Apolipoprotein B/apolipoprotein A-I ratio in relation to various definitions of metabolic syndrome among Saudi patients with type 2 diabetes mellitus

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ABSTRACT

الأهداف: لتقييم ما إذا كانت نسبة أبوليبوبروتين ب / أبوليبوبروتين أ1 لدى المرضى السعوديين المصابين بالسكري من النوع الثاني T2DM ذات علاقة بإعتلالات الإستقلاب.

الطريقة: أجريت هذه الدراسة على 250 مريضاً مصاباً بالسكري من النوع الثاني T2DM، أعمارهم فوق 40 عام، وذلك بمركز السكري بمستشفى الملك عبد العزيز الجامعي بالرياض، في الفترة من 1 يناير وحتى 31 ديسمبر 2006م. تم تعريف المتلازمة الاستقلابية باستخدام ثلاثة تعريفات هي: برنامج الكولسترول التعليمي الوطني– هيئة مستشارين علاج البالغين الثالثة، واتحاد منظمات السكري العالمية، ومنظمة الصحة العالمية.

النتائج: أظهرت الدراسة وجود زيادة ذات مغزىً في نسبة أبوليبوبروتين ب / أبوليبوبروتين أ1، لدى مرضى السكري من النوع الثاني T2DM، والذين يعانون من المتلازمة الاستقلابية. وقد وُجد ارتباط إيجابي قوي بين هذه النسبة و بين الدهون الثلاثية، و كولسترول ليبوبروتين قليل الكثافة، و إجمالي الكولسترول (r=0.43–0.54,p<0.0001)، وارتباط ضعيف ، ولكنه ذو مغزىً (r=0.14–0.21,p<0.05) مع محيط الخصر، ونسبة محيط الخصر إلى الورك، ومستوى سكر الدم حال الصوم، وهيموغلوبين (A1c) ، بينما لم يوجد ارتباط مع معدل كثافة الجسم (r=0.01,p=0.88). وفي المقابل، وجد ارتباط سالب قوي بين نسبة أبوليبوبروتين ب / أبوليبوبروتين أ1 وبين كولسترول ليبوبروتين عالي الكثافة (r =–0.7, p<0.0001).

خاتمة: إن نسبة أبوليبوبروتين ب / أبوليبوبروتين أ1 ترتبط ارتباطاً هاماً بالمتلازمة الاستقلابية في المرضى السعوديين المصابين بالسكري من النوع الثاني T2DM. و تتوافق هذه النتائج مع النتائج المستخلصة من مجموعات عرقية أخرى.

Objective: To assess if the apolipoprotein (Apo) B/Apo A-I ratio in Saudi patients with type 2 diabetes mellitus (T2DM) is associated with metabolic syndrome (MetS).

Methods: This cross-sectional study was conducted on 250 patients with T2DM, above 40 years of age, at King Abdulaziz University Hospital Diabetes Center in Riyadh, Saudi Arabia, between January and December 2006. Metabolic syndrome was defined, and compared according to 3 criteria, namely, National Cholesterol Education Program Adult Treatment Panel III, International Diabetes Federation, and World Health Organization.

Results: In the 250 patients studied, all 3 definitions demonstrated significant increase in the Apo B/Apo A-I ratio, in Saudi type 2 diabetics with the MetS. There was a strong positive correlation between the Apo B/Apo A-I ratio and triglycerides, low-density lipoprotein cholesterol, and total cholesterol (r=0.43-0.54, p<0.0001), and a weak, yet significant, correlation (r=0.14-0.21, p<0.05) with waist circumference, waist-hip ratio, fasting glucose, and hemoglobin A1c, however, not with body mass index (r=0.01, p=0.88). In contrast, the ratio showed strong negative correlation with high-density lipoprotein cholesterol (r =-0.7, p<0.0001).

Conclusion: Apolipoprotein B/apolipoprotein A-I ratio is significantly associated with MetS in Saudi patients with T2DM, similar to observations made in other ethnic groups.

