Central Asian Journal of Medical Sciences
CAJMS

Original Article

Cent Asian J Med Sci. 2017 Feb;3(1): 41-46

Higher Leptin Level among Mongolians with Metabolic Syndrome as a Predictor of Cardiovascular Risk

Batnaran Dagdan[1,2], Ariunbold Chuluun-Erdene[1], Orgil Sengeragchaa[1], Purevjal Sanjmyatav[1] , Munkhtsetseg Janlav[1]

[1]Department of Biochemistry and Laboratory Medicine, School of Pharmacy and Biomedicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; [2]Coronary Care Unit, Cardiovascular center, Ulaanbaatar, Mongolia

Submitted: Dec 26, 2016
Revised: Jan 20, 2017
Accepted: Jan 24, 2017

Corresponding Author
Munkhtsetseg Janlav, MD, PhD
Department of Biochemistry and Laboratory Medicine, School of Pharmacy and Biomedicine, Mongolian National University of Medical Sciences, Zorig street, Ulaanbaatar 14210, Mongolia
Tel: : +976-9909-2287
Fax: +976-11319065
E-mail: munkhtsetseg.j@mnums.edu.mn

Objectives: The focus of our research was to determine and identify the cutoff level of leptin in Mongolian adults with metabolic syndrome (MS). **Methods:** This observed case-controlled study was performed with 259 adults (mean age 40.35±10.75; range 18-71 years old). A questionnaire and anthropological measurements were used for obtaining data. Fasting blood sugar, serum triglyceride, total cholesterol, HDL, adiponectin, leptin, and insulin were measured in fasting blood together with LDL and HOMA-IR calculations. Sensitivity and specificity were estimated for each leptin measurement, using MS as the outcome. These values were used to construct a receiver operating characteristic (ROC) curve. **Results:** Average leptin levels of the group with MS were 10.97±11.32 ng/ml and 23.86±11.32 ng/ml in males and females, respectively. The average leptin level of participants with MS was 17.23±1.59 ng/ml, which was significantly higher than the control group by 10.80±1.58. The MS exposed group had a much higher level of leptin than the control group ($p<0.001$). Leptin was the predictor of MS in both sexes (AUC-0.839, $p<0.0001$ for men and AUC-0.737, $p<0.0001$ for women). **Conclusion:** Leptin levels in the MS exposed group were higher than in the control group. Leptin may be a useful biomarker of cardiovascular risk in Mongolian adults.

Keywords: Metabolic Syndrome X, Insulin Resistance, Adipokines, Leptin, Waist Circumference

Introduction

The prevalence of metabolic syndrome and obesity is increasing among all nation groups. Metabolic syndrome (MS) is characterized by obesity, hypertension, low level of high-density lipoprotein cholesterol and insulin resistance. All these factors contribute to the development of heart disease [1-3]. This represents a serious cardiovascular health hazard with significant morbidity and mortality. Several previous studies have shown that MS is associated with increased risk for

cardiovascular disease and diabetes [4, 5]. Therefore, a number of studies focusing on MS and obesity has increased worldwide, as well as in our country [6]. Several organizations have outlined diagnostic criteria for MS. The main difference concerns the measurement for central obesity. Thus, these organizations have released recommendations for populations regarding how country specific cutoff points of waist circumference can be determined [2, 7].

Leptin is a protein hormone mainly produced in adipose tissue whose mass regulates food intake and energy metabolism. The gene product of the Ob gene is leptin. Leptin has been suggested as a potential biomarker of MS and cardiovascular risk. Among the factors affecting the serum leptin concentration are the amounts of adipose tissue and body mass index (BMI) which are known to be closely related to the serum leptin concentration [8]. Recent studies have suggested that the adipocyte-derived hormone leptin may have an important role in obesity, MS, and cardiovascular disease with a link to all three [8].

Our research aimed to determine and identify the cutoff level of leptin in Mongolian adults with MS.

Materials and Methods

1. Subjects and methods

It was an unmatched population based case control-study which included 259 adults (46.3% male, 53.7 % female) aged 18-71 years old and citizens of Mongolia's capital Ulaanbaatar. An IDF criterion was used to define the MS of all participants. Diagnostic criteria were defined as follows: 1) high blood pressure (a systolic blood pressure ≥ 130 mmHg and/or diastolic pressure ≥85 mmHg, under treatment, or already diagnosed with hypertension); 2) high serum triglyceride (≥ 150 mg/dL or under treatment); 3) decreased HDL-C (< 40 mg/dL for males and < 50 mg/dL for females or under treatment) and; 4) hyperglycemia (FBG ≥ 100 mg/dL, under treatment, or previously diagnosed with diabetes mellitus) and abdominal obesity. Waist circumference cutoffs were used for Asian populations (waist circumference ≥ 90 cm for men and ≥ 80 cm for women).

