ORIGINAL RESEARCH

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Adiponectin/leptin ratio and Metabolic Syndrome in a Mexican American population

Abstract

Objective: Adiponectin and leptin play critical roles in the development of Metabolic Syndrome (MetS). This study was designed to assess the feasibility of using circulating levels of adiponectin and leptin for the early diagnosis of MetS.

Methods: A cross-sectional study was performed using data from 367 participants randomly selected from a well-characterized cohort of Mexican-Americans living at the US-Mexico border.

Results: Significant differences in circulating levels of adiponectin and leptin were observed between males and females. Adiponectin/leptin correlated significantly with MetS in this population. A receiver-operator characteristic (ROC) analysis demonstrated that adiponectin/leptin showed a high sensitivity (70.9% for males, 78.9% for females) and specificity (90.2% for males and 69.8% for females) for the diagnosis of MetS, independent of BMI measurements.

Conclusion: These data support the central role of adiponectin and leptin in MetS, and demonstrated that adiponectin/leptin can be used as a highly sensitive and specific biomarker for MetS.

Manuscript submitted 4th May, 2011
Manuscript accepted 11th August, 2011

Clin Invest Med 2011; 34 (5): E290-E297.

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Adipocytes-derived hormones, also known as adipokines, serve as mediators linking adipocyte dysfunction to Metabolic Syndrome (MetS). Two of the most studied adipokines, adiponectin and leptin, have been shown to be critical in the development of MetS [1,2]. Adiponectin, the most abundant adipokine in circulation, has direct effects on insulin sensitivity, glucose metabolism and central fat distribution. Adiponectin exerts its effect on glucose metabolism by regulating mRNA expression of the hepatic gluconeogenic enzymes [3,4]. Lower levels of adiponectin are associated with insulin resistance and endothelial cell dysfunction, and are also observed in pro-inflammatory and prothrombotic states. Leptin, on the other hand plays a critical role in regulating food intake [5], maintaining energy expenditure [6] and regulating immune function [7]. Increased leptin levels in plasma suggest the development of leptin resistance; an early manifestation of MetS [8].

Because of their critical roles in the development of MetS, adiponectin, leptin and the adiponectin/leptin ratio have been suggested to be useful serum markers for diagnosis of MetS [9-11]. Adiponectin and leptin have been evaluated independently for their ability to diagnose MetS in several ethnic and racial backgrounds, such as Chinese [11,12], Japanese, Caucasian [12] and Korean [9], using a case-control design. Despite the higher prevalence of MetS in Mexican-Americans [13], no study has assessed the relative importance of adiponectin, leptin and adiponectin/leptin ratio in MetS in this population. In the present cross-sectional study, the performance of circulating levels of adiponectin and leptin and adiponectin/leptin ratio to diagnose MetS in a Mexican-American population residing on the Texas-Mexico border. This population presents with severe health issues, including obesity, type 2 diabetes and cardiovascular disease [14,15]. Given these health issues, any efforts to provide early diagnoses of MetS would allow for early treatment and would reduce long-term complications.

Methods

Study population

The study was conducted on 367 randomly selected individuals from the Cameron County Hispanic Cohort (CCHC) [14]. Written, informed consent was obtained from participants at the time of enrollment and the study was approved by the UT-Health Science Center, Institutional Review Board (IRB) and the Committee for the Protection of Human Subjects (CPHS). Characteristics of these participants are described in Table 1. The plasma specimen were obtained and stored as described previously [14].

