高血圧

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降圧薬治療の基本的な考え方

高血圧の治療目標は単に血圧値自体の正常化を図ることでなく，血圧の適正化により高血圧性合併症としての脳・心・腎などの重要臓器の障害を回避することにある。この際，非薬剤治療が中心となる軽症例はもとより，降圧療法の適応例および治療経過においても，①体重の適正化，②過剰なアルコール摂取の是正，③有酸素運動の励行，④減塩，⑤禁煙・飽和脂肪酸およびコレステロールの摂取制限などのライフスタイルの改善は高血圧治療の基本となる。**表1**に日本高血圧学会の高血圧治療ガイドラインJSH-2004[1]における生活習慣改善のまとめを示す。

非薬剤治療

JSH-2004

今日，作用機序が異なる多くの降圧薬が使用可能である。薬剤選択においては，①年齢・性，②高血圧重症度と臓器障害の程度，③脳血管疾患，心臓病，腎疾患などの合併疾患，④糖尿病・高脂血症などの病態に与える影響，⑤治療にかかわる費用，⑥薬剤による大規模介入試験の成績，⑦生活の質（quality of life；QOL）などが考慮される。

薬剤選択

大規模介入試験

欧米を中心に治療指針が発表され，それぞれ複数の改定が行われている[2-4]。わが国においても2000年に高血圧学会よりJSH-2000[5]が提唱されているが，2004年12月，JSH-2004[5]が発表されている。本項では，JSH-2004を中心に，最近の降圧薬使用の趨勢について概説する。

血圧の測定と評価

正しい血圧測定・評価法に関して，家庭血圧測定は2003年発行の「家庭血圧測定条件設定の指針」を，またABPM（自動行動下血圧測定）は「24時間血圧計の使用

血圧測定

ABPM

表1 ▶ 生活習慣の修正項目

①食塩制限6g/日未満
②野菜・果物の積極的摂取*
　コレステロールや飽和脂肪酸の摂取を控える
③適正体重の維持：BMI（体重（kg）÷［身長（m）］^{2}）で25を超えない
④運動療法：心血管病のない高血圧患者が対象で，有酸素運動を毎日30分以上を目標に定期的に行う
⑤アルコール制限：エタノールで男性は20～30ml/日以下，女性は10～20ml/日以下
⑥禁煙
生活習慣の複合的な修正はより効果的である

*ただし，野菜・果物の積極的摂取は，重篤な腎障害を伴うものでは，高K血症をきたす可能性があるので推奨されない。また，果物の積極的摂取は摂取カロリーの増加につながることがあるので，糖尿病患者では推奨されない。

(ABPM)基準に関するガイドライン」(Jpn Circ J 2000)をベースにし一部変更した内容となっている。家庭血圧測定時間は起床時1時間以内，就寝前1時間以内としている点はそのままであるが，1回目の測定値をとる部分は変更され，2，3回目の安定した血圧値をとってもいいと変更された。また，家庭血圧基準値については，高血圧，確実な高血圧という紛らわしい表現をやめて，高血圧135/85mmHg以上，正常血圧125/80mmHg未満，またABPMでは1日平均で高血圧135/80mmHg以上としている。家庭血圧とABPMの有用性として，薬効持続性の評価，早朝高血圧や逆白衣高血圧(仮面高血圧)の診断をはじめ，予後予測能，服薬・受診コンプライアンスの改善などがあげられる。早朝高血圧や逆白衣高血圧の患者に対しては，まず長時間作用薬を選択すること，また必要に応じて長時間作用薬を朝と就寝前に分割投与する。なお，血圧値分類とリスク層別化はJSH-2000と基本的には変わらず，心血管病の危険因子として，内臓肥満と尿中微量アルブミンが入っている。

家庭血圧
仮面高血圧
早朝高血圧
内臓肥満
尿中微量アルブミン

降圧治療の開始基準と薬剤選択

◇降圧治療の開示基準

診断では二次性高血圧を含めた診断と重症度の評価がまず肝要となる。JSH-2004では，複数回測定された随時血圧で収縮期血圧140mmHgまたは拡張期血圧90mmHg以上を高血圧としている(**表2**)。また，その経過観察の指針および治療法の選択基準(**図1**)においては，①安易な降圧薬使用は控える，②1日1回の長時間作用薬より開始する，③管理困難例では低用量の複数の降圧薬を使用することが基本となる。また，具体的な薬剤の投薬開始基準は，合併症および危険因子により大きく異なる。JSH-2004では糖尿病，腎機能障害例，心不全，虚血性心臓病などでリスクによる層別分類を行っており，治療開始基準の階層分けを行っている(**表3**)。ことに糖尿病や腎障害合併例では，臓器合併症が明らかでない例であっても130/80mmHgで薬剤治療の適応とし，目標血圧もより低く設定されているが，このような考えは世界的な趨勢といえる。

糖尿病
腎機能障害例
心不全
虚血性心臓病

◇薬剤の選択

降圧治療の目的は心血管病と死亡リスクを低下させることであり，その効果は降圧度と相関する。JSH-2000では第一選択薬として6つの薬剤を推奨したが，JSH-2004では高血圧による合併症予防にあたっては，まず降圧が重要であるとの立場

心血管病
JSH-2000
JSH-2004

表2 ▶ 成人における血圧値の分類

分類	収縮期血圧		拡張期血圧
至適血圧	<120	かつ	<80
正常血圧	<130	かつ	<85
正常高値血圧	130~139	または	85~89
軽症高血圧	140~159	または	90~99
中等症高血圧	160~179	または	100~109
重症高血圧	≧180	または	≧110
収縮期高血圧	≧140	かつ	<90

図1 ▶ 初診時の高血圧管理計画

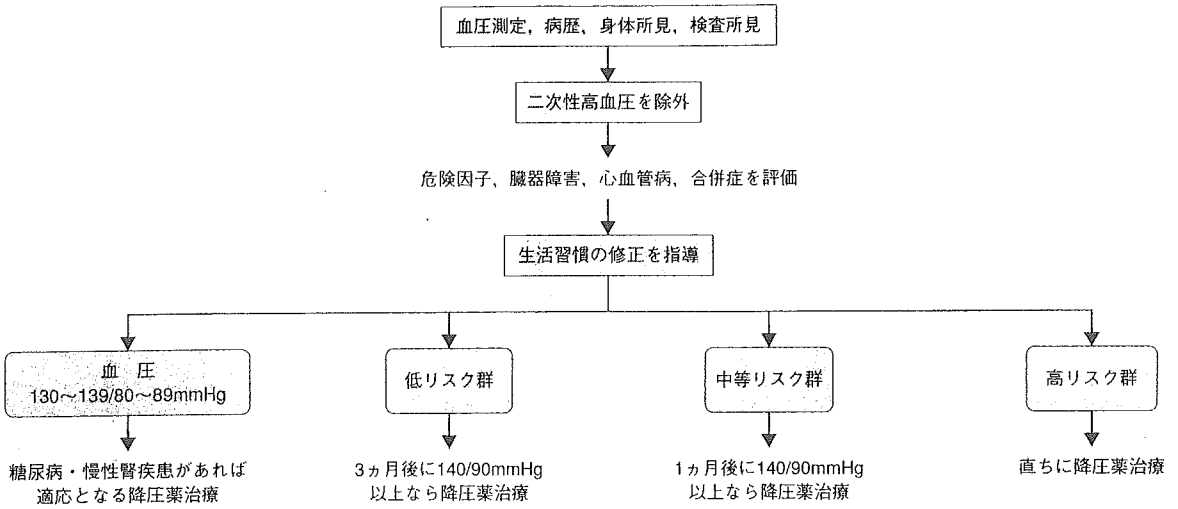

表3 ▶ 高血圧患者のリスクの層別化

血圧分類 / 血圧以外のリスク要因	軽症高血圧 140~159/90~99 mmHg	中等症高血圧 160~179/100~109 mmHg	重症高血圧 ≧180/≧110 mmHg
危険因子なし	低リスク	中等リスク	高リスク
糖尿病以外の1~2個の危険因子あり	中等リスク	中等リスク	高リスク
糖尿病，臓器障害，心血管病，3個以上の危険因子，のいずれかがある	高リスク	高リスク	高リスク

から，1日1回，かつ長時間作用薬を推奨し，主要降圧薬としてCa拮抗薬，AⅡ受容体拮抗薬，ACE阻害薬，利尿薬，β遮断薬，α遮断薬を提示し，第一次薬はこれらのなかから選択することにしている。降圧利尿薬を第一次薬とする米国の立場より，欧州の立場に近い考えとなっている。ただし，α遮断薬は他薬剤に比べてエビデンスが少ないため他5剤よりはトーンが落ちている。また，第一次薬は低用量から開始し，病態に合わせて増量・変更・併用し，利尿薬を含まない2薬の併用で降圧が不十分な場合には，3薬目として利尿薬を追加することが付記されている。なお，降圧薬の積極的適応に関して，β遮断薬に心不全が加わり，α遮断薬の糖尿病は削除されている。