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It is well established that diabetes mellitus, and hypercholesterolemia are strongly independent risk factors for coronary heart disease.[1,2] Furthermore, it is well known that the synergistic effects of the atherogenic components of the metabolic syndrome (MetS), predispose to increased risk of cardiovascular mortality.[3,4] This prediction is independent of other well known risk factors, including total and low-density lipoprotein (LDL) cholesterol.[5] Insulin resistance, and MetS are associated with certain lipid disturbances, including high fasting, and postprandial levels of triglyceride-rich lipoproteins (mainly very low-density lipoprotein [VLDL]), as well as instability in the high-density lipoprotein, and the non-HDL cholesterol levels.[6] Circulating levels of apolipoproteins indicate the number of lipoprotein particles, instead of its cholesterol concentration. The level of apolipoprotein (Apo)-B reflects the total number of potentially atherogenic particles, as it is present in VLDL, intermediate density lipoprotein, large buoyant LDL, and small dense LDL. However, the level of apoA-I reflects the number of HDL particles. Thus, the ratio of apolipoproteins B and A-I (ApoB/ApoA-I) would be, theoretically, an ideal indicator for the lipid disturbances associated with MetS.[7] It has been shown that ApoB/ApoA-I ratio is better than any cholesterol measure to predict cardiovascular risk.[8,9] Although some studies have shown the association of ApoB/ApoA-I ratio with the features of MetS in certain populations,[10-13] no study has explored this association in Saudi patients with type 2 diabetes. Therefore, we conducted this study to assess whether ApoB/ApoA-I ratio is associated with MetS in Saudi patients with type 2 diabetes.

Methods. In this cross-sectional study, 250 Saudi patients with type 2 diabetes (T2DM) participated in this study, which took place at the Diabetes Center of King Abdulaziz University Hospital (KAUH) Riyadh, Saudi Arabia between January and December 2006. All patients included in this study were more than 40 years of age, not on any lipid-lowering drugs, and with serum triglycerides level of less than 3.38 mmol/l. The exclusion criteria were significant liver disease, renal failure requiring renal-replacement therapy, and the usage of oral contraceptives, or hormone replacement therapy. The KAUH ethics committee approved the study, and an informed consent was obtained from each patient. Height and weight were taken with subjects wearing light clothes, and without shoes. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Waist circumference was obtained as the minimum value, between the iliac crest and the lateral costal margin, and the hip circumference was defined, as the maximum value over the buttocks. Measurements were carried out with a standardized tape measure, and were rounded off to the nearest centimeter (cm). Serum glucose, total cholesterol, and triglycerides were determined by enzymatic techniques, while ApoB, and ApoA-I was determined by immuno turbidimetric assays (Kone Instruments, Espoo, Finland). High-density level cholesterol was measured after precipitation of VLDL and LDL, with phosphotungstic acid and magnesium chloride. Low-density level cholesterol was calculated using Friedewald's equation.[14] Uric acid was measured using oxidation method to allantoin by uricase, and creatinine was determined by modified Jaffé method, using alkaline picrate solution (Kone instruments, Finland). Glycosylated hemoglobin (HbA1c) was measured through Nyocard-HbA1c (Nyocard, Norway) utilizing a boronated affinity assay. Urinary albumin was assessed using Chemstrip Micral, with cut-off value of 20 mg/l (Roche Diagnostics, Mannheim, Germany). We utilized 3 definitions of MetS for this analysis. Metabolic syndrome, according to the World Health Organization (WHO), is defined as glucose intolerance, diabetes or insulin resistance with 2 or more of the following: 1) blood pressure ≥140/90 mm Hg, 2) triglycerides ≥1.7 mmol/l, or HDL cholesterol <0.9 mmol/l for men and <1.0 mmol/l for women, 3) waist-to-hip ratio (WHR) >0.9 for men and >0.85 for women, or body mass index (BMI) >30 kg/m^2, and 4) urinary albumin excretion rate ≥20 µg/min.[15] Urinary albumin was determined using a test-strip method, with a cut-off value of 20mg/l. The WHO definition was modified using urinary albumin concentration instead of excretion rate. In the definition of MetS according to the National Cholesterol Education Program-Third Adult Treatment Panel (NCEP ATP III), 3 or more of the following criteria must be fulfilled: fasting blood glucose level ≥5.6 mmol/l, blood pressure ≥130/85 mm Hg, triglycerides ≥1.7 mmol/l, HDL cholesterol <1.03 mmol/l for men and <1.29 mmol/l for women, and waist circumference >102 cm for men and >88 cm for women.[16] The third definition used was the International Diabetes Federation (IDF) definition for MetS, that required a measure of central obesity (gender and ethnic-specific waist circumference) in addition to 2 or more of the following criteria: triglycerides ≥1.7 mmol/l or specific treatment for this lipid abnormality, HDL cholesterol <1.03 mmol/l in men and <1.29 mmol/l in women,