2. Clinical and biochemical assessment

A questionnaire and anthropological measurements were used for data collection. Height, weight, waist circumference (WC), hip circumference (HC) and systolic and diastolic blood pressures were measured in duplicate, and results averaged. Weight and height were measured in kg and cm, respectively, down to two decimal points. The BMI was calculated by dividing the weight (kg) with the square of the height (m2). Blood samples were taken after overnight fasting; serum was separated and analyzed at a later time. Fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) were measured. The hexokinase method was used to measure blood glucose levels, and an enzymatic colorimetric test was used to measure the TC, TG and HDL-C levels. The serum leptin level was measured using radioimmunoassay (DGR Instruments GmbH company Leptin (Sandwich) EIA-2395 kit, USA). The adiponectin level was measured using an enzyme-linked immunosorbent assay (Mesdia company, AdipoMark® human adiponectin ELISA (Cat №AM056711-RUO). LDL and HOMA-IR [fasting insulin (mIU/mL) × fasting blood glucose (mg/dL)]/405) and calculated as described previously.

3. Statistical analysis

Statistical analyses were conducted using the SPSS version 19.0 software package. The data are presented as the mean ± S.D and the significance of the comparisons was determined using Student's t-test, Pearson's correlation, receiver operator characteristic (ROC) curves, the Youden's index (J=Sensitivity+Specifity-1) calculated leptin concentration and waist circumference. All statistical tests were two-tailed, and statistical significance was accepted for P-values <0,05. The collected data were analyzed by SPSS 20.1 and MedCalc 17.0.4 version.

4. Ethical review

The Institutional Review Board of Ministry of Health of Mongolia approved the study design and all participants signed written informed consent forms. (Protocol #07 at 25th March 2011).

Results

Table 1 shows the anthropometric status of study participants by gender according to the presence or absence of MS. In both sexes, weight, BMI, WC, HC, WC/HC ratio in the group with MS were statistically significantly higher than the control group. Interestingly, WC of the control group, that is one criteria of MS,

was 92.37 ± 10.77 cm in men and 84.65 ± 13.6 cm in women (Table 1). It was higher than the Asian WC cutoff point.

Table 1. Anthropometric status of study participants by gender and according to the presence or absence of MS

	Male (n = 120)			Female (n = 139)		
	With MS (n = 54) m±SD	Without MS (n = 66) m±SD	p-value	With MS (n = 51) m±SD	Without MS (n = 88) m±SD	p-value
Age, years	37.85±11.27	35.79±10.05	0.29	46.29±9.89	42.94±9.52	0.01
Height, cm	172.49±7.18	169.94±7.31	0.060	157.36±6.12	158.68±6.21	0.28
Weight, kg	94.95±16.9	78.43±12.02	0.001	76.3±11.46	67.55±10.82	0.001
BMI, kg/m^2	31.82±4.70	27.14±3.74	0.001	30.84±4.53	26.83±4.10	0.001
WC, cm	104.75±11.09	92.37±10.77	0.001	97.44±11.2	84.65±13.6	0.001
HC, cm	109.2±8.9	101.9±6.7	0.001	109.26±10.48	101.35±9.30	0.001
WC/HC ratio	0.95±0.06	0.91±0.06	0.001	0.89±0.05	0.83±0.09	0.001
BMR	1127.6±263.1	913.48±182.1	0.001	575.8±107.7	513.1±106.2	0.001

The serum leptin level of the group with MS was 10.97±11.32 ng/ml which was significantly higher than the related control group by 7.04 ng/ml (p<0.001) in males. In females, the serum leptin level was 23.86±11.32 ng/ml in the group with MS which was significantly higher than the related control group by 8 ng/ml (p<0.001) in males (Table.2).