Ca拮抗薬
AⅡ受容体拮抗薬
ACE阻害薬
利尿薬
β遮断薬
α遮断薬

早朝高血圧や逆白衣（仮面）高血圧などを含めて24時間にわたる降圧の重要性，Ca拮抗薬とR-A系抑制薬中心の併用治療の有効性，利尿薬の適切な使用などが重要である。

特殊な病態と治療薬の選択

◇若年，高齢者および妊婦時高血圧

若年性高血圧は，二次性高血圧が高頻度である。仮に降圧療法を開始した場合は

若年性高血圧
二次性高血圧

長期間に及ぶことが予想され，まず厳重な非薬剤療法が施行されるべきである。老年者高血圧治療においては，JSH-2004では前期高齢（65歳以上）と後期高齢（75歳以上）に区分するものの，降圧目標はともに140/90mmHg未満としている。ただし，後期高齢で収縮期血圧160mmHgを超える場合は150/90mmHg未満を暫定的目標値とし，慎重に降圧する必要性が強調されている。なお，超高齢者については降圧治療が心血管疾患発症抑制に有用ではあるが，エビデンスが十分でないため，日本の臨床試験結果を待つことになる。降圧薬としては，Ca拮抗薬，AⅡ受容体拮抗薬，ACE阻害薬，少量の利尿薬が推奨される。合併症を伴う場合については**表4**に示すように推奨されている。

老年者高血圧

前期高齢

後期高齢

◇臓器障害（脳，心，腎），合併症（糖尿病その他の代謝異常）を伴う高血圧の治療

まず，糖尿病合併高血圧の降圧目標はJSH-2000の130/85mmHg未満から，130/80mmHg未満となった。次に，大規模臨床試験のエビデンスに基づき，第一次薬としてAⅡ受容体拮抗薬が加わり，α遮断薬が除かれた結果，JSH-2004ではACE阻害薬，AⅡ受容体拮抗薬，長時間型Ca拮抗薬の3種に変更されている。第一次薬の基準として，主に大規模臨床試験HOT，Syst-Eur，LIFE，ALLHATの成績が根拠となっている。

糖尿病合併高血圧

大規模臨床試験

また，新たにメタボリックシンドロームが追加され，インスリン抵抗性に配慮した薬物療法の必要性が付記されているが，わが国においてもメタボリックシンドロームの意義が明らかになってきており，本症候群の合併に対する十分な配慮が必要である。メタボリックシンドロームの定義としてはNCEP ATPⅢをもとに，日本でも現在，動脈硬化学会を中心に，7学会からなる委員会で検討されている。

メタボリックシンドローム

インスリン抵抗性

NCEP ATPⅢ

脳血管障害合併高血圧においては，急性期治療に大きな変更はないが慢性期患者

脳血管障害合併高血圧

表4 ▶ 合併症を有する高齢者高血圧に対する降圧薬の選択

合併症	Ca拮抗薬（ジヒドロピリジン）	ARB/ACE阻害薬	利尿薬	β遮断薬	α遮断薬
脳血管障害慢性期	○	○	○*1		
虚血性心疾患	○	○		○*2	
心不全		○	○	△*3	△
腎障害	○	○*4	○*5		
糖尿病	○	○	△	△	△*6
高脂血症	○	○	△	△	○
痛風	○	○	×		
慢性閉塞性肺疾患				×	
閉塞性動脈硬化症	○	○	△	×	
骨粗鬆症			○*7		
前立腺肥大					○

○：積極的適応　空欄：適応可　△：使用に際して注意が必要　×：禁忌
*1：脱水に注意，*2：冠攣縮性狭心症は禁忌，*3：少量から開始し臨床経過を観察しながら慎重に使用，*4：クレアチニン2mg/dl以上は慎重投与，*5：ループ利尿薬，*6：起立性低血圧に注意，*7：サイアザイド系利尿薬，ARB：アンジオテンシンⅡ受容体拮抗薬

については，降圧一次目標150/95mmHg未満，最終目標140/90mmHg未満とJSH-2000に比べても厳格な，かつ緩徐な降圧が推奨されている。PROGRESSの結果をみても，脳卒中患者においては，高めの血圧設定は必要ないと思われる。

心疾患合併患者については，心不全の標準的治療としてR-A系抑制薬，β遮断薬，利尿薬の3剤がすすめられ，血圧コントロール不十分な場合に長時間作用型Ca拮抗薬の追加が推奨されている。また，心肥大の第一次薬としてJSH-2000の降圧が重要で降圧薬の種類を問わないとの立場から，JSH-2004では降圧自体非常に重要であるが，加えて，降圧薬としてはエビデンスの証明されているR-A系抑制薬とCa拮抗薬が提唱されている。

さらに慢性腎疾患では，最終的な降圧目標130/80mmHg未満となるほか，R-A系の抑制と，尿蛋白減少が重要である。

PROGRESS

慢性腎疾患

◇高血圧緊急症と悪性高血圧

高度の急速な血圧上昇（通常は拡張期血圧130mmHg以上）により，脳・心・腎合併症が進行し，短期間の降圧を必要とする病態をさす。臨床的には，①高血圧性脳症，②脳出血，③肺水腫を伴う急性心不全，④解離性大動脈瘤，⑤子癇などが代表的な高血圧緊張症である。しかし，急激な降圧はときに主要臓器の障害を引き起こす可能性があり，慎重であるべきである。静注薬としては硝酸薬・Ca拮抗薬が使用される。長期管理の場合には，それぞれ病態によってβ遮断薬，Ca拮抗薬，利尿薬の経口薬が選択される。

高血圧緊急症

悪性高血圧

おわりに

降圧薬使用の最近の趨勢を，最近発表されたJSH-2004を中心に概説した。わが国の使用状況および降圧薬の考え方とは異なる点も多い。背景に米国における医療経済上の事情と過去の大規模研究の成績がある。今後，わが国でも薬剤による大規模介入試験による降圧薬の使用指針が必要となろう。また，降圧薬は臨床医にとって最も一般的な治療薬である。治療指針を熟知するとともに，症例による治療計画をもって診療にあたることが重要である。

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Original Article

Metabolic Syndrome and Cardiac Disease in Japanese Men: Applicability of the Concept of Metabolic Syndrome Defined by the National Cholesterol Education Program–Adult Treatment Panel III to Japanese Men—The Tanno and Sobetsu Study

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Results of a 6-year follow-up study were used to determine whether the concept of and the criteria for metabolic syndrome as defined by the National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATP III) can be applied to Japanese men for prediction of the occurrence of cardiac disease. The subjects were 808 men who underwent mass health check-ups in 1993 and who were not on medication for hypertension, diabetes or hyperlipidemia. Individuals who had hypertriglyceridemia, hypo-high density lipoprotein (HDL) cholesterolemia, high blood pressure, and/or high fasting plasma glucose levels were identified on the basis of the NCEP-ATP III criteria. Not in conformity with the NCEP-ATP III, however, *a cut-off* value of 85 cm was used for waist girth as an indicator of abdominal obesity. The subjects who had 3 or more risk factors were judged as having metabolic syndrome. The proportion of subjects having metabolic syndrome was 25.3%. In the 6-year follow-up study, cardiac disease occurred in 11.7% of the subjects in the metabolic syndrome group and in 6.7% of the subjects in the non-metabolic syndrome group. Results of regression analysis using Cox's proportional hazards model showed that subjects in the metabolic syndrome group had a 2.2-times greater risk of developing cardiac disease than did subjects in the non-metabolic syndrome group. The concept of metabolic syndrome as defined in the NCEP-ATP III was therefore considered to be useful for predicting the occurrence of cardiac disease in Japanese men. (*Hypertens Res* 2005; 28: 203–208)

Key Words: **metabolic syndrome, National Cholesterol Education Program–Adult Treatment Panel III, insulin resistance, prognosis**

Introduction

The third revision of the Adult Treatment Panel (ATP III) (*1*) is a guideline for cholesterol testing and management in the United States published by the National Cholesterol Education Program (NCEP) in 2001. The NCEP-ATP III emphasizes, in addition to the importance of cholesterol control, the importance of other risk factors for development of cardiovascular diseases, especially coronary heart disease, and proposes that concurrence of risk factors in individuals be designated as metabolic syndrome. This indicates that rigid control of the serum cholesterol level alone cannot completely prevent the occurrence of coronary heart diseases and

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Table 1. Characteristics of Subjects with and without Metabolic Syndrome at Baseline (1993)

	Subjects with metabolic syndrome (n=197)	Subjects without metabolic syndrome (n=583)	p
Age (years)	61.8±11.2	59.8±12.1	0.050
BMI (kg/m^2)	25.2±2.9	22.5±2.8	<0.001
Waist (cm)	89.9±6.8	80.5±8.6	<0.001
SBP (mmHg)	140.6±14.4	131.3±18.5	<0.001
DBP (mmHg)	84.8±8.2	80.0±9.1	<0.001
T-cho (mg/dl)	192.8±34.1	184.8±30.4	0.004
HDL (mg/dl)	45.4±13.6	57.2±13.3	<0.001
TG (mg/dl)	211.1±99.2	124.3±64.3	<0.001
FPG (mg/dl)	103.5±25.7	90.7±15.2	<0.001

BMI, body mass index; Waist, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; T-cho, total cholesterol level; HDL, high density lipoprotein-cholesterol level; LDL, low density lipoprotein-cholesterol level; TG, triglyceride level; FPG, fasting plasma glucose. Values are means±SDs.

that risk factors other than low density lipoprotein (LDL)-cholesterol and their concurrence in individuals are crucial to the development of coronary heart diseases.

