Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K	Adiponectin and adiponectin receptors in obesity-linked insulin resistance.	Fatty Acids and Lipotoxicity in Obesity and Diabetes (Novartis Foundation Symposium 286), John Wiley & Sons, Ltd,		164-182	2007
Sadagurski M, Nofech-Mozes S, Weingarten G, White MF, Kadowaki T, Wertheimer E	Insulin receptor substrate 1 (IRS-1) plays a unique role in normal epidermal physiology.	J. Cell. Physiol.	213	519-527	2007
Ochi M, Osawa H, Hirota Y, Hara K, Tabara Y, Tokuyama Y, Shimizu I, Kanatsuka A, Fujii Y, Ohashi J, Miki T, Nakamura N, Kadowaki T, Itakura M, Kasuga M, Makino H:	Frequency of the G/G genotype of resistin single nucleotide polymorphism at -420 appears to be increased in vounger onset type 2 diabetes.	Diabetes	56	2834-2838	2007
Kawamura N, Kugimiya F, Oshima Y, Ohba S, Ikeda T, Saito T, Shinoda Y, Kawasaki Y, Ogata N, Hoshi K, Akiyama T, Tobe T, Kadowaki T, Azuma Y, Nakamura K, Chung UI, and Kawaguchi H	Akt1 in osteoblasts and osteoclasts controls bone remodeling.	PLoS ONE	2	e1058	2007
Horikoshi M, Hara K, Ito C, Shojima N, Nagai R, Ueki K, Froguel P, Kadowaki T	Variations in the HHEX gene are associated with increased risk of type 2 diabetes in the Japanese ppulation.	Diabetologia	50	2461-2466	2007
Nishimura S, Manabe I, Nagasaki M, Seno K, Yamashita H, Hosoya Y, Ohsugi M, Tobe K, Kadowaki T, Nagai R, Sugiura S	In vivo imaging in mice reveals local cell dynamics and inflammation in obese adipose tissue.	J.Clin.Invest.	118	710-721	2008
Kadowaki T, Yamauchi T, Kubota N	The physiological and pathophysiological role of adiponectin and adiponectin receptors in the peripheral tissues and CNS.	FEBS Letters	582	74-80	2008

Okamoto M, Ohara-Imaizumi M, Kubota N, Hashimoto S, Eto K, Kanno T, Kubota T, Wakui M, Nagai R, Noda M, Nagamatsu S, Kadowaki T	Adiponectin stimulates insulin release via inducing increased fusion events by newcomer insulin granules at a low glucose concentration	Diabetologia	in press		2008
Oishi Y, Manabe I, Tobe K, Ohsugi, M, Kubota, T, Fujiu K, Maemura K, Kubota N, Kadowaki T, Nagai R	SUMOylation of KLF5 is a molecular switch regulating PPAR-delta-containing transcriptional programs of lipid metabolism.	Nature Medicine	in press		2008

別紙4

著者氏名	論文タイトル名	発表雑誌名	巻号	ページ	出版年
門脇孝	糖尿病の治療に関する最近の知見 PROactive Study の結果とその解釈 2型糖尿病患者における心血管イベントの発症抑制効果	分子糖尿病学の進歩: 基礎から臨床まで	2007	102-107	2007
門脇孝、植木浩二郎、野田光彦	【糖尿病の新しい治療戦略】合併症の治療戦略　糖尿病予防のための戦略研究　J-DOIT3	最新医学	62(4)	910-915	2007
山内敏正、門脇孝	【糖尿病の新しい治療戦略】糖尿病の治療戦略　インスリン抵抗性改善薬の現状と未来	最新医学 62	62(4)	867-879	2007
戸辺一之、植木浩二郎、中江淳、門脇孝	【アンチエイジングに迫る】 インスリンはアンチエイジングの鍵分子か?	Life Style Medicine	1(2)	140-147	2007
原一雄、門脇孝	糖尿病の病態と診断に関する最近の知見　高分子量アディポネクチン測定の臨床的意義	分子糖尿病学の進歩: 基礎から臨床まで	2007	80-85	2007
窪田直人、窪田哲也、門脇孝	インスリン作用の分子機構　血管内皮におけるインスリン作用	分子糖尿病学の進歩: 基礎から臨床まで	2007	80-85	2007
亀井望、戸辺一之、窪田直人、山内敏正、門脇孝	【動脈硬化と炎症】 アディポカインと炎症	炎症と免疫	15(3)	321-326	2007
岡崎由希子、植木浩二郎、門脇孝	女性と生活習慣病　女性とアディポカイン	産科と婦人科	74(4)	426-431	2007
山内敏正、門脇孝	特集　糖尿病の新しい治療戦略　インスリン抵抗性改善薬の現状と未来	最新医学社	62(4)	35-47	2007
山内敏正、門脇孝	【糖尿病による心血管合併症】 インスリン抵抗性と動脈硬化症	BIO Clinica	22(5)	388-394	2007
羽田裕亮、山内敏正、門脇孝	【脂質】脂質代謝異常と疾病　メタボリックシンドロームと脂質代謝異常	臨床検査	51(5)	493-498	2007
金子和真、植木浩二郎、門脇孝	【メタボリックシンドローム研究の進展】 Metabolic syndrome の成因	内分泌・糖尿病科	24(5)	414-424	2007
門脇孝	【メタボリックシンドローム up to date】 基礎　アディポサイトカイン	日本医師会雑誌	136(1)	S71-S75	2007