Table 2. Biochemical status of study participants by gender according to the presence or absence of MS

	Male (n=120)			Female (n=139)		
	With MS (n = 54) m±SD	Without MS (n = 66) m±SD	p-value	With MS (n = 51) m±SD	Without MS (n = 88) m±SD	p-value
Total cholesterol, mg/dL	163.87±38.96	149.62±38.81	0.048	146.51±40.99	139.78±39.39	0.35
Triglyceride, mg/dL	196.93±137.77	82.00±51.00	0.001	97.45±55.86	63.20±27.13	0.001
HDL-C, mg/dL	33.93±12.10	43.61±14.30	0.011	38.63±9.90	46.14±14.99	0.01
LDL-C, mg/dL	94.07±39.63	96.58±38.57	0.73	91.25±40.18	91.88±41.21	0.932
FBG, mg/dL	87.37±39.84	70.57±13.94	0.002	98.75±81.40	71.58±14.47	0.003
Fasting insulin, mIU/mL	19.42±19.85	10.91±18.77	0.001	17.72±21.36	10.11±26.65	0.01
HOMA-IR	4.61±6.71	2.27±3.54	0.001	4.23±7.14	1.93±5.37	0.01
Adiponectin, ng/mL	6.10±3.04	7.76±10.46	0.31	8.23±3.89	11.95±11.37	0.05
Leptin, ng/mL	10.97±11.32	3.93±4.53	<0.001	23.86±18.19	15.89±24.61	<0.001

The Insulin level in the MS exposed group was 18.54±1.72μU/ml, which was significantly higher than the non MS group by 8.05±1.82 (CI95% 4.48-11.63, p<0.001) μU/ml. The Adiponectin level in the MS exposed group was 7.03±0.03μg/ml, which was significantly lower than the control group by 2.54±0.71 (CI95% 1.15-3.93, p<0.001).

Insulin resistance in participants with MS was evaluated by HOMA-IR (homeostasis model assessment). HOMA-IR in the MS group was 4.42+0.54 and directly correlated with the serum leptin level (r=0.300; p<0.001) (Table 4).

ROC curves, best Youden's index and area under the curve (AUC) for leptin as predictors of MS were shown for males and females, respectively. (Figure 1). It can be seen that the cutoff point for leptin was 4.38ng/ml (sensitivity-85.19%; specificity-72.73%, J-0.579, AUC-0.839, 95% CI 0.76-0.90,

p<0.0001) which corresponded to the shoulder of the curve and had the best Youden's index for males. In female subjects, the cutoff point of leptin was 15.3ng/ml (sensitivity-66.67%; specificity-73.86%, J-0.405, AUC-0.737, 95%CI 0.656-0.808, p<0.0001).

corresponded to the shoulder of the curve and had the best Youden's index for males. In female subjects, the cutoff point of leptin was 82 cm (sensitivity-96.47%; specificity-54.82%, J-0.513, AUC-0.833, 95%CI 0.795-0.866, p<0.0001).

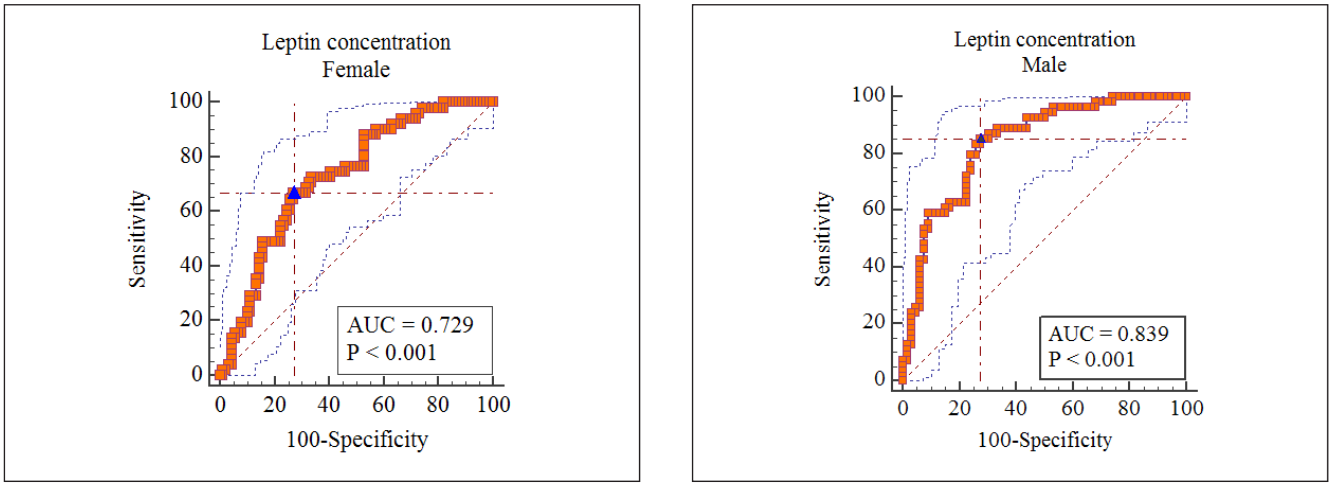

Figure 1. ROC curves for leptin as predictors of MS (a.male, b.female). On both charts, best cutoff point is represented by the intersection of dotted lines. The area under the curve shows the overall accuracy of the test.

