectin multimers to determine specifically how the HMW, hexameric, and trimeric forms of adiponectin correlate with a wide array of anthropometric and clinical variables in obese and diabetic individuals.

Adiponectin is known to mediate insulin-mimetic effects on liver to suppress glucose production and on skeletal muscle to enhance glucose uptake (2). However, studies to date have not clearly addressed the significance of each multimeric form of the protein, and with the discovery of adiponectin receptor isoforms exhibiting different affinities for adiponectin multimers and tissue-specific distributions, it is clear that the physiological regulation of adiponectin bioactivity is complex and highly dependent on multimeric composition. Indeed, there is currently great interest in determining the intracellular mechanisms controlling the oligomerization and secretion of adiponectin in adipocytes (25).

As expected, we observed that total adiponectin, as well as HMW and MMW, decreased as BMI increased. The circulating level of trimeric adiponectin is known to be much lower than hexameric or HMW forms, and in our study we did not find a significant correlation between this LMW form of adiponectin and BMI. Indeed, multiple linear regression analyses failed to highlight a significant correlate with LMW or MMW adiponectin among those variables measured in our study. This does not exclude the possibility that these forms of adiponectin mediate important physiological effects, and further studies are likely to highlight these roles. Interestingly, a recent study supports our conclusion that the metabolic effects of adiponectin are mediated via the HMW form because after biliopancreatic diversion surgery, there was a significant increase in both total and HMW adiponectin, and improvement in metabolic profile (26). Another study of obese individuals found that circulating levels of all multimers were effectively increased via diet-induced weight loss (27).

Our findings indicate that both total and HMW adiponectin correlated inversely with insulin resistance, and further analysis by linear regression models showed that total and HMW were significantly inversely associated with increased fasting blood glucose levels. This is in agreement with previous work showing that the quantity of HMW adiponectin in serum is associated with increased insulin sensitivity, reduced abdominal fat, and high basal lipid oxidation (24). However, in the same study, total adiponectin (r = 0.45), HMW (r = 0.47), LMW (r = 0.31), and HMW to total adiponectin ratio (r = 0.29) were significantly correlated with insulin-stimulated glucose disposal rate. It has also been suggested that the improved insulin sensitivity occurring as a result of diet-induced weight loss was associated with an increased amount of HMW, MMW, and LMW adiponectin complexes in plasma (27).

We also observed that total and HMW adiponectin inversely correlated with TG levels and that HMW positively correlated with HDL levels. These findings are in agreement with a study by Bobbert *et al.* (28), demonstrating that total adiponectin, and especially HMW adiponectin, were closely

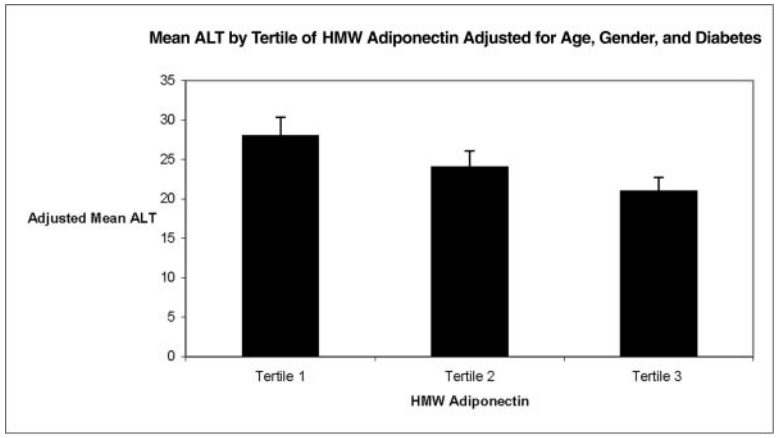

FIG. 1. Plot of mean ALT by tertile of HMW adiponectin, adjusted for age, gender, and diabetes.

related to circulating HDL-C (28). In a study of 182 Korean subjects, Kim *et al.* (29) recently showed that HDL-C, sex, and HOMA-IR were associated independently with plasma adiponectin levels. Finally, reduced quantities of HMW were shown to recapitulate independently the lipoprotein subclass profile associated with insulin resistance after correcting for glucose disposal rate and BMI (24).

A particularly intriguing aspect of our analyses is that serum ALT was the strongest univariate correlate of HMW adiponectin, and an independent covariate of both total and HMW adiponectin on multiple linear regression analysis. Furthermore, after adjustment for age, gender, and diabetes status, mean ALT levels showed a progressive decrease as HMW adiponectin levels increased. It is well established that, in the absence of other causes, overweight and obesity increase the risk of nonalcoholic fatty liver disease (30), which is recognized as a leading cause of elevated serum ALT (31). In a recent study of patients with type 2 diabetes, it was observed that ALT levels were inversely correlated with total adiponectin, leading the authors to conclude that hypoadiponectinemia was linked with liver injury in these individuals (32). Even in juveniles, hepatic steatosis has been associated with hypoadiponectinemia (33). Several additional studies have demonstrated an inverse correlation between total adiponectin and ALT levels (34–38). Our findings extend these data by demonstrating that it is specifically the HMW form of adiponectin that is inversely and independently correlated with ALT, and suggest that deficiency of this isoform may be associated with liver injury. Further study of this novel relationship between HMW adiponectin and ALT is warranted.

This analysis must be interpreted in the context of certain limitations. First, the sample size is relatively modest (n = 121), which may limit the statistical power for detecting associations. Second, HOMA-IR has limitations as a measure of insulin resistance. However, in this context it is encouraging that the previously reported inverse associations between insulin resistance and total adiponectin and HMW adiponectin, respectively, were indeed observed using HOMA-IR in this analysis. Finally, the cross-sectional nature of this study precludes comment on causality in the relationships under study. Nevertheless, this study represents one of the first investigations of the specific relationships of each of HMW, hexameric, and trimeric adiponectin with metabolic parameters, and should subsequently lead to further studies.

In summary, we have demonstrated that HMW and total adiponectin share similar metabolic correlates, in contrast to the hexameric and trimeric forms. Furthermore, an independent inverse association was demonstrated between serum ALT and HMW adiponectin. Overall, these data support an emerging consensus that the HMW complex is the major physiological determinant of the metabolic effects of adiponectin.

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