TABLE 1. General characteristics of the 367 subjects

Attribute	Values
Age (yr, mean $\pm$ sd)	43.2 $\pm$ 15.9
Gender	Females=249; Males=118
BMI	30.7 $\pm$ 7.5
Waist circumference (cm)	
Female	99.4 $\pm$ 14.8
Male	102.0 $\pm$ 16.2
FPG (mg/dL)	111.8 $\pm$ 42.5
FPI (mU/L)	17.8 $\pm$ 18.3
HOMA-IR	5.1 $\pm$ 6.7
Total cholesterol(mg/dL)	172.7 $\pm$ 37.9
Serum triglycerides (mg/dL)	149.7 $\pm$ 147.2
Diastolic blood pressure (mmHg)	71.8 $\pm$ 10.5
Systolic blood pressure (mmHg)	116.9 $\pm$ 16.7
ALT (U/L)	41.8 $\pm$ 29.3
AST (U/L)	36.7 $\pm$ 23.6
MetS diagnosed by*	
ATP III	Females=121; Males=41
IDF	Females=127; Males=52
CAD	Females=129; Males=57

* Abbreviations: ATP III, Adult Treatment Panel III; IDF, International Diabetes Federation; CAD, computer-aided diagnosis.

Measurement of adiponectin and leptin

The levels of total adiponectin and total leptin were measured in frozen plasma specimen using a multiplex ELISA (Milliplex Map, Millipore Corp., Temecula, CA) and read in a Luminex 200 system (Luminex Corp., Austin, TX). The two adipokines were run in separate panels because of the dilution factor. The panels were evaluated for the coefficient of variation, linearity of dilution and spike/recovery. The inter-assay variability for adiponectin was 5.6% and intra-assay variation was 15%. The accuracy (spike recovery) was measured by using known standards where data represent the mean percent recovery of the different levels of spiked standards in serum matrices in several independent experiments. Values of adiponectin were reported as micrograms/ml (μ g/ml) and leptin as picograms/ml (pg/ml).

K-means classification for MetS

The two official guidelines available for the diagnosis of MetS are the Adult Treatment Panel III (ATP III) guidelines (<http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf>) and the International Diabetes Federation (IDF) guidelines (http://www.idf.org/webdata/docs/IDFMeta_def).

Final.pdf). Many individuals with suspected MetS in our CCHC did not meet the definition criteria for MetS proposed in these guidelines. We therefore used the unsupervised learning algorithm, the K-means clustering method, for a computer-aided diagnosis (CAD) of MetS. The K-means classification was based on five groups of variables: (i) body mass index (BMI) and waste circumference; (ii) fasting plasma glucose (FPG), fasting plasma insulin (FPI) and homeostasis model assessment estimated insulin resistance (HOMA-IR) index; (iii) fasting serum triglycerides and total cholesterol; (iv) blood pressure; and, (v) serum alanine aminotransferase (ALT) and aspartate amino transferase (AST) levels. The reference ranges of BMI, waist circumference, serum triglycerides and total cholesterol and blood pressure were based on the recommendation of the American Heart Association (www.americanheart.org). The reference range of FPG was based on the 2010 Clinical Practice Recommendations of the American Diabetes Association (ADA) [16]. The reference for HOMA-IR was based on previous research using the CCHC that included 1854 Mexican-Americans (manuscript submitted to Diabetes Care). The references ranges are listed in Supplementary Table 1.

Receiver operator characteristic (ROC) analysis

To assess the diagnostic value of adiponectin/leptin for diagnosis of MetS, receiver operator characteristics (ROC) analyses were performed based on the sensitivity and specificity values of a series of cutoffs of $-\log_{10}$ (adiponectin/leptin). In the investigation of a new diagnostic marker of disease, ROC analysis provides a direct assessment of the sensitivity (true positive rate) and the specificity (true negative rate) of using this marker for diagnosis. The performances of a series of cutoffs were assessed using the maximum Matthews correlation coefficient (MCC).

Statistical method

K-means classification, linear regression and independent sample t-tests used in this study were performed using the SPSS Statistics version 19 (IBM Corp., Chicago, IL).