In the NCEP-ATP III, metabolic syndrome in men is defined as the coexistence in an individual of at least three of the following: 1) waist girth over 102 cm, 2) serum triglyceride level over 150 mg/dl, 3) serum high density lipoprotein (HDL)-cholesterol level below 40 mg/dl, 4) systolic blood pressure (SBP) over 130 mmHg and/or diastolic blood pressure (DBP) over 85 mmHg, and 5) fasting plasma glucose level over 110 mg/dl. The existence of insulin resistance seems to underlie metabolic syndrome. We previously reported that the existence of insulin resistance contributes to the development of metabolic syndrome in Japanese men (*2–4*). In Japanese people with a genetic predisposition to low mean serum cholesterol levels, insulin resistance is relatively more influential than the other risk factors for cardiovascular diseases, including coronary heart disease (*4, 5*). The designation of metabolic syndrome in the NCEP-ATP III appears to be useful for prevention of arteriosclerotic diseases in Japanese people as in the United States. However, to our knowledge, there has been no report on the association between metabolic syndrome and cardiac diseases in Japanese people.

The aim of this study was to determine whether the concept of and the criteria for metabolic syndrome proposed by the NCEP-ATP III can be applied to Japanese men to predict onset of cardiac diseases and whether the criterion of three or more risk factors for the diagnosis of metabolic syndrome is a reasonable one on the basis of the results of a 6-year follow-up study.

Methods

The subjects were 808 men who underwent health examinations in the towns of Tanno and Sobetsu in Hokkaido, Japan (*6*) and who were not receiving treatment for hypertension, diabetes or hyperlipidemia. The mean age of the subjects was 60.3±11.9 years. Information on medication being taken by the subjects was obtained through questionnaires distributed by a health nurse. Informed consent for inclusion in this study was obtained from all subjects. Blood samples were collected early in the morning from subjects more than 10 h after the last dietary intake. The plasma level of glucose (determined by the glucose-oxidize electrode method), and the serum total cholesterol (cholesterol-oxidize–dimethoxy-anilinehydroxy-3-sulfopropyl [DAOS] method), serum HDL-cholesterol (dextran-sulfate magnesium-hydrochloride precipitation method) and serum triglyceride levels (glycerol-3-phosphate-oxidize–DAOS method) were measured. Waist girth was measured (*7*) after expiration at the level of the navel by the same technician. Blood pressure was measured twice in the sitting position using a mercury sphygmomanometer (the first phase of Korotkoff's sound was taken as the SBP and the fifth phase was taken as the DBP). The average of the two measurements was used for analysis.

Subjects having one or more of the following criteria for metabolic syndrome in the NCEP-ATP III were identified: serum triglyceride level over 150 mg/dl (hypertriglyceridemia [HTG]), serum HDL-cholesterol level below 40 mg/dl (low-HDL cholesterolemia [LHDL]), SBP over 130 mmHg and/or DBP over 85 mmHg (high blood pressure [HBP]), fasting plasma glucose level over 110 mg/dl (high fasting plasma glucose level [HFPG]), and waist girth over 85 cm (abdominal obesity [AO]). The criterion for abdominal obesity defined by the NCEP-ATP III is waist girth over 102 cm. Of the 808 subjects in the present study, only 17 (2.7%) fulfilled this criterion (waist girth over 102 cm). We therefore used waist girth over 85 cm, which is the criterion for obesity of visceral fat type of the Japan Society for the Study of Obesity (*7, 8*), as the criterion for AO. Subjects who had 3 or more of the risk factors were judged as having metabolic syndrome (MS group), and subjects who had 2 or less risk factors were judged as not having metabolic syndrome (non-MS group). Twenty-eight men for whom data on waist circumference or

Table 2. Characteristics of Subjects with and Subjects without Cardiac Disease at Baseline (1993)

	Subjects with cardiac disease (n=49)	Subjects without cardiac disease (n=566)	p
Age (years)	64.6±7.4	61.6±10.6	0.014
BMI (kg/m^2)	23.3±3.2	23.2±4.2	0.727
Waist (cm)	85.0±9.8	82.6±9.3	0.104
SBP (mmHg)	136.5±17.6	134.3±18.1	0.399
DBP (mmHg)	81.6±8.1	81.7±9.3	0.944
T-cho (mg/dl)	181.4±31.9	187.0±31.1	0.240
HDL (mg/dl)	53.6±14.9	54.6±14.4	0.676
TG (mg/dl)	139.0±62.2	144.3±85.2	0.584
FPG (mg/dl)	95.8±20.9	93.5±17.9	0.446

Abbreviations are the same as in Table 1. Cardiac diseases are angina pectoris, myocardial infarction, heart failure and death from such cardiac diseases. Values are means±SDs.

on biochemical measures included in the definition of MS were missing were excluded, leaving 780 men for analysis.

The subjects were followed up for 6 years. The end-point was the occurrence of cardiac diseases, including angina pectoris, myocardial infarction, and heart failure, or death from such cardiac diseases. Occurrence of cardiac diseases was determined by interviews with the subjects and their families, notification from district health nurses, and distribution of questionnaires to family doctors who had treated subjects with cardiac disease. Diagnosis of cardiac disease was made from clinical symptoms and results of laboratory examinations such as ECG, chest X-ray photograph (XP) and blood tests. Diagnosis of coronary heart disease was made on the basis of the criteria of the MONICA project (available from: http://www.ktl.fi/publications/monica/manual/index.htm). The incidence of cardiac diseases during the 6-year period was compared between the MS group and the non-MS group. Moreover, the incidences of cardiac diseases in subjects who had 2 or more risk factors (2, 3, 4 or 5 risk factors) and in subjects who had 4 or more risk factors (4 or 5 risk factors) in the first year were compared with the incidences in subjects who had less than 2 risk factors (0 or 1 risk factor) and in subjects who had less than 4 risk factors (1, 2 or 3 risk factors), respectively. Follow-up was started in August 1993 and completed in August 1999.

The Japanese Windows Edition of the Statistical Package for Social Science (SPSS) Ver. 11 was used for statistical analysis. All numerical values are expressed as the means±SD. The unpaired t-test was used for examination of intergroup differences. For analysis of factors determining prognosis, Cox's proportional hazards model was used. A p-value less than 0.05 was considered statistically significant.

Results

The mean age of all subjects was 60.3±11.9 years, the mean body weight was 61.3±9.8 kg, the mean body mass index (BMI) was 23.1±3.0 kg/m^2 and the mean waist girth was 82.8±9.2 cm. The mean SBP and DBP were 133.7±18.0 mmHg and 81.2±9.1 mmHg, respectively, and the mean plasma levels of total cholesterol, HDL-cholesterol, triglyceride and fasting blood glucose were 186.8±31.6 mg/dl, 54.3±14.4 mg/dl, 146.2±83.6 mg/dl and 94.1±19.3 mg/dl, respectively.

The proportions of subjects with AO, HTG, LHDL, HBP and HFPG were 43.1%, 35.7%, 16.5%, 59.4% and 13.8%, respectively. The proportions of subjects without risk factors was 18.1%, and the proportions of subjects with 1, 2, 3, 4 and 5 risk factors were 29.7%, 26.9%, 17.5%, 6.8% and 1.0%, respectively. The proportionsof subjects with 2 or more, 3 or more and 4 or more risk factors were 52.2%, 25.3% and 7.8%, respectively. Subjects who had 3 or more risk factors were assigned to the MS group.

Table 1 compares the profiles of subjects in the MS group with those of subjects in the non-MS group (*i.e.*, subjects with two or less risk factors). There were no significant differences between the two groups in age. The values of BMI, waist girth and blood pressure and the levels of total cholesterol, triglycerides and fasting plasma glucose were significantly higher in the MS group. The HDL-cholesterol level was significantly lower in the MS group.