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or specific treatment for this lipid abnormality, systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, or treatment of previously diagnosed hypertension, and fasting plasma glucose ≥5.6 mmol/l or previously diagnosed T2DM.[17]

Statistical analysis. The SPSS version 11.5 (Chicago, Illinois) was utilized to analyze the data. All data are presented as mean±SD, as all variables of interest were normally distributed. Independent student's t-test, and ANOVA with post-hoc analysis were used for comparison of variables from groups. Spearman's correlation coefficients between the variables were performed, to determine relationships between variables of interest. Results were considered statistically significant when $p<0.05$.

Results. The patient's clinical and metabolic characteristics are shown in **Table 1**. It is evident that the prevalence of MetS is high, regardless of the definition used, and was highest using the NCEP-ATP III definition (**Table 1**). Spearman's correlation revealed a weak although significant positive correlation between ApoB/ApoA-I ratio and waist circumference (r=0.14, p=0.04), WHR (r=0.21, p=0.001), fasting glucose(r=0.18, p=0.004), and HbA1c (r=0.15; p=0.03), moderate and significant positive correlations with triglycerides (r=0.54, $p\leq0.0001$), LDL-cholesterol (r=0.52, $p\leq0.0001$), and total cholesterol (r=0.43, $p\leq0.0001$), and a strong negative correlation with HDL-cholesterol (r=-0.70; $p\leq0.0001$). There was no correlation between the ApoB/ApoA-I ratio, and BMI. Further analysis by the number of features of the MetS as defined by WHO, NCEP-ATP III, and IDF were performed. Regardless of the criteria used to define MetS, there was significant increase in the levels of ApoB, ApoB/ApoA-I ratio, and triglycerides, with a concomitant decrease in HDL levels in correlation to increasing features of the MetS (**Tables 2 & 3**).

Table 1 - Clinical characteristics of subjects (N=250).

Variables	Result
Age (years)	51.88 ± 9.5
Gender (male/female, %)	127/123 (50.8/49.2)
Metabolic syndrome by WHO (n, %)	76 (30.4)
Metabolic Syndrome by NCEP-ATP III (n, %)	146 (58.4)
Metabolic Syndrome by IDF (n, %)	143 (57.2)
Body-mass index (kg/m^2)	30.5 ± 5.7
Waist-hip ratio	0.96 ± 0.7
Fasting glucose (mmol/l)	9.1 ± 3.9
HbA1c (%)	8.5 ± 2.0
Triglycerides (mmol/l)	1.7 ± 1.0
HDL-cholesterol (mmol/l)	1.2 ± 0.3
LDL-cholesterol (mmol/l)	3.1 ± 0.9
Total cholesterol (mmol/l)	5.0 ± 1.0
ApoA-I (g/l)	1.4 ± 0.3
ApoB (g/l)	1.1 ± 0.3
ApoB/apoA-I	0.81 ± 0.25

Data presented as mean±SD, WHO - World Health Organization, NCEP-ATP III - National Cholesterol Education Program-Third Adult Treatment Panel, IDF - International Diabetes Federation, HbA1c - Hemoglobin A1c, HDL- cholesterol - high density lipoprotein-cholesterol, LDL- cholesterol - low density lipoprotein-cholesterol. Apo - apolipoprotein