Results

Table 1 summarizes the basic characteristics of our study population. Significant differences were observed in circulating levels of adiponectin and leptin between males and females (adiponectin, males 12.78 ± 6.68 pg/ml, females 17.29 ± 8.79 pg/ml, $P = 1.20 \times 10^{-6}$; leptin, males 11190 ± 9631 ng/ml, females 31408 ± 27676 ng/ml, $P = 1.47 \times 10^{-13}$; $-\log_{10}$ (adiponectin/leptin), males 2.82 ± 0.52 , females 3.19 ± 0.39 , $P = 2.13 \times 10^{-13}$;

TABLE 2. The specificity and sensitivity for MetS of the series of $-\log_{10}$ (adiponectin/leptin ratio) cutoff values

Cutoff	Sensitivity	Specificity	MCC
Males			
1.4	1	0.033	0.127
1.5	1	0.049	0.156
1.6	1	0.049	0.156
1.7	1	0.098	0.224
1.8	1	0.115	0.243
1.9	1	0.164	0.294
2	1	0.164	0.294
2.1	1	0.18	0.31
2.2	1	0.246	0.369
2.3	1	0.295	0.41
2.4	0.965	0.344	0.39
2.5	0.947	0.443	0.448
2.6	0.912	0.525	0.471
2.7	0.895	0.639	0.549
2.8	0.86	0.721	0.585
2.9	0.807	0.803	0.61
3	0.719	0.902	0.634
3.1	0.579	0.951	0.575
3.2	0.421	0.984	0.495
3.3	0.351	0.984	0.437
3.4	0.193	0.984	0.292
3.5	0.123	1	0.26
3.6	0.088	1	0.218
3.7	0.053	1	0.167
3.8	0.035	1	0.136
Females			
1.9	1	0.008	0.063
2	1	0.008	0.063
2.1	1	0.024	0.109
2.2	1	0.04	0.141
2.3	1	0.063	0.18
2.4	1	0.071	0.191
2.5	1	0.095	0.222
2.6	0.984	0.111	0.193
2.7	0.959	0.198	0.242
2.8	0.951	0.254	0.285
2.9	0.927	0.317	0.307
3	0.886	0.429	0.353
3.1	0.829	0.54	0.385
3.2	0.789	0.698	0.489
3.3	0.626	0.833	0.47
3.4	0.488	0.929	0.465
3.5	0.35	0.937	0.354
3.6	0.244	0.976	0.325
3.7	0.122	0.992	0.232
3.8	0.098	0.992	0.201
3.9	0.073	1	0.196
4	0.049	1	0.159

FIGURE 1. The ROC analysis for the association of $-\log_{10}(\text{adiponectin/leptin ratio})$ and MetS. X-axis represents false positive (FP) rate (or 1-specificity); Y-axis represents true positive (TP) rate (sensitivity). (a) Males with MetS classified by K-means; (b) Females with MetS classified by K-means; (c) Males with MetS diagnosed by the IDF standard; (d) Females with MetS diagnosed by the IDF standard; (e) Males with MetS diagnosed by the ATP III standard; (f) Females with MetS diagnosed by the ATP III standard. As an independent biomarker, the adiponectin/leptin ratio has highly sensitive and specific association with computer-aided diagnosis (CAD) of MetS. Instead, the adiponectin/leptin ratio is poorly associated with MetS diagnosed by the official guidelines of the IDF and the ATP III. Our results highlight both the central role of adiponectin and leptin in MetS, and deficiencies in the current official standards in the diagnosis of MetS.

Supplementary Table 2). In addition to gender, age also correlated with the levels of adiponectin and leptin (adiponectin, males $r=0.206$, $P=0.25$, females $r=0.300$, $P=1.44 \times 10^{-6}$; leptin, males $r=0.208$, $P=0.024$, females $r=0.215$, $P=6.38 \times 10^{-4}$). No obvious correlation was observed between adiponectin/leptin and age ($-\log_{10}(\text{adiponectin/leptin})$, males $r=0.005$, $P=0.955$, females $r=0.009$, $P=0.893$), which suggested that adiponectin/leptin, was a better diagnostic marker than either of the adipokines alone (Supplementary Table 3). Consequently, the population was stratified by gender to investigate the association between adiponectin/leptin and MetS. The observation that adiponectin/leptin is a better marker than either adipokine or leptin alone was further supported by our test of their correlations with MetS diagnosis: after adjusting for age and gender, the correlation between leptin levels and MetS diagnosis was $r=0.294$, and the correlation between adiponectin levels and MetS diagnosis was $r=0.360$, whereas the correlation between adiponectin/leptin and MetS diagnosis was $r=0.500$.