During the follow-up study, from 1993 to 1999, 193 subjects dropped out. There was no significant difference between the subjects who dropped out and the remaining subjects in terms of the proportion of subjects with metabolic syndrome. The remaining 615 subjects were followed for a mean period of 4.8 years. Cardiac disease occurred in 49 subjects (angina pectoris occurred in 30 subjects, myocardial infarction in 15 subjects and heart failure in 4 subjects), or 31 subjects in the non-MS group and 18 subjects in the MS group.Thirty-two of the subjects with 2 or more risk factors and four of the subjects with 4 or more risk factors developed cardiac disease. Table 2 shows a comparison of clinical characteristics at baseline between subjects with and those without cardiac disease. There were no significant differences between the two groups in the values of BMI, waist girth or

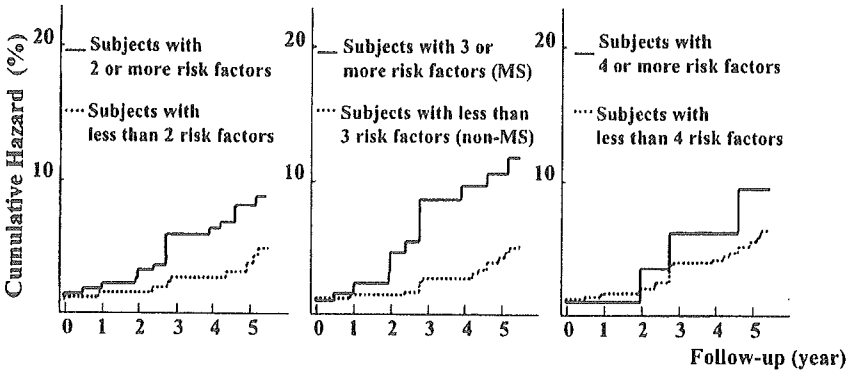

Fig. 1. *Kaplan-Meier hazard curves for onset of cardiac disease. The relative risk in the MS group was 2.23 (95% CI: 1.14–4.34,* p = *0.019)-times higher than that in the non-MS group. The risk in the subjects with 2 or more risk factors relative to the risk in the subjects with less than 2 risk factors was 1.43 (0.73–2.81,* p = *0.301). The risk in the subjects with 4 or more risk factors relative to the risk in the subjects with less than 4 risk factors was 1.74 (0.61–4.93,* p = *0.299). Relative risk was determined by Cox's proportional hazards model adjusted for age, smoking and total cholesterol.*

blood pressure or in the levels of total cholesterol, triglycerides, fasting plasma glucose and HDL-cholesterol. The Kaplan-Meier hazard curve showed that the incidence of cardiac diseases was significantly higher in the MS group than in the non-MS group during the follow-up study (Fig. 1). The relative risk of occurrence of cardiac diseases in the MS group was 2.23 (95% confidence interval [CI]: 1.14–4.34; p=0.019)-times higher than that in the non-MS group according to the results of analysis using Cox's proportional hazards model adjusted for age, smoking and total cholesterol. The risks of occurrence of cardiac diseases in the subjects with 2 or more risk factors and in those with 4 or more risk factors relative to the risks in the subjects with less than 2 risk factors and in those with less than 4 risk factors were 1.43 (0.73–2.81, p=0.301) and 1.74 (0.61–4.93, p=0.299), respectively (Table 3).

Discussion

Hyperlipidemia, hypertension, disorders in glucose tolerance, and obesity are well-known risk factors for cardiovascular diseases. It was clarified by epidemiological studies in the 1990s that even if the risks of individual factors were not serious, the probability of the occurrence of ischemic cardiac diseases would increase when many risk factors coexisted in an individual (*9–16*). The clinical findings for metabolic syndrome as defined by the NCEP-ATP III reflect this state. The definition of metabolic syndrome by NCEP-ATP III emphasizes the importance of abdominal obesity and includes in the diagnostic criteria mild risk factors such as blood pressure at high levels within the normal range and hyperglycemia under a fasting condition. The diagnostic criteria for individual risk factors are shown more clearly in the criteria of metabolic syndrome as defined by NCEP-ATP III. High blood pressure and hyperglycemia are defined as risk factors in MS, even though in general they are less severe conditions than hypertension or diabetes as defined in the Sixth Report of the Joint National Committee (JNC VI) (*17*), or by the criteria of the World Health Organization-International Society of Hypertension (WHO/ISH) (*18*), the World Health Organization (WHO) (*19*), or the American Diabetes Association (ADA) (*20*) . This indicates that the concurrence of mild risk factors is crucial for the development of arteriosclerosis in the concept of metabolic syndrome.

In the present study, the criteria for metabolic syndrome in the NCEP-ATP III were applied to Japanese men with the modification that 85 cm instead of 102 cm was used for the cut-off value of waist girth for AO. Using the original NCEP-ATP III criteria, only 2.7% of the present subjects fulfilled the criterion of waist girth over 102 cm, and the prevalence of the metabolic syndrome was 12%. We therefore used as the criterion for AO waist girth over 85 cm, which is the criterion of the Japan Society for the Study of Obesity (*7, 8*) for obesity of visceral fat type. Waist girth of 85 cm in Japanese men is known to correspond to an area occupied by visceral fat of 100 cm^2 in transverse CT images at the level of the navel (*8*). The incidences of hypertension, diabetes, hyperlipidemia and diseases of the circulatory organs are high in men in whom the area of visceral fat exceeds 100 cm^2 in transverse CT images (*8, 21*). An increase in the amount of visceral fat, which causes abdominal obesity, tends to induce insulin resistance and is associated with arteriosclerosis (*8, 21, 22*). Measurement of waist girth is a simple but apparently useful method for diagnosing abdominal obesity. In Asians, decreasing the criterion of waist circumference increased the prevalence of the metabolic syndrome. When the criterion of waist

Table 3. Hazard Ratio for Occurrence of Cardiac Diseases According to the Results of Cox's Proportional Hazards Model Adjusted for Age, Smoking and Total Cholesterol

Subjects	Hazard ratio (95% confidence interval)
With 2 or more risk factors†	1.43 (0.73–2.81)
With 3 or more risk factors (MS)††	2.23 (1.14–4.34)*
With 4 or more risk factors†††	1.74 (0.61–4.93)

*$p<0.05$. †The risk of occurrence of cardiac diseases in the subjects with 2 or more risk factors relative to the risk in those with less than 2 risk factors. ††The risk in the MS group relative to the risk in the non-MS group. †††The risk in the subjects with 4 or more risk factors relative to the risk in those with less than 4 risk factors.

circumference was decreased from 102 cm to 90 cm, the prevalence of the metabolic syndrome increased 13% to 21% in the Singapore male population (*23*), and 16% to 29% in the Korean male population (*24*). This suggests that NCEP-ATP III criteria may underestimate the population at risk in the Asian population. There is thus need of a new abdominal obesity criterion for metabolic syndrome that is suitable for the Japanese population.

Lakka *et al.* (*25*) reported in 2002 that the risk of mortality from coronary heart diseases was higher in individuals with metabolic syndrome in the ordinary Finnish male population that included subjects who were receiving treatment for hypertension or hyperlipidemia, and they emphasized the importance of prevention of development of metabolic syndrome and the importance of its diagnosis and therapy in an early stage. In the present study, in the subjects who were not receiving treatment for hypertension, diabetes or hyperlipidemia, the relative risk of mortality and morbidity from cardiac disease in the metabolic syndrome group, even after adjusting for age, smoking and total cholesterol, was 2.2-times greater than that in the non-metabolic syndrome group.

On the other hand, there were no significant differences between cardiac disease mortality/morbidity in the subjects with 2 or more risk factors and those with less than 2 risk factors or between cardiac disease mortality/morbidity in the subjects with 4 or more risk factors and those with less than 4 risk factors. This indicates that the NCEP-ATP III criterion for metabolic syndrome, *i.e.*, the presence of 3 or more risk factors, is reasonable for predicting cardiac disease in the Japanese population.

Our results indicate that the concept of metabolic syndrome defined by the NCEP-ATP III is useful for prediction of onset of cardiac disease in Japanese men.

The concept of metabolic syndrome seems to be strategically important for prevention of arteriosclerotic diseases in Japan as well as in the United States, Finland or other countries, because individuals with metabolic syndrome can be easily identified according to the criteria. It is important to control risk factors for cardiovascular diseases, such as lipid metabolic disorders, high blood pressure, disorders in glucose tolerance, and obesity, in persons with metabolic syndrome (*i.e.*, in persons having three or more of these risk factors), even if the risk of each factor is not serious. A strategy for the control of these risk factors is therefore needed.

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ORIGINAL ARTICLE

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Incidence of insulin resistance in obese subjects in a rural Japanese population: The Tanno and Sobetsu study

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Objectives: Although it is well known that obesity is closely related to insulin resistance, the incidence of the development of insulin resistance in people with obesity is not known. In this study, we investigated the incidence of insulin resistance in citizens of two rural communities in Japan.

Subjects and methods: The subjects were 102 men and 126 women over the age of 30 years selected from 1035 citizens who had undergone medical examinations in the towns of Tanno and Sobetsu, Hokkaido, in 1991 and 1998. Those who were on medication for hypertension, diabetes, hyperlipidaemia, coronary heart disease and cerebral vessel disease were excluded. The simple index to determine insulin resistance [i.e. homeostasis model assessment (HOMA-R) $\geq$ 1.73] was used, and subjects who were determined to be positive for insulin resistance according to this index in 1991 were also excluded in order to determine the incidence of insulin resistance in subjects who had no abnormalities other than obesity. The systolic blood pressure (SBP), diastolic blood pressure, body mass index (BMI), triglyceride level, high-density lipoprotein level, blood sugar level, serum insulin value and HOMA-R were measured in all subjects in 1991 and in 1998. Moreover, the subjects were divided into two groups according to BMI, a normal group consisting of subjects with BMI < 25 and an obesity group consisting of subjects with BMI $\geq$ 25. We also compared the incidences of insulin resistance in normal and obesity groups of subjects who were newly determined to be positive for insulin resistance on the basis of data obtained from medical examinations conducted in 1998.