Discussion. Recent studies have shown that the ApoB/ApoA-I ratio is associated with MetS, and its components.[13] In this study, we confirmed this association in Saudi type 2 diabetic patients. The findings were consistent with the other studies, patients with increasing numbers of factors constituting MetS had parallel increase in the ApoB/ApoA-I ratio, regardless of what criteria was used to define the MetS.[18] Wallenfeldt et al[19] described a relation between the ApoB/ApoAI ratio and MetS. They studied 313 Caucasian men (mean age 58 years) with different degrees of obesity and insulin sensitivity, and the study reported a close association of the ApoB/ApoA-I ratio with the factors constituting MetS. However, the study was carried out in a different population, it does not include women, and it used only, the WHO definition of MetS. In another study carried out in the United States whose sample composed of 2,964 subjects, the ApoB/ApoA-I ratio was strongly associated with the presence of individual MetS components, with the MetS itself, and with insulin resistance.[13] However, their results may not be applicable to other ethnic groups. Our study is the first to demonstrate a significant association of the Apo/Apo-I ratio with 3 definitions of the MetS (WHO, NCEP ATP-III, and IDF) in the Saudi population with T2DM. Ethnic differences do exist in cardiovascular risk factors, and could have potential clinical implications.[20] Obesity, as well as visceral fat distribution are considered as components of the MetS.[21] The WHR is used as a marker for central obesity, and it has been shown to be associated with cardiovascular risk.[22] We found an association between ApoB/ApoA-I ratio and WHR, however, not with BMI, which is agreeable with the current understanding that links central fat accumulation with poorer plasma lipid profile.[23] ApolipoproteinB/ApoA-I ratio is significantly associated with the major aspects of dyslipidemia, as well as insulin resistance, and the metabolic syndrome, making it an ideal marker for increased cardiovascular risk aside from the conventional lipid markers.[24]

Table 2 - Clinical and metabolic parameters according to the number of features of the WHO definition of metabolic syndrome.

Parameter	Number of features of metabolic syndrome			
	0 (n=31)	1 (n=71)	2 (n=72)	≥ 3 (n=76)
Fasting glucose (mmol/l)	8.4 ± 4.6	8.0 ± 3.4‡	9.3 ± 3.7	10.4 ± 3.9
HbA1c (%)	7.8 ± 2.4	8.2 ± 2.0	8.7 ± 1.8	8.7 ± 1.9
Total cholesterol (mmol/l)	4.8 ± 0.8‡	5.0 ± 0.8	4.6 ± 1.0*‡	5.4 ± 1.1
Triglycerides (mmol/l)	1.2 ±0.3‡	1.4 ± 1.4‡	1.2 ± 0.3‡	2.5 ± 0.8
HDL-cholesterol (mmol/l)	1.3 ± 0.3†‡	1.3 ± 0.4†‡	1.1 ± 0.3	1.0 ± 0.3
LDL-cholesterol (mmol/l)	2.9 ± 0.8†	3.1 ± 0.7†	2.9 ± 1.0	3.2 ± 1.0
ApoA-I (g/l)	1.4 ± 0.3†	1.5 ± 0.2†	1.3 ± 0.2	1.4 ± 0.3
ApoB (g/l)	0.97 ± 0.3‡	1.0 ± 0.3‡	1.0 ± 0.2‡	1.3 ± 0.3
ApoB/apoA-I ratio	0.69 ± 0.2†‡	0.72 ± 0.2†‡	0.82 ± 0.3‡	0.94 ± 0.2

Data presented as mean±SD, *significance compared to 1, †significance compared to 2, ‡significance compared to ≥3, significance at $p<0.05$, WHO - World Health Organization, HbA1c -hemoglobin A1c, HDL - high density lipoprotein, LDL - low density lipoprotein, Apo - apolipoprotein

Table 3 - Clinical and metabolic parameters according to the number of features of the IDF and NCEP-ATP III definition of metabolic syndrome.