別紙 4

原一雄、門脇孝	【メタボリックシンドローム up to date】 トピックス 倹約遺伝子仮説	日本医師会雑誌	136(1)	S288-S289	2007
松下由実、戸辺一之、原一雄、門脇孝	【メタボリックシンドローム up to date】 メタボリックシンドロームは予防医学のなかで、どのように位置づけられますか？	日本医師会雑誌	136(1)	S259-S260	2007
山内敏正、原一雄、門脇孝	【メタボリックシンドローム up to date】 検査・診断 アディポネクチン	日本医師会雑誌	136(1)	S179-S184	2007
松下由実、戸辺一之、原一雄、門脇孝	【メタボリックシンドローム up to date】 病態 メタボリックシンドロームとインスリン抵抗性・糖代謝異常	日本医師会雑誌	136(1)	S114-S119	2007
山内敏正、門脇孝	【メタボリックシンドローム up to date】 アディポサイトカインとメタボリックシンドロームの病態との関連は？	日本医師会雑誌	136(1)	S107	2007
伊藤裕、門脇孝	糖尿病合併高血圧治療について考える 高血圧治療約の位置づけ	Progress in Medicine	27(6)	1367-1373	2007
門脇孝	糖尿病・メタボリックシンドロームの分子機構と治療戦略	阿蘇シンポジウム記録	30 回	77-93	2007
山内敏正、門脇孝	オスモチン	臨床栄養	111(1)	10-11	2007
門脇孝	メタボリックシンドロームの病態と治療戦略	Osteoporosis Japan	15(3)	61(403)-73(415)	2007
山内敏正、門脇孝	アディポネクチンの臨床応用の現状・展望(Q&A)	日本医事新報	4344	86-87	2007
山内敏正、門脇孝	【脂質代謝異常、高脂血症、低脂血症】 高脂血症と動脈硬化 動脈硬化発症にかかわるアディポサイトカインの役割	日本臨床	65(7)	63-70	2007
岡崎由希子、植木浩二郎、門脇孝	糖尿病予防のための戦略研究課題3(J-DOIT3)とは何か その意義と展望	プラクティス	24(4)	425-430	2007
山内敏正、門脇孝	脂質代謝異常–高脂血症・低脂血症–I概論 高脂血症と動脈硬化 動脈硬化発症にかかわるアディポサイトカインの役割	日本臨牀	65(7)	63-70	2007

原眞澄、門脇孝	【肥満の治療は必要か】なぜ肥満は問題なのか	臨牀と研究	84(8)	1041-1045	2007
門脇孝、伊藤千賀子、加来浩平、難波光義	2 型糖尿病を糖尿病治療薬からアプローチ 2 型糖尿病を糖尿病治療薬からアプローチ	糖尿病 UP-DATE	23	134-153	2007
門脇孝	2 型糖尿病を糖尿病治療薬からアプローチ 2 型糖尿病とオーダーメイドによる経口糖尿病治療薬の選択とは	糖尿病 UP-DATE	23	82-105	2007
原 一雄、門脇 孝	糖尿病とゲノム	最新医学	第 62 巻 9 月増刊号 臨床遺伝学'07	2164-2176	2007
窪田直人, 門脇孝	【解明が進むメタボリックシンドローム 脂肪細胞の機能からエネルギー代謝・摂食・心血管系の制御機構、予防と治療まで】 メタボリックシンドロームの予防と治療 PPARγを介するメタボリックシンドロームの治療	実験医学	25 (15)	2458-2464	2007
山内敏正、門脇孝	アディポサイトカイン調節を改善する食事療法	Adiposcience	4 (3)	281-289	2007
山内敏正、門脇孝	【メタボリックシンドロームと循環器疾患】アディポネクチン受容体異常からみたメタボリックシンドローム	呼吸と循環	55(9)	969-975	2007
岡崎由希子、植木浩二郎、門脇孝	【メタボリックシンドローム】糖尿病	心療内科	11(5)	296-301	2007
吉川敏一、大澤俊彦、桜井弘、中村丁次、門脇孝	【創刊記念座談会】いま、なぜ機能性食品なのか？	Functional Food	1(1)	6-16	2007
堀越桃子、原一雄、門脇孝	TCF7L2 2 型糖尿病の主要遺伝子	BIO Clinica	22 (11)	990-995	2007
窪田直人、山内敏正、門脇孝	肥満・インスリン抵抗性に対する分子標的治療	細胞工学	27(1)	44-47	2007