Results: The incidence of insulin resistance was significantly higher in the obesity group than in the normal group (25.0 vs. 4.5%). The results of logistic regression analysis showed that obesity was closely related to insulin resistance and that the relative risk of development of insulin resistance adjusted for age, sex, SBP, FPG and HDL was 3.193 (95% CI 1.085–9.401).

Conclusions: The incidence of insulin resistance was significantly higher in the obesity group than in the normal group in this study, suggesting that improvement in obesity is important for prevention of the occurrence of type 2 diabetes or atherosclerotic disease based on insulin resistance.

Keywords: community-based survey, HOMA-R, incidence, insulin resistance, obesity

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Introduction

In recent years, the incidences of lifestyle-related diseases, such as hypertension, diabetes and dyslipidaemia, have been increasing, and much interest has been shown in insulin resistance as a common cause of these lifestyle-related diseases. In addition, there have been many reports recently on insulin resistance and the

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development and seriousness of coronary artery diseases [1–4]. Although it is well known that obesity is closely related to insulin resistance, the incidence of insulin resistance in people with obesity is not known. In this study, we investigated the incidence of insulin resistance in citizens of two rural communities in Japan.

Materials and Methods

The subjects were 102 men and 126 women over the age of 30 years selected from 1035 citizens who had undergone medical examinations in the towns of Tanno and Sobetsu, Hokkaido, both in 1991 and 1998. Levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP), body mass index (BMI), fasting plasma glucose (FPG), fasting immunoreactive insulin (FIRI), total cholesterol (TC), triglyceride and high-density lipoprotein cholesterol (HDL-C) were measured in each subject. Blood samples were collected early in the morning, when more than 10 h had passed since dietary intake and subjects felt hungry. Subjects in whom any of the following data had been obtained in medical examinations in 1991 were excluded: diabetes mellitus of 126 mg/dl or more in FPG, based on the standards of America Diabetes Association (ADA) [5]; hypertension of 140 mmHg or more in SBP and/or 90 mmHg in DBP, based on the standards of JNC–VI [6] and WHO/ISH [7]; obesity of 25.0 or more in BMI, which is the standard of the Japan Society of the Study of Obesity [8] and dyslipidaemia (i.e. hyperlipidaemia of 220 mg/dl or more in TC and/or 150 mg/dl or more in triglyceride and HDL level below 40 mg/dl), as described in the treatment standards of the Japan Atherosclerosis Society [9]. Those who were on medication for hypertension, diabetes, hyperlipidaemia, coronary heart disease or cerebral vessel disease were also excluded. HOMA-R [10] was used as an indicator of insulin resistance. HOMA-R was calculated by the formula 'fasting insulin value × fasting blood sugar level/405'. The simple index reported by Oimatsu *et al.* [11] to determine insulin resistance (i.e. HOMA-R $\geq$ 1.73) was used. Only a simple outline of each procedure is given below. The tests using the GC method and 75-g glucose tolerance tests (OGTTs) were carried out in 57 men and women with normotension or essential hypertension (EHT). Using the M value of 167.3 mg/m^2/min (mean value minus one s.d. of the mean value), which is the rate of infusion of glucose in the GC method that serves as an index of insulin resistance, as the reference point for determination of insulin resistance, the subjects were divided into an insulin resistance group (EHT-R group) and insulin non-resistance group (EHT-N group), and data in the two groups were compared. Also, from data on temporal blood sugar levels, insulin values and HOMA-R obtained from simultaneously performed OGTTs, the cut-off values for distinguishing EHT-R classified according to the results of the GC tests were examined using the receiver operator characteristic curve. When the cut-off value for positive insulin resistance was set to $\geq$1.73 in HOMA-R, the sensitivity and the specificity for evaluation of insulin resistance were 64.3 and 78.9%, respectively. The sensitivity and specificity by using HOMA-R were lower than those by using plasma insulin level at 120 min after glucose loading (sensitivity of 71.4% and specificity of 94.7%), but HOMA-R is considered to be useful for mass medical examinations and mass studies, because it can be assessed with only single blood sampling. Therefore, it was concluded that HOMA-R $\geq$ 1.73 was useful for evaluation of insulin resistance in an epidemiological study.

Subjects who were determined to have insulin resistance according to this index (HOMA-R $\geq$ 1.73 in 1991) were also excluded in order to determine the incidence of insulin resistance in subjects who had no abnormalities other than obesity. The subjects were divided into two groups according to BMI, a normal group consisting of subjects with BMI < 25 and an obesity group consisting of subjects with BMI $\geq$ 25, and the measured items in the two groups were compared.

We also compared the incidences of insulin resistance in normal and obesity groups of subjects who were newly determined to be positive for insulin resistance on the basis of data obtained from medical examinations conducted in 1998.

The SPSS package (Ver. 11.5J) was used for statistical analysis. All numerical values are expressed as mean ± s.d. The unpaired *t*-test and the χ^2 test were used for examination of intergroup differences and for frequency comparison, respectively. The significance level was set at $p < 0.05$.

Results

In this study, frequencies of obesity (BMI $\geq$ 25) were 14.9% in 1991 and 19.7% in 1998. Frequencies of obesity in both men and women were higher in 1998 than in 1991 (men 16.7 vs. 11.8% and women 22.2 vs. 17.5%). The prevalence of type 2 diabetes in 1991 was 6.5% (8.9% in men and 4.9% in women), and 77% of the subjects with diabetes were on medication.

The prevalence of insulin resistance (HOMA-R $\geq$ 1.73) in 1991 was 49.3% (44.6% in men and 52.6% in women).

Table 1 shows the characteristics of the subjects in the normal and obesity groups in 1991. FIRI and HOMA-R were higher in the obesity group than those in the normal group. Table 2 shows the characteristics of the subjects in these groups in 1998. FIRI and HOMA-R were also higher in the obesity group than those in the normal group. HOMA-R in 1998 had significant positive correlations with BMI in 1991 and BMI in 1998 (BMI in 1991, $r = 0.298$, $p < 0.0001$ and BMI in 1998, $r = 0.363$, $p < 0.0001$).

The results of 7 years follow-up were shown in figure 1. Seventeen of the 197 subjects in the normal group with BMI $\geq$ 25 in 1998 and six of the 34 subjects in the obesity group with BMI < 25 in 1998 were excluded. Eight subjects in the normal group and seven subjects in the obesity group were newly defined as positive for insulin resistance in 1998. The incidence of insulin resistance was significantly higher in the obesity group than that in the normal group (25 vs. 4.5%) (figure 2). Table 3 shows the characteristics of the subjects in the non-IR group (HOMA-R in 1998 < 1.73) and the IR group (HOMA-R in 1998 $\geq$ 1.73). BMI, FPG, FIRI and HOMA-R were higher in the IR group than those in the non-IR group. The results of logistic regression analysis showed that obesity was closely related to insulin resistance and that the relative risk of occurrence of insulin resistance adjusted for age, sex, SBP, FPG and HDL was 3.193 (95% CI 1.085–9.401) (table 4).

Table 1 Characteristics of subjects in the normal and obesity groups in 1991

Parameters in 1991	Normal group (n = 194)	Obesity group (n = 34)
Age	54.7 ± 11.0	54.2 ± 7.2
Male	46.4	35.3
BMI (kg/m^2)	21.6 ± 1.9	26.1 ± 1.3*
SBP (mmHg)	118.4 ± 11.2	120.5 ± 10.1
DBP (mmHg)	71.2 ± 7.6	72.7 ± 6.3
TC (mg/dl)	177.7 ± 25.2	180.5 ± 20.0
Triglyceride (mg/dl)	89.1 ± 28.5	97.2 ± 28.0
HDL-C (mg/dl)	58.5 ± 11.0	54.9 ± 11.0
FPG (mg/dl)	85.4 ± 9.9	87.1 ± 8.7
FIRI (mU/l)	3.8 ± 1.8	4.8 ± 1.7*
HOMA-R	0.79 ± 0.39	1.02 ± 0.35*

BMI, body mass index; DBP, diastolic blood pressure; FIRI, fasting immunoreactive insulin; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol; SBP, systolic blood pressure; TC, total cholesterol. For normal group, BMI < 25.0 and obesity group, BMI $\geq$ 25.0. FIRI and HOMA-R were higher in the obesity group than in the normal group.

*$p < 0.05$, unpaired *t*-test and χ^2-test.

Discussion

In recent years, the incidences of lifestyle-related diseases, such as hypertension, diabetes and dyslipidaemia, have been increasing, and much interest has been shown in insulin resistance as a common cause of these lifestyle-related diseases. The prevalence of cardiovascular disease risk factors increases with increase in frequency of obesity [12]. It is well known that obesity is one of the important component elements of insulin resistance syndrome [13] and is one of the background factors of insulin resistance.