Parameter	Number of features of metabolic syndrome					
	IDF			NCEP-ATP III		
	1 (n=45)	2 (n=62)	≥3 (n=143)	1 (n=38)	2 (n=66)	≥3 (n=146)
Fasting glucose (mmol/l)	8.6 ± 4.8	8.2 ± 3.4*	9.7 ± 3.7	8.0 ± 4.5*	8.0 ± 3.2*	9.9 ± 3.8
HbA1c (%)	8.2 ± 2.6	8.3 ± 1.8	8.6 ± 1.8	8.0 ± 2.6	8.2 ± 1.9	8.7 ± 1.8
Total cholesterol (mmol/l)	4.8 ± 0.8	4.9 ± 1.1	5.1 ± 1.0	4.8 ± 0.8	4.9 ± 0.9	5.1 ± 1.1
Triglycerides (mmol/l)	1.1 ± 0.3*	1.5 ± 0.8	1.9 ± 1.2	1.1 ± 0.3*	1.3 ± 0.4*	2.0 ± 1.0
HDL-cholesterol (mmol/l)	1.3 ± 0.4*	1.2 ± 0.3	1.1 ± 0.3	1.4 ± 0.3*	1.3 ± 0.3*	1.1 ± 0.3
LDL-cholesterol (mmol/l)	3.0 ± 0.7	3.0 ± 1.0	3.1 ± 0.9	2.9 ± 0.7	3.0 ± 0.8	3.1 ± 1.0
Apo A-I (g/l)	1.4± 0.3	1.4 ± 0.2	1.4 ± 0.3	1.5 ± 0.3*	1.4 ± 0.2	1.3 ± 0.3
Apo B (g/l)	0.96 ± 0.2*	1.0 ± 0.2	1.1 ± 0.3	0.92 ± 0.2*	1.0 ± 0.3*	1.2 ± 0.3
Apo B/Apo A-I ratio	0.7 ± 0.3*	0.79 ± 0.3	0.85 ± 0.2	0.64 ± 0.2*	0.7 ± 0.2*	0.9 ± 0.3

Data presented as mean±SD, *significance compared to ≥3, significance at $p<0.05$, IDF - international diabetes federation, NCEP-ATP III - national cholesterol education program-third adult treatment panel III, HbA1c - hemoglobin A1c, HDL - high density lipoprotein, LDL - low density lipoprotein, Apo - apolipoprotein

Our study has a number of limitations. First, in order to avoid the confusing effect of lipid-lowering medications, we included only patients not taking these drugs. Secondly, with the aim of using Friedewald's formula for calculating LDL-cholesterol, we excluded those with a triglyceride level >3.38 mmol/l. This might have led to under-representation of patients with the most marked lipid abnormalities. The results of this study support that the elevation of ApoB/ApoA-I ratio may be an important feature of the MetS, and may provide an additional mechanism to explain the elevated cardiovascular risk associated with this syndrome. Published data supports that ApoB/ApoA-I ratio can be considered as a new risk factor for cardiovascular disease, the lower the ApoB/ApoA-I ratio, the lower the risk. Methods for determining ApoB and ApoA-I are internationally standardized and automated, analyses are cheap, and more importantly, can be performed on non-fasted samples.

We conclude that in this cohort of Saudi type 2 diabetic patients, the ApoB/ApoA-I ratio was closely associated with the MetS, and its components. This data will support using this test in assessing cardiovascular risk in Saudi subjects with MetS.