Secondly, the performance of the K-means clustering of MetS was assessed. Major components of MetS between the two K-means clusters were compared; i.e., the MetS cluster *vs.* the healthy cluster. Results indicated significant differences in components of MetS between those two clusters as assessed by K-means (Supplementary Table 4: males and Supplementary Table 5: females). Further analysis showed that the K-means classification of MetS is significantly correlated with the IDF and ATP III guidelines (K-means *vs.* IDF, males $r=0.508$, $P=4.19 \times 10^{-9}$, females $r=0.470$, $P=4.19 \times 10^{-15}$; K-means *vs.* ATP III, males $r=0.912$, $P=1.72 \times 10^{-13}$, females $r=0.502$, $P=2.71 \times 10^{-17}$). Compared with the IDF and ATP III guidelines, the K-means classification was more closely associated with the adiponectin/leptin ratio (MetS diagnosis *vs.* K-means, males $r=0.628$, $P=2.79 \times 10^{-14}$, females $r=0.491$, $P=1.72 \times 10^{-16}$; MetS *vs.* IDF, males $r=0.399$, $P=7.84 \times 10^{-6}$, females $r=0.232$, $P=2.20 \times 10^{-4}$; MetS *vs.* ATP III, males $r=0.471$, $P=7.44 \times 10^{-8}$, females $r=0.260$, $P=3.34 \times 10^{-5}$).

A receiver operator characteristic (ROC) analysis was performed to assess the performance of adiponectin/leptin as a diagnostic marker for MetS (Fig 1, Table 2). The ROC analysis indicated that, in males, $-\log_{10}(\text{adiponectin/leptin})$ at the cut-off of 3.0 had the maximum MCC. With this cutoff, $-\log_{10}(\text{adiponectin/leptin})$ has a sensitivity of 71.9% and a specificity of 90.2% for the diagnosis of MetS. A total of 39.8% males in our study population had $-\log_{10}(\text{adiponectin/leptin}) \geq 3.0$, a cut-off value that is suggestive of MetS. For females, $-\log_{10}(\text{adiponectin/leptin})$ at the cutoff of 3.2 had the maximum MCC, where $-\log_{10}(\text{adiponectin/leptin})$ can be used to

assist the diagnosis of MetS with a sensitivity of 78.9% and a specificity of 69.8%. A total of 54.2% of females in our study had $-\log_{10}(\text{adiponectin/leptin})$ of ≥ 3.2 , suggesting MetS. These robust results of the ROC analysis with high sensitivity and specificity highlighted the adiponectin/leptin as a valuable biomarker for diagnosis of MetS. In addition, our analysis demonstrated the role of adiponectin/leptin for the diagnosis of MetS, independent of BMI. Taking BMI into consideration, the correlation between adiponectin/leptin and the diagnosis of the MetS has $r=0.301$, $p=4.12 \times 10^{-9}$.

Conclusion

Because of their critical roles in MetS, adiponectin, leptin, especially their ratio, have been proposed as potential serum markers for MetS [9-12]. In this study, both adiponectin and leptin were found to be independently associated with age, while the ratio of two remained unaffected by age. Aging is an important biological factor for MetS and has been shown to be associated with a pro-inflammatory state and subsequent alterations in levels of metabolic markers, including adiponectin and leptin. The observation that age was independently associated with leptin and adiponectin, suggests that age is a confounder, when either marker is used alone. As the ratio of the two markers is independent of age, it would serve as a better diagnostic marker of MetS than the two adipokines separately.