It is known that obesity, particularly abdominal obesity, is closely related to development of insulin resistance. The activity levels of steatogenesis and lipolysis in visceral fat are much higher than those in the panniculus adiposus. As visceral fat is anatomically connected to the portal vein, most of the free fatty acid (FFA) that is released from visceral fat flows into the liver. It is thought that when high concentrations of FFA flow into the liver, the catabolism of insulin becomes disordered and insulin receptors at target cells are disordered due to the high plasma insulin level. One hypothesis is that FFA flowing into the liver causes impairment of the glycolytic pathway, resulting in increases in glyconeogenesis and plasma glucose level, and another hypothesis is that high concentrations of FFA inhibit glucose uptake in skeletal muscles [14]. It has recently been reported that adipocytokines are closely related to development of insulin resistance. It is thought that TNF-α released from enlarged adipocytes

Table 2 Characteristics of subjects in the normal and obesity groups in 1998

Parameters in 1998	Normal group (n = 194)	Obesity group (n = 34)
Age	60.7 ± 1.1	60.3 ± 7.4
BMI (kg/m^2)	22.0 ± 2.2	26.2 ± 2.4*
SBP (mmHg)	130.7 ± 16.9	135.2 ± 17.1
DBP (mmHg)	77.0 ± 10.8	80.6 ± 9.6
TC (mg/dl)	188.9 ± 28.4	189.3 ± 25.0
Triglyceride (mg/dl)	88.1 ± 46.5	92.9 ± 36.1
HDL-C (mg/dl)	62.1 ± 14.1	57.2 ± 13.1
FPG (mg/dl)	92.4 ± 9.5	91.4 ± 10.6
FIRI (mU/l)	4.0 ± 1.9	5.3 ± 2.8*
HOMA-R	0.91 ± 0.47	1.21 ± 0.66*

BMI, body mass index; DBP, diastolic blood pressure; FIRI, fasting immunoreactive insulin; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol; SBP, systolic blood pressure; TC, total cholesterol. For normal group, BMI < 25 and obesity group, BMI $\geq$ 25. FIRI and HOMA-R were higher in the obesity group than in the normal group.

*$p < 0.05$, unpaired *t*-test.

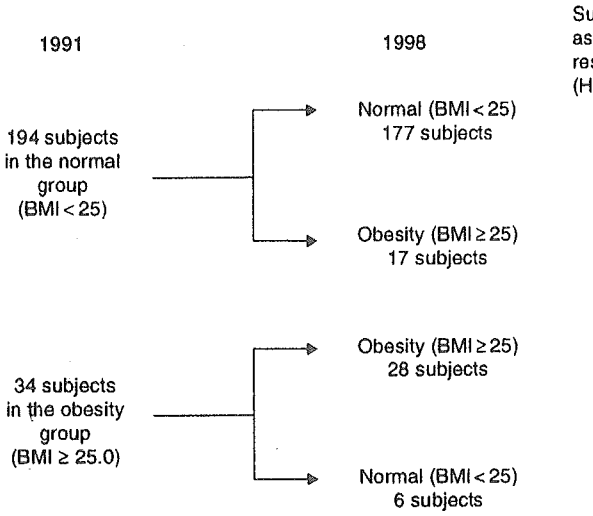

Fig. 1 Seventeen of the 197 subjects in the normal group with body mass index (BMI) ≥ 25 in 1998 and six of the 34 subjects in the obesity group with BMI < 25 in 1998 were excluded. Eight subjects in the normal group and seven subjects in the obesity group were newly defined as positive for insulin resistance in 1998.

impairs 'insulin-signal transmission' [15] and that a decrease in adiponectin results in the development of a state of insulin resistance [16]. Therefore, it is suggested that improvement in obesity leads not only to improvement in type II diabetes, hypertension and hyperlipidaemia but also to improvement in insulin resistance, which is a common background of diabetes, hypertension and hyperlipidaemia.

Although it is known that obesity is closely related to insulin resistance, there are a very few reports on incidence of insulin resistance in obese subjects who have no lifestyle-related diseases. In this study, we investigated the incidence of insulin resistance in citizens of two rural communities in Japan. The incidence of insulin resistance was significantly higher in the obesity group than that in the normal group. The results of logistic regression analysis showed that obesity was closely related to insulin resistance and that the relative risk of development of insulin resistance adjusted for age, sex, SBP, FPG and HDL was 3.193.

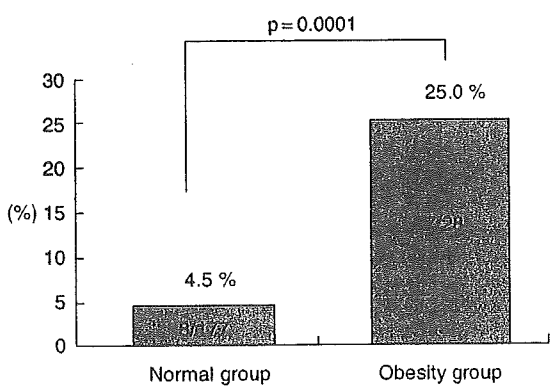

Fig. 2 Incidence of insulin resistance was significantly higher in the obesity group than that in the normal group. Insulin resistance: HOMA ≥ 1.73.

The Adult Treatment Panel III of the National Cholesterol Education Program [17] has proposed specific criteria for diagnosis of metabolic syndrome, a clustering of cardiovascular risk factors that is closely associated with insulin resistance. Epidemiological studies have shown that individuals with metabolic syndrome and insulin resistance have a threefold higher incidence of cardiovascular disease and a significantly higher cardiovascular mortality rate [18]. In recent study, the prevalence of metabolic syndrome was estimated to be one in four US

Table 3 Characteristics of subjects in the non-insulin resistance (IR) and IR groups in 1991

Parameters in 1991	Non-IR group (n = 209)	IR group (n = 19)
Age	54.9 ± 10.6	52.1 ± 9.3
Male	46.9	31.1
BMI (kg/m^2)	22.1 ± 2.3	23.9 ± 2.8*
SBP (mmHg)	118.4 ± 11.2	122.4 ± 9.3
DBP (mmHg)	70.9 ± 7.3	77.0 ± 5.6
TC (mg/dl)	177.4 ± 24.3	185.8 ± 26.1
Triglyceride (mg/dl)	90.7 ± 28.8	86.1 ± 25.6
HDL-C (mg/dl)	58.1 ± 11.1	56.4 ± 11.0
FPG (mg/dl)	85.2 ± 9.6	91.1 ± 9.8*
FIRI (mU/l)	3.8 ± 1.8	5.1 ± 1.9*
HOMA-R	0.80 ± 0.35	1.13 ± 0.40*

BMI, body mass index; DBP, diastolic blood pressure; FIRI, fasting immunoreactive insulin; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol; SBP, systolic blood pressure; TC, total cholesterol. Non-IR group, HOMA-R in 1998 < 1.73; IR group, HOMA-R ≥ 1.73. BMI, FPG, FIRI and HOMA-R in 1991 were higher in the IR group than in the non-IR group.
*$p < 0.05$, unpaired t-test and χ^2-test

Table 4 Relative risk of incidence of insulin resistance adjusted for age, sex, systolic blood pressure (SBP), fasting plasma glucose (FPG) and high-density lipoprotein-cholesterol (HDL-C)

	Wald	p value	Exp (B)	95% CI
Age	1.505	0.220	0.966	0.913–1.021
Sex	3.139	0.076	2.991	0.890–10.053
SBP	2.053	0.152	2.991	0.890–10.053
FPG	5.725	0.017	1.069	1.012–1.129
HDL-C	0.094	0.759	0.946	0.946–1.041
Obesity	4.441	0.035	3.193	1.085–9.401

The results of logistic regression analysis showed that the relative risk of development of insulin resistance adjusted for age, sex, SBP, FPG and HDL was 3.193.

adults [19]. We also previously reported estimation using the insulin resistance index obtained from the reference value by HOMA-R which indicated that approximately 20% of ordinary citizens have insulin resistance [20]. Identification of these high-risk individuals is crucial to provide appropriate therapy using currently available disease-modifying treatments. Effective means for not only diagnosing and treating insulin resistance but also for preventing the occurrence of insulin resistance are needed.

In conclusion, improvement in obesity is thought to be very important for prevention of the occurrence of type 2 diabetes or atherosclerotic disease based on insulin resistance. However, the limitation of this study is that the data do not support this statement, as subjects without obesity also developed insulin resistance.

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CLINICAL STUDY

Influence of gender, age and renal function on plasma adiponectin level: the Tanno and Sobetsu study

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Abstract

Design: The aim of this study was to determine the association between aging and adiponectin level from the aspect of the influence of renal function and sex hormones in humans.

Methods: Serum adiponectin and blood urea nitrogen (BUN) levels were measured in 964 subjects (372 males) aged 60.3±12.5 years. Testosterone and free testosterone levels were measured in 123 males, and estrone and estradiol levels were measured in 114 females. The subjects were divided into two age groups: 65 years of age or older (Age ≥65 group) and less than 65 years of age (Age <65 group).