厚生労働科学研究費補助金(循環器疾患等生活習慣病対策総合研究事業)
分担研究報告書

保健指導への活用を前提としたメタボリックシンドロームの診断・管理のエビデンス創出のための横断・縦断研究（端野・壮瞥町研究）

分担研究　島本　和明　札幌医科大学医学部

研究要旨　地域一般住民を対象にメタボリックシンドローム(MetS)の実態を解析した。本年度は北海道北見市端野地区・有珠郡壮瞥町で実施した地域一般住民健診における健診成績の縦断研究より MetS の 2 型糖尿病(T2DM)発症への影響を検討した。住民健診者 827 名を腹部肥満(AO)群と非腹部肥満(Non-AO)群、および、非メタボリックシンドローム(Non-MetS)群と MetS 群の 2 群に分類、10 年間の T2DM 発症率を比較した。その結果 T2DM 発症は Non-AO 群の 5.8%、AO 群 15.6%であり、ロジスティック回帰分析では AO の T2DM 発症リスクは 2.08（95%CI: 1.03-4.19)、Non-MetS 群 6.2%、MetS 群 26.9%、MetS の発症リスクは年 3.61(95%CI: 1.74-0.75）であった。

A．研究目的

わが国では糖尿病は増加の一途をたどっており、細小血管障害や大血管障害の合併による個人あるいは社会への影響は極めて大きくなっている。メタボリックシンドローム（MetS）は動脈硬化性疾患の危険因子であることに加え 2 型糖尿病発症との関連が主に欧米から報告されている。しかしながら、日本人における MetS と 2 型糖尿病発症の関連の報告は少なく、加えて BMI と MetS および糖尿病発症の相互効果の検討はない。今回は地域一般住民の前向き疫学研究から日本人における MetS と腹部肥満における 2 型糖尿病発症を検討し、喫煙の影響を解析した。

B．研究方法

対象は 1994 年の端野・壮瞥町の住民健診を受診した 827 名（男性 347 名；平均年齢 59.6±9.0、女性 480 名;平均年齢 58.3±8.5 歳)。94 年の腹囲データより腹部肥満（AO）群（男性腹囲≧85cm、女性腹囲≧90cm）と非腹部肥満（Non-AO）群で、10 年後の 2003、2004 年までに新規に 2 型糖尿病と判定された者の発症率を比較した。
同様に非メタボリックシンドローム（Non-MetS）群と MetS 群の 2 群に分け、10 年間での糖尿病の発症率を比較した。MetS は内科学会基準により分類した。すなわち血圧基準：SBP≧130mmHg または DBP≧85 mmHg または降圧薬服用、血糖基準：FPG≧110mg/dl または糖尿病治療、脂質基準 TG≧150 mg/dl または HDL<40 mg/dl、腹部肥満基準（上述）であり、腹部肥満基準を満たした上に他の 2 項目以上を持つものを MetS とした。また、多変量解析により AO、MetS の糖尿病発症の相対リスクを解析した。

健診受診者は地域保健師による問診により既往歴、喫煙、飲酒、服薬状況のアンケート調査を行った。

(倫理面への配慮)

個人データの利用のあっては検診受診者からインフォームコンセントを得た。また、個人情報が保護のために、個人識別が困難なデータベースを作成して解析を行った。

C．研究結果

Non-AO 群 654 名中 2003,2004 年に糖尿病と判定された者は 38 名（5.8%）であったのに対し、AO 群 173 名から新規に糖尿病と判定された者は 27 名（15.6%）と有意に高率であった。新規糖尿病発症を従属変数としたロジスティック回帰分析を行うと腹部肥満の糖尿病発症に対するリスクは年齢、性別、Body Mass