The remarkable sensitivity and specificity observed in our study indicates that adiponectin/leptin is a valuable marker for MetS - a pathological condition for which there is currently no sensitive diagnostic test. Adiponectin/leptin and the K-means classification of MetS, which are two independent diagnostic systems, showed significantly high association with each other. This highly specific association highlights the central role of adiponectin/leptin in predicting MetS. The strong association between adiponectin/leptin and the Computer Aided Diagnosis (CAD) of MetS also suggests that the IDF and ATP III guidelines lack the sensitivity required to diagnose MetS.

In order to prevent the downstream effects of MetS, it is essential to identify the disease in its early stages and to initiate early treatment. Supplementary to previously conducted case-control studies [11,17,18], this cross-sectional study provides an empirical assessment of adiponectin/leptin as a potentially valuable biomarker for diagnosing MetS.

Acknowledgments

We thank our cohort recruitment team, particularly Rocío Uribe, Elizabeth Braunstein and Julie Ramirez, at the Hispanic Health Research Center in the Lower Rio Grande Valley. We

also thank Marcela Montemayor and other laboratory staff, at the University of Texas School of Public Health Brownsville Campus, for their contribution, and Christina Villarreal, at the University of Texas School of Public Health Brownsville Campus, for administrative support. We thank Valley Baptist Medical Center, Brownsville for providing us space for our Center for Clinical and Translational Science Clinical Research Unit. We also thank the community of Brownsville and the participants who so willingly participated in this study in their city.

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Supplemental Material

Supplementary Table 1. Reference ranges of the MetS correlated factors

Attribute	Reference values ^b
BMI ^a	1: Normal<25; 2: Overweight 25.0-29.9; 3: Obese 30-39.9; 4: Morbid obese ≥40
Waist circumference (cm) ^a	Males 1: Normal<102; 2: High≥102 Females 1: Normal<88; 2: High≥88
FPG (mg/dL) ^b	1: Normal<100; 2: Medium high 100-125; 3: High >125
FPI (mU/L)	1: Normal<12; 2: High≥12
HOMA-IR	1: Normal<2.60; 2: Medium high 2.60-3.80; 3: High >3.80
Serum triglycerides (mg/dL) ^a	1: Normal<150; 2: Borderline high=150-199; 3: High=200-499; 4: Very high≥500
Diastolic blood pressure (mmHg) ^a	1: Normal<80; 2: Prehypertension=80-89; 3: Hypertension Stage 1=90-99; 4: Hypertension Stage 2≥100
Systolic blood pressure (mmHg) ^a	1: Normal<120; 2: Prehypertension=120-139; 3: Hypertension Stage 1=140-159; 4: Hypertension Stage 2≥160
ALT (U/L)	1: Normal≤40; 2: High>40
AST (U/L)	1: Normal≤40; 2: High>40
Total cholesterol(mg/dL) ^a	1: Normal<200; 2: Borderline high=200-239; 3: High≥240

^a Reference ranges were based on the recommendations of the American Heart Association (www.americanheart.org); ^b A number was assigned to each category of each factor for the K-means analysis;

^b Reference ranges were based on the 2010 Clinical Practice Recommendations of the American Diabetes Association (ADA). Source of this table: Qu et al. The definition of insulin resistance using HOMA-IR for Americans of Mexican Descent using machine learning. *PLoS ONE*, 6(6): e21041.