Results: Adiponectin level increased linearly with aging in males, whereas it increased dramatically in females until their 50s. The patterns of changes in adiponectin were similar to those in BUN. In multiple-regression analysis using adiponectin as a dependent variable BUN was selected as a significant independent variable in all subjects and in subjects in the Age ≥65 group, whereas bioactive sex hormones were not selected.

Conclusions: A decrease in adiponectin clearance in the kidney may be the cause of high levels of adiponectin in the elderly. Adiponectin level seems to be influenced more strongly by BUN than by sex hormones and to be increased by a decline in renal function with aging.

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Introduction

Adiponectin is a 244-amino-acid plasma protein (1) that was identified from a gene, *apM1*, specifically expressed in fat tissue. Adiponectin has been shown to circulate as a trimer, hexamer or higher-molecular-mass form in the blood of healthy subjects and to be present at a high level of 5–10 μg/ml (2–6). It has been shown that the ratios among these forms determine their activity (7–9). There are also significant sex differences in the circulating concentrations of adiponectin and in the ratios of their subunits (7, 10). Differences between adiponectin levels were found in normotensive and hypertensive men with abnormal renal function, but not in women (10). It has been reported that the level is low in subjects carrying excessive organ fat and that the level increases with a reduction in body weight and is correlated negatively with body mass index (BMI) (3). In addition, adiponectin level has been shown to be correlated negatively with blood pressure and triglyceride level and positively with high-density lipoprotein (HDL) level and to be decreased in patients with hypertension (11) and hyperlipidemia (12, 13). It has also been shown to be correlated negatively with fasting plasma glucose (FPG) level, plasma glucose level 2 h after a meal and fasting insulin concentration (14, 15), and to be closely associated with insulin resistance (16–20).

On the other hand, it has been reported that adiponectin levels are elevated in the elderly (21, 22). This seemingly contradictory finding that levels of adiponectin, which has anti-atherosclerotic properties, were elevated in elderly subjects who were presumed to have developed atherosclerosis due to the accumulation of risk factors is intriguing. Previous studies showed that there is an inverse relationship between adiponectin and creatinine clearance in essential hypertensives and that adiponectin level was increased in patients with a combination of decline of renal function and hypertension (10). It has also been reported that adiponectin level was increased in patients with end-stage renal disease (23) and that adiponectin level was positively associated with impaired renal function, assessed by urinary albumin-to-creatinine ratio, in patients with diabetes (24). However, the mechanisms by which adiponectin is metabolized and excreted are not known,

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and the relationship between renal function and adiponectin level in humans who are relatively healthy has not been determined. Most of serum testosterone binds to albumin and sex-hormone-binding globulins, and serum free testosterone, which accounts for 1–2% of total serum testosterone, exhibits biological activity in humans (25). However, the mechanisms by which androgen affects adiponectin level have also not been determined, and there has been little investigation of the relationship between free testosterone and adiponectin levels.

In this study, we examined the association between aging and adiponectin level from the aspect of the influence of a decline of renal function or sex hormones in participants in mass-screening tests for residents in a region of Hokkaido, Japan.

Subjects and methods

Of 1519 participants in mass-screening tests for the residents of the towns Tanno and Sobetsu in Hokkaido, Japan, in 2003, 964 males and females with an average age of 60.3±12.5 years (372 males with an average age of 62.8±12.4 years and 592 females with an average age of 58.8±12.3 years) were selected after exclusion of patients undergoing treatment for hypertension, diabetes and hyperlipidemia (subjects from the first selection), and 237 males and females with an average age of 58.3±16.2 years (123 males with an average age of 59.8±16.7 years and 114 females with an average age of 56.6±15.6 years) were randomly selected from seven 10-year age brackets (30s to 90s) in males and from six 10-year age brackets (30s to 80s) in females, with a maximum of 21 subjects from each bracket, after exclusion of patients undergoing treatment for hypertension, diabetes and hyperlipidemia (subjects from the second selection). Since the number of subjects in the 90s bracket in males was only four, they were included in the 80s bracket in males. Patients with reproductive organ disease that might affect sex hormones were not included in this study.

The mass-screening tests were carried out between 0600 and 0800 h in the morning. Height and body weight were measured before blood-pressure measurement, and blood was collected from the subjects under fasting conditions before breakfast. Blood pressure was measured more than once from the right arm after resting for several minutes in a sitting position, and the average was calculated. Blood was collected from the median cubital vein in a sitting position with a vacuum tube. The items measured were systolic blood pressure (SBP), diastolic blood pressure (DBP), BMI, FPG, total cholesterol, triglyceride, HDL, blood urea nitrogen (BUN), serum creatinine and serum adiponectin concentrations. Serum was stored in a freezer at −20 °C. The frozen serum was used to measure testosterone and free testosterone concentrations in males and estrone (E1) and estradiol (E2) concentrations in females after 4 months. Biochemical data were assayed as follows: FPG, the glucose-oxidase electrode method; total cholesterol, the cholesterol oxidase enzymatic assay method; triglyceride, the enzymatic colorimetric method; HDL, the direct liquid-stable assay; BUN, urease- glutamate dehydrogenase method; serum creatinine, Jaffe reaction method; adiponectin, the sandwich ELISA method (human adiponectin ELISA kit; Otsuka Pharmaceutical Co., Tokyo, Japan); testosterone and free testosterone, solid-phase RIA method (Coat-A-Count TotalTestosterone and Coat-A-Count Free Testosterone Diagnostic Products Corp., Los Angeles, CA, USA); E1, the double-antibody RIA method (ESTRONE RIA; Diagnostic Systems Laboratories, Inc., Webster, TX, USA); and E2, solid-phase RIA method (Coat-A-Count Estradiol; Diagnostic Products Corp.). The minimum detectable values for testosterone, free testosterone, E1 and E2 were < 5.0 ng/dl (0.17 nM), < 0.5 pg/ml (1.73 pM), < 15.0 pg/ml (55.5 pM) and < 8.0 pg/ml (29.4 pM), respectively.

The subjects from the first selection were divided into two age groups, 65 years of age or older (Age ≥65 group) and less than 65 years of age (Age <65 group), to compare indices in middle-aged and elderly subjects. Multiple-regression analysis was performed with adiponectin as a dependent variable for both data from subjects from the first selection and data from subjects from the second selection.

The present study was carried out in accordance with the Declaration of Helsinki (1981) of the World Medical Association, and the study protocol was approved by the Research Committee of Sapporo Medical University, Sapporo, Japan. Written, informed consent was obtained from each subject after full explanation of the purpose, nature and risk of all procedures used.

Statistical analysis was performed with Windows SPSS version 12.0 in Japanese (SPSS Japan). Since adiponectin showed an *F* distribution, natural logarithmic-transformed values (LnAdipo) were used, and each value is presented as a mean±S.D. The unpaired *t*-test was used to compare data in two groups. A *P* value of less than 0.05 was considered statistically significant.

Results

The characteristics of subjects from the first selection are shown in Table 1. Adiponectin concentrations were 6.02±3.33 μg/ml in males and 8.91±4.20 μg/ml in females, the concentration being significantly higher in females than in males. LnAdipo correlated positively with age, HDL and BUN and negatively with BMI, DBP, FPG, total cholesterol and triglyceride in males and correlated positively with age, HDL and BUN and negatively with BMI, FPG and triglyceride in females. Age, BMI, SBP, DBP, FPG, triglyceride, BUN and serum creatinine were

Table 1 Background of subjects from the first selection (mean values and correlations related to adiponectin).

	Males ($n = 372$)		Females ($n = 592$)	
	Mean±S.D.	r	Mean±S.D.	r
Age (years)	62.8±12.4*	0.359†	58.8±12.3	0.175†
BMI (kg/m^2)	23.8±3.3*	−0.314†	23.1±3.2	−0.248†
SBP (mmHg)	133.5±21.1*	0.020	129.2±23.2	0.031
DBP (mmHg)	75.9±11.9*	−0.120†	73.0±12.2	−0.004
FPG (mg/dl)	97.2±16.5*	−0.122†	93.3±16.4	−0.200†
TC (mg/dl)	193.2±33.0*	−0.162†	205.3±32.7	0.038
TG (mg/dl)	115.4±75.4*	−0.346†	89.3±43.5	−0.181†
HDL (mg/dl)	51.4±11.6*	0.285†	59.3±13.5	0.201†
BUN (mg/dl)	16.5±4.1*	0.179†	15.0±4.0	0.147†
Cr (mg/dl)	1.10±0.33*	0.082	0.89±0.26	0.071
Adipo (μg/ml)	6.02±3.33*		8.91±4.20	

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; BUN, blood urea nitrogen; Cr, serum creatinine; Adipo, adiponectin.
r, versus LnAdipo, Pearson's correlation coefficient.
* $P < 0.05$ versus females, unpaired t-test.
† $P < 0.05$ versus LnAdipo, Pearson's correlation.
Conversion factors: FPG, mM = mg/dl × 0.05551; TC, mM = mg/dl × 0.02586; TG, mM = mg/dl × 0.01129; HDL, mM = mg/dl × 0.02586; BUN, mM = mg/dl × 0.3570; Cr, μM = mg/dl × 88.40.

significantly higher in males than in females, and total cholesterol and HDL were significantly lower in males than in females.