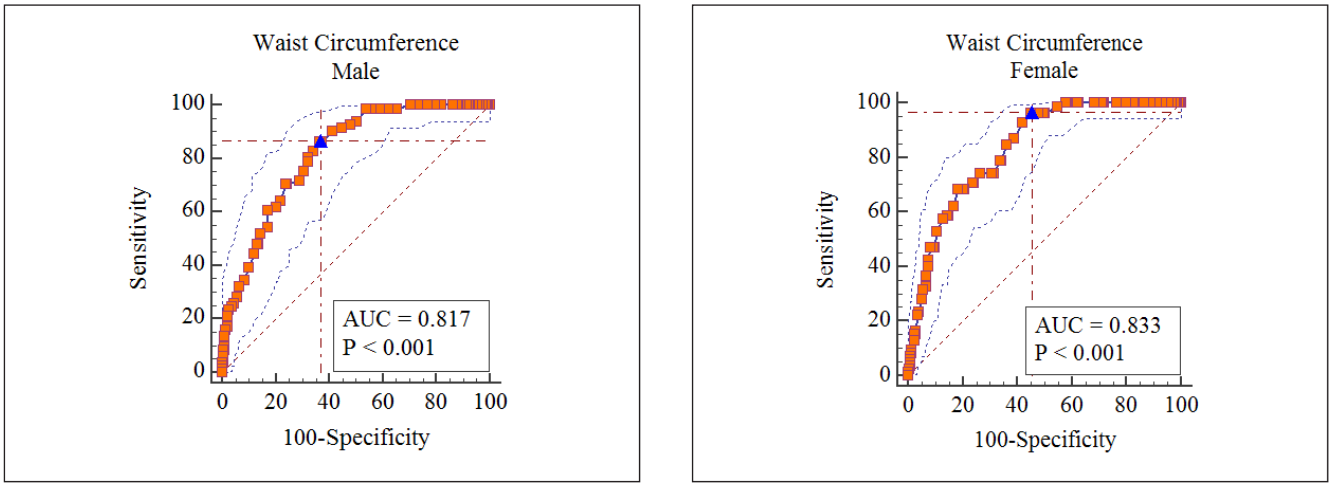

Figure 2. ROC curves for waist circumference as criteria of MS, by gender (a.male, b.female). On both charts, best cutoff point is denoted by intersection of dotted lines. The area under the curve shows the overall accuracy of the test.

It can be seen that the cutoff point for waist circumference was 94.5 cm (sensitivity-86.42%; specificity-63.27%, J-0.497, AUC-0.817, 95% CI 0.767-0.861, p<0.0001) which

The cutoff point of WC was compared to other cutoff points of waist circumference that had the highest sensitivity and specificity of 94.5 cm for men and 82 cm for women. (Table 3)

Table 3. Sensitivity, specificity and cutoff values for waist circumference (WC) by gender.

	Coordinates of the curves			
	WC	**Sensitivity**	**Specificity**	**Youden's index (J)**
Female	88cm	74.12%	73.28%	0.474
	82cm	96.47%	54.82%	0.513
	80cm	96.47%	49.86%	0.463
Male	102cm	60.49%	82.65%	0.431
	94.5cm	86.42%	63.27 %	0.497
	90cm	93.83%	49.49%	0.433

Table 4. Coefficients of correlations between leptin and other factors.