Supplementary Table 4. K-means classification of the 118 males^a

Attribute	MetS group center (n=57)	Healthy group center (n=61)	ANOVA test P value
BMI	2.81	1.92	1.97×10^{-10}
Waist circumference	1.82	1.23	1.20×10^{-12}
FPG	1.91	1.41	1.35×10^{-4}
FPI	1.91	1.25	7.81×10^{-17}
HOMA-IR	2.82	1.41	1.31×10^{-28}
Serum triglycerides	2.14	1.18	4.15×10^{-9}
Total cholesterol	1.28	1.18	0.257
Systolic blood pressure	1.46	1.31	0.179
Diastolic blood pressure	1.54	1.15	3.65×10^{-4}
ALT	1.54	1.41	0.161
AST	1.46	1.43	0.754

^a The categorization of each variable is as described in Supplementary Table 1 from our previous report [1]

Supplementary Table 2. Gender difference in adiponectin and leptin levels

Adipokine	Male (n=118)	Female (n=249)	Pvalue
Adiponectin (pg/ml)	12.78±6.68	17.29±8.79	1.20×10^{-6}
Leptin (ng/ml)	11190±9631	31408±27676	1.47×10^{-13}
-log ₁₀ (Adiponectin/Leptin)	2.82±0.52	3.19±0.39	2.13×10^{-13}

Mean +/- standard deviation. P values less than 0.05 considered significant.

Supplementary Table 3. Correlation of age with adiponectin and leptin

Adipokine	Male (n=118)	Female (n=249)
Adiponectin	r=0.206, P=0.025	r=0.300, P= 1.44×10^{-6}
Leptin	r=0.208, P=0.024	r=0.215, P= 6.38×10^{-4}
-log ₁₀ (Adiponectin/Leptin)	r=0.005, P=0.955	r=0.009, P=0.893

Supplementary Table 5. K-means classification of the 249females^a

Attribute	MetS group center (n=123)	Healthy group center (n=126)	ANOVA test P value
BMI	2.92	1.87	6.92×10^{-23}
Waist circumference	1.94	1.61	3.06×10^{-10}
FPG	1.94	1.27	3.45×10^{-15}
FPI	1.95	1.30	8.29×10^{-34}
HOMA-IR	2.80	1.50	2.11×10^{-48}
Serum triglycerides	1.69	1.29	2.69×10^{-5}
Total cholesterol	1.35	1.22	0.075
Systolic blood pressure	1.67	1.39	1.97×10^{-3}
Diastolic blood pressure	1.32	1.09	1.12×10^{-4}
ALT	1.35	1.10	2.52×10^{-6}
AST	1.28	1.15	0.014

^a The categorization of each variable is as described in Supplementary Table 1 from our previous report[1].

Supplemental Material

Supplemental Table 6. Correlation between K-means classification and the official standards of MetS diagnosis

K-means <i>vs.</i>	Males (n=118)	Females (n=249)
IDF	$r=0.508$, $P=4.19 \times 10^{-9}$	$r=0.470$, $P=4.19 \times 10^{-15}$
ATPIII	$r=0.912$, $P=1.72 \times 10^{-13}$	$r=0.502$, $P=2.71 \times 10^{-17}$

* The concordance between two diagnostic methods is shown as a correlation coefficient r ; $r=1$ represents two diagnostic methods are completely concordance in diagnosing MetS. P values are the statistical significance of each concordance test of two diagnostic methods.

Supplement Reference

1. Qu HQ, Li Q, Rentfro AR, Fisher-Hoch SP, McCormick JB (2011) The Definition of Insulin Resistance Using HOMA-IR for Americans of Mexican Descent Using Machine Learning. PLoS One 6: e21041

Supplemental Table 7. Correlation between $-\log_{10}(\text{adiponectin/leptin ratio})$ and MetS

MetS diagnosis	Males (n=118)	Females (n=249)
K-means	$r=0.628$, $P=2.79 \times 10^{-14}$	$r=0.491$, $P=1.72 \times 10^{-16}$
IDF	$r=0.399$, $P=7.84 \times 10^{-6}$	$r=0.232$, $P=2.20 \times 10^{-4}$
ATPIII	$r=0.471$, $P=7.44 \times 10^{-8}$	$r=0.260$, $P=3.34 \times 10^{-5}$

* The concordance between two diagnostic methods is shown as a correlation coefficient r ; $r=1$ represents two diagnostic methods are completely concordance in diagnosing MetS. P values are the statistical significance of each concordance test of two diagnostic methods.