The mean values of adiponectin and BUN in relation to age are shown in Figs 1 and 2. Adiponectin increased linearly with aging in males, whereas in females it increased sharply until the 50s age bracket with a convex curve and then increased gradually (Fig. 1). The patterns of changes in adiponectin were similar to the patterns of changes in BUN (Figs 1 and 2).

In multiple-regression analysis of sex differences, age, BMI, SBP, FPG, total cholesterol, triglyceride, HDL and BUN with LnAdipo as a dependent variable, BUN was selected as a significant independent variable as well as sex differences, age, BMI, FPG, triglyceride and HDL (Table 2). SBP, BUN and adiponectin were significantly higher and BMI and triglyceride were significantly lower in males in the Age ≥ 65 group than in males in the Age < 65 group, and BMI, SBP, DBP, FPG, total cholesterol, triglyceride, BUN, serum creatinine and adiponectin were significantly higher and HDL was significantly lower in females in the Age ≥ 65 group than in females in the Age < 65 group (Table 3). In males, BUN showed a positive correlation with adiponectin in the Age ≥ 65 group ($r = 0.219$, $P = 0.002$) but not in the Age < 65 group. In females, BUN showed a stronger positive correlation with adiponectin in the Age ≥ 65 group than in the Age < 65 group ($r = 0.134$, $P = 0.045$ vs $r = 0.128$, $P = 0.014$; Table 3). In multiple-regression analysis using LnAdipo as a dependent variable, BUN was selected as a significant independent variable along with sex differences, age, BMI, FPG, triglyceride and HDL in the Age ≥ 65 group, while BUN was not selected as a significant independent variable in the Age < 65 group (Table 4).

Characteristics of subjects from the second selection are shown in Table 5. Adiponectin concentrations were 6.26±3.94 μg/ml in males and 8.84±4.71 μg/ml in females, the concentration being significantly higher in females than in males. LnAdipo correlated positively with age and testosterone in males and negatively with BMI and free testosterone in males. There was no statistical gender-based difference in age, and BMI was significantly higher in males than in females.

The mean values of testosterone, free testosterone, E1 and E2 in relation to age are shown in Figs 3 and 4. In subjects from the second selection, the changes in mean values of adiponectin in relation to age were similar to those in subjects from the first selection (Fig. 1). In males, testosterone gradually decreased in their 30s

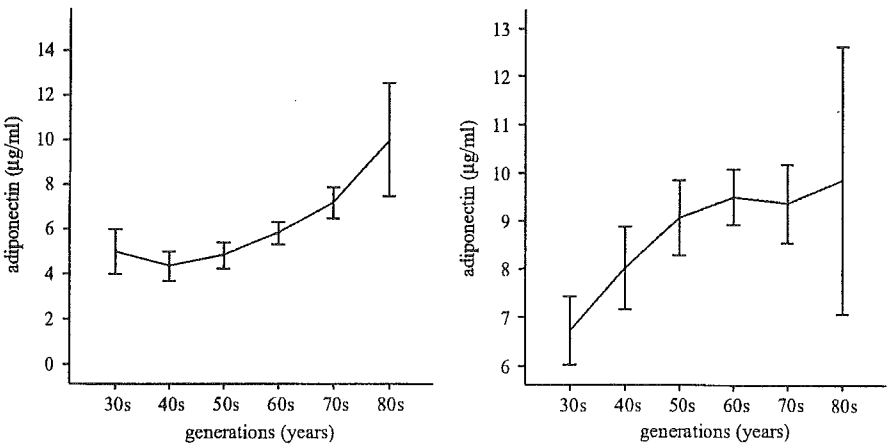

Figure 1 Mean plasma adiponectin levels for each generation in males and females. Numbers of male subjects in each age group were as follows: 30s, $n = 19$; 40s, $n = 44$; 50s, $n = 62$; 60s, $n = 130$; 70s, $n = 96$; 80s, $n = 21$. Numbers of female subjects: 30s, $n = 53$; 40s, $n = 88$; 50s, $n = 129$; 60s, $n = 209$; 70s, $n = 104$; 80s, $n = 9$.

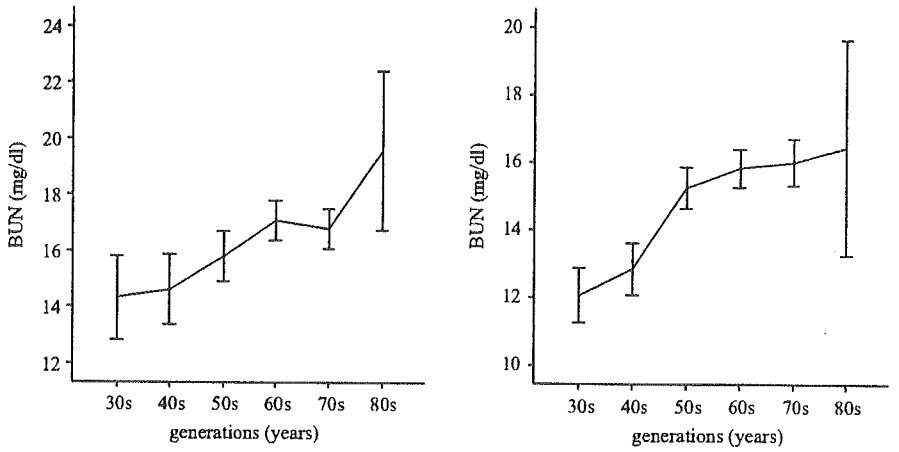

Figure 2 Mean BUN levels for each generation in males and females. Numbers of male and females subjects in each age group are given in the Fig. 1 legend. Conversion factor: mM = mg/dl × 0.357.

and free testosterone decreased almost linearly with aging, a pattern of change opposite to that of adiponectin (Fig. 3). In females, E1 and E2 sharply decreased up to the 50s age bracket, in contrast to the pattern of change in adiponectin (Fig. 4).

In multiple-regression analysis of age, BMI and sex hormones with LnAdipo as a dependent variable, free testosterone, which exhibits biological activity in humans, was not selected as a significant independent variable, whereas age and BMI were selected as significant independent variables in males. In females, E1 and E2 were also not selected as significant independent variables (Table 6).

Discussion

Previous studies showed that there is an inverse relationship between adiponectin level and creatinine clearance in essential hypertensives (10) and that aggravated renal function is one of the reasons for increase an in adiponectin level with aging (23). Another previous study showed that adiponectin level is positively associated with abnormal renal function, assessed by urinary albumin-to-creatinine ratio, in patients with diabetes (24). These studies suggest that a decrease in adiponectin clearance in the kidney may be the cause of high levels of adiponectin in the elderly, although it is unlikely to be the sole mechanism. Previous studies have shown that renal function declines with aging (26–29) and BUN is known as an indicator of renal function. It has been reported that BUN level is affected by aging (30) and that there is a significant positive correlation between BUN level and age (31). Therefore, we used BUN level as an indicator of renal function in this study.

Adiponectin increased linearly with aging in males, whereas in females it increased sharply until the 50s age bracket with a convex curve and then increased gradually (Fig. 1). The patterns of changes in adiponectin were similar to the patterns of changes in BUN (Fig. 2). In multiple-regression analysis using LnAdipo as a dependent variable, BUN was selected as a significant independent variable as well as sex differences, age, BMI, FPG, triglyceride and HDL in all subjects (Table 2) and BUN was also selected as a significant independent variable in the Age ≥ 65 group, whereas BUN was not selected as a significant independent variable in the Age < 65 group (Table 4). These results suggest that decline of renal function with aging contributes independently to the elevation of adiponectin level. Since the biological significance of this elevation in adiponectin in the elderly is not known, further investigation is necessary to clarify the effects of increase in adiponectin in the elderly.

Studies conducted in Japan and other countries have demonstrated that sex hormone levels change with aging (25, 32–36). In Japan, the average age of

Table 2 Results of multiple-regression analysis related to LnAdipo in subjects from the first selection.

	β	*r*	V (%)	*P* value
Sex	0.331	0.373	12.3	<0.001
Age	0.240	0.170	4.1	<0.001
BMI	−0.170	−0.291	4.9	<0.001
SBP	−0.002	−0.010	0.0	0.946
FPG	−0.131	−0.197	2.6	<0.001
TC	−0.035	0.026	0.1	0.257
TG	−0.140	−0.318	4.5	<0.001
HDL	0.139	0.312	4.3	<0.001
BUN	0.086	0.078	0.7	0.002

Sex, males = 0, females = 1; BMI, body mass index; SBP, systolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; BUN, blood urea nitrogen; β, standardized regression coefficient; *r*, versus LnAdipo, Pearson's correlation; V, variation of LnAdipo, calculated by β × *r* × 100 in absolute value.