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References

1. Gould AL, Davies GM, Alemao E, Yin DD, Cook JR. Cholesterol reduction yields clinical benefits: meta-analysis including recent trials. ***Clin Ther*** 2007; 29: 778-794.
2. Gonzalez-Clemente JM, Palma S, Arroyo J, Vilardell C, Caixas A, Gimenez-Palop O, et al. [Is diabetes mellitus a coronary heart disease equivalent? Results of a meta-analysis of prospective studies]. ***Rev Esp Cardiol*** 2007; 60: 1167-1176.
3. Pischon T, Hu FB, Rexrode KM, Girman CJ, Manson JE, Rimm EB. Inflammation, the metabolic syndrome, and risk of coronary heart disease in women and men. ***Atherosclerosis*** 2008; 197: 392-399 .
4. Hong Y, Jin X, Mo J, Lin HM, Duan Y, Pu M, et al. Metabolic syndrome, its preeminent clusters, incident coronary heart disease and all-cause mortality-results of prospective analysis for the Atherosclerosis Risk in Communities study. ***J Intern Med*** 2007; 262: 113-122.
5. Asia Pacific Cohort Studies Collaboration. Cholesterol, diabetes and major cardiovascular diseases in the Asia-Pacific region. ***Diabetologia*** 2007; 50: 2289-2297.
6. Christen A, Efstathiadou Z, Laspa E, Johnston DG, Godsland IF. Rate of change and instability in body mass index, insulin resistance, and lipid metabolism as predictors of atherosclerotic vascular disease. ***J Clin Endocrinol Metab*** 2007; 92: 3780-3787.
7. Mudd JO, Borlaug BA, Johnston PV, Kral BG, Rouf R, Blumenthal RS, et al. Beyond low-density lipoprotein cholesterol: defining the role of low-density lipoprotein heterogeneity in coronary artery disease. ***J Am Coll Cardiol*** 2007; 50: 1735-1741.
8. Sniderman AD. Non-HDL cholesterol versus apolipoprotein B in diabetic dyslipoproteinemia: alternatives and surrogates versus the real thing. ***Diabetes Care*** 2003; 26: 2207-2208.
9. Walldius G, Jungner I. Apolipoprotein B and apolipoprotein A-I: risk indicators of coronary heart disease and targets for lipid-modifying therapy. ***J Intern Med*** 2004; 255: 188-205.
10. Solymoss BC, Bourassa MG, Campeau L, Sniderman A, Marcil M, Lesperance J, et al. Effect of increasing metabolic syndrome score on atherosclerotic risk profile and coronary artery disease angiographic severity. ***Am J Cardiol*** 2004; 93: 159-64.
11. Kim BJ, Hwang ST, Sung KC, Kim BS, Kang JH, Lee MH, et al. Comparison of the relationships between serum apolipoprotein B and serum lipid distributions. ***Clin Chem*** 2005; 51: 2257-2263.
12. Lind L, Vessby B, Sundstrom J. The apolipoprotein B/AI ratio and the metabolic syndrome independently predict risk for myocardial infarction in middle-aged men. ***Arterioscler Thromb Vasc Biol*** 2006; 26: 406-410.
13. Sierra-Johnson J, Somers VK, Kuniyoshi FH, Garza CA, Isley WL, Gami AS, et al. Comparison of apolipoprotein-B/apolipoprotein-AI in subjects with versus without the metabolic syndrome. ***Am J Cardiol*** 2006; 98: 1369-1373.
14. 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.
15. World Health Organization. Definition, Diagnosis, and Classification of Diabetes Mellitus and Its Complications: Report of a WHO Consultation. Part I: Diagnosis and Classification of Diabetes Mellitus. Geneva, Switzerland: World Health Organization; 1999.
16. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). ***JAMA*** 2001; 285: 2486-2497.
17. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome-a new world-wide definition. A Consensus Statement from the International Diabetes Federation. ***Diabet Med*** 2006; 23: 469-480.
18. Relimpio F, Losada F, Pumar A, Mangas MA, Morales F, Astorga R. Relationships of apolipoprotein B(100) with the metabolic syndrome in Type 2 diabetes mellitus. ***Diabetes Res Clin Pract*** 2002; 57: 199-207.
19. Wallenfeldt K, Bokemark L, Wikstrand J, Hulthe J, Fagerberg B. Apolipoprotein B/apolipoprotein A-I in relation to the metabolic syndrome and change in carotid artery intima-media thickness during 3 years in middle-aged men. ***Stroke*** 2004; 35: 2248-2252.
20. Davis TM, Cull CA, Holman RR. Relationship between ethnicity and glycemic control, lipid profiles, and blood pressure during the first 9 years of type 2 diabetes: U.K. Prospective Diabetes Study (UKPDS 55). ***Diabetes Care*** 2001; 24: 1167-1174.
21. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. ***Diabetes Care*** 1991; 14: 173-194.
22. Katzmarzyk PT, Janssen I, Ross R, Church TS, Blair SN. The importance of waist circumference in the definition of metabolic syndrome: prospective analyses of mortality in men. ***Diabetes Care*** 2006; 29: 404-409.
23. Pascot A, Despres JP, Lemieux I, Bergeron J, Nadeau A, Pru d'homme D, et al. Contribution of visceral obesity to the deterioration of the metabolic risk profile in men with impaired glucose tolerance. ***Diabetologia*** 2000; 43: 1126-1135.
24. Sierra-Johnson J, Romero-Corral A, Somers VK, Lopez-Jimenez F, Walldius G, Hamsten A, et al. ApoB/apoA-I ratio: an independent predictor of insulin resistance in US non-diabetic subjects. ***Eur Heart J*** 2007; 28: 2637-2643.