	Leptin, ng/ml	
	r	**p-value**
Age, years	0.218	<0.001
Body weight, kg	0.232	<0.001
BMI, kg/m^2	0.499	<0.001
Waist circumference	0.309	<0.001
WC/HC ratio	0.032	0.614
Fasting blood glucose, mg/dl	0.127	0.042
Total cholesterol, mg/dl	-0.152	0.015
Triglyceride, mg/dl	-0.019	0.761
HDL-Cholesterol, mg/dl	0.149	0.018
LDL-Cholesterol, mg/dl	-0.184	0.004
Adiponectin, ng/ml	-0.045	0.555
HOMA-IR	0.300	<0.001
Fasting insulin, μU/ml	0.386	<0.001

Discussion

Our study demonstrates serum leptin is associated with MS in Mongolian adults. The serum leptin level of a group with MS was 10.97±11.32 ng/ml which was significantly higher than the related control group by 7.04 ng/ml (p<0.001) in males. In females, it was 23.86±11.32 ng/ml in the group with MS and was significantly higher than control group by 8 ng/ml (p<0.001). Table 2 shows the biochemical status of study participants by gender. Serum leptin level was twofold higher in women than in men with MS. Leptin is produced mainly in adipose tissue in quantities proportional to its mass and governed by the Ob gene. It is now known to be an important regulator of body weight, triggering various physiological mechanisms according to the state of the body's energy balance. However, in obese individuals, these mechanisms are impaired and high leptin levels do not have these effects. This means leptin resistance. These mechanisms are complex and not fully understood [8, 9]. The gender difference in serum leptin levels is already established. It has been proposed that the higher leptin level in women involves a different pattern of the deposition and the role of sex hormone. In humans, it has been demonstrated that after menopause women have lower serum leptin concentrations than during their fertile period [10].

Leptin was the main predictor of insulin resistance [8]. MS is known as the cluster of changes associated with insulin resistance, which plays an important role in patients with coronary heart disease. Insulin resistance in participants with MS was evaluated by using HOMA-IR. HOMA-IR in the MS group. The result was 4.42+0.54 and directly correlated with serum leptin level (r=0.300; p<0.001). Leptin is a risk marker for myocardial infarction and hemorrhagic stroke in the population-based cohort. According to the prospective study WOSCOPS cohort on the association between leptin and cardiovascular diseases, leptin was an independent, predictive factor for the incidence of coronary artery disease during a 5-year follow-up [11, 12].

In conclusion, leptin level in the MS exposed group was higher than in the control group. Leptin may be a useful biomarker of cardiovascular risk in Mongolian adults. Research findings suggest that the cutoff point for waist circumference for MS criteria of Mongolians is higher than Asians but lower than Europeans.

Conflict of Interest

The authors declare that they have no competing interests.

Acknowledgements

Current study was financially supported by a grant "Metabolic syndrome: key to diabetes and cardiovascular disease" (#75-105), which was supported by Health Project of the Millennium Challenge Account Mongolia (2012-2013).

References

1. Yun JE, Kimm H, Jo J, Jee SH. Serum leptin is associated with metabolic syndrome in obese and nonobese Korean populations. Metab Clin Exp 2010; 59: 424-429.
2. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; World heart federation; international atherosclerosis society; and international association for the study of obesity. Circulation 2009; 120: 1640-1645.
3. Grundy SM. Obesity, metabolic syndrome, and coronary atherosclerosis. Circulation 2002; 105: 2696-2698.
4. Grundy SM. Metabolic syndrome: a multiplex cardiovascular risk factor. J Clin Endocrinol Metab 2007; 92: 399-404.
5. Yang W, Reynolds K, Gu D, Chen J, He J. A comparison of two proposed definitions for metabolic syndrome in the Chinese adult population. Am J Med Sci 2007; 334: 184-189.
6. Bayasgalan T. Prevalence of metabolic syndrome in Mongolia [dissertation]. Ulaanbaatar, Mongolia. Health Sciences University of Mongolia; 2008
7. Grundy SM. Metabolic syndrome pandemic. Arterioscler Thromb Vasc Biol 2008; 28: 629-636.
8. Martins Mdo C, Lima Faleiro L, Fonseca A. [Relationship between leptin and body mass and metabolic syndrome in an adult population]. Rev Port Cardiol 2012; 31: 711-719.
9. Park HK, Ahima RS. Leptin signaling. F1000Prime Rep 2014; 6: 73.
10. Isidori AM, Strollo F, Morè M, Caprio M, Aversa A, Moretti C, et al. Leptin and aging: correlation with endocrine changes in male and female healthy adult populations of different body weights. J Clin Endocrinol Metab 2000; 85:1954-1962.
11. Kimm H, Lee SW, Lee HS, Shim KW, Cho CY, Yun JE, et al. Associations between lipid measures and metabolic syndrome, insulin resistance and adiponectin. - Usefulness of lipid ratios in Korean men and women. Circ J 2010; 74: 931-937.
12. Wallace AM, McMahon AD, Packard CJ, Kelly A, Shepherd J, Gaw A, et al. Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS). Circulation 2001; 104: 3052-3056.