Index (BMI)、総コレステロール値 (TC)、収縮期血圧 (SBP)、喫煙で補正しても 2.08 (95%CI: 1.03-4.19) であった。また、Non-MetS 群 760 名中 47 名 (6.2%) が新規に糖尿病を発症したのに対し、MetS 群 67 名から新規に糖尿病を発症したものは 18 名 (26.9%) と有意に高率であった。新規糖尿病発症を従属変数としたロジスティック回帰分析を行うと、MetS の糖尿病発症に対するリスクは年齢、性別、BMI、TC、喫煙で補正しても 3.61 (95%CI : 1.74-0.75) であった。

D．考察

今回の検討より、我が国における MetS の診断基準を用いると、腹部肥満からは約 2 倍、メタボリックシンドロームからは約 3.6 倍新規に糖尿病を発症することが示された。2 型糖尿病発症予防の観点からは、一般健診においても腹囲径の測定や新基準による MetS の判定を行うことで糖尿病発症のハイリスク者を判定できる可能性が示された。

ウエスト周囲径は、BMI とウエスト・ヒップ比 (WHR) より有意に内臓脂肪蓄積を反映することが二重エネルギーX線吸光光度法やコンピュータ断層撮影 (CT) の検討から示されている[4-6]。また、すでに国外からはウエス周囲径と 2 型糖尿病の有意な関連が報告されている[7-10]。今回の検討でも、日本人においてもウエスト周囲径と BMI を同時に多変量解析モデルに加えたとき、ウエスト周囲径のみが 2 型糖尿病発症危険因子となり、内臓脂肪蓄積型肥満が 2 型糖尿病に関与することが示された。

国際糖尿病学会 (IDF) の MetS の診断基準では各人種により異なる腹部肥満のウエスト周囲径が示されている。日本基準では CT による内臓脂肪面積の解析より日本人の腹部肥満基準としてウエスト周囲径、男性 85cm、女性 90cm が用いられている。今回の解析ではこれを用いて腹部肥満と 2 型糖尿病発症の関連を検討したが、この基準値については感度、特異度を含めた検討が必要であり今後のデータの集積が必要であろう。

今回の検討ではウエスト周囲径による腹部肥満は、2 型糖尿病発症の危険度を評価するための BMI より役立つ可能性があることを示唆した。

E．結論

日本人おける腹部肥満およびメタボリックシンドロームは 2 型糖尿病発症の強いリスクとあることが示され、糖尿病発症予防には腹部肥満とメタボリックシンドロームの発見と管理が重要であると考えられる。

F．健康危険情報

なし

G．研究発表

1. 論文発表

医学と薬学, 2007 57 : 169-171.
Hypertens. Research, 2007 30 : 229-236.
Hypertens. Research, 2007 30 : 315-324.
Diabetes Care, 2007 30 : 1533-1538.
Hypertens. Research. 2007 30 : 663-668.
Hypertens. Research. 2007 30 : 677-682.

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別紙4

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
島本和明 斎藤重幸	端野・壮瞥町研究.	熊谷裕生，小室一成，堀内正嗣，森下竜一	高血圧ナビゲーター．第2版	メディカルビュー社	東京	2008	46-47
島本和明他	メタボリックシンドロームと生活習慣病	島本和明	メタボリックシンドロームと生活習慣病	診断と治療社	東京	2007	1-338
島本和明	メタボリックシンドロームの考え方と臨床的意味.	門脇孝、島本和明、寺本民夫、松澤佑次	メタボリックシンドローム Up-to data	協和企画	東京	2007	29-31

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
東浦勝浩，斎藤重幸，竹内宏，高木覚，浦信行，島本和明	メタボリックシンドロームにおける高尿酸血症の意義	医学と薬学	57	169-171.	2007
Chiba Y, Saitoh S, Takagi S, Ohonishi H, Katoh N, Ohohata J, Nakagawa M, Shimamoto K,	Relationship between visceral fat and cardiovascular disease risk factors: The Tanno-Sobetsu study.	Hypertens. Research	30	229-236	2007
Eguchi M, Tsutihashi K, Saitoh S, Odawara Y, Hirano T, Nakata T, Miura T, Ura N, Kareyama M, Shimamoto K	Visceral obesity in Japanese patients with metabolic syndrome: Reappraisal of diagnostic criteria by CT scan.	Hypertens. Research	30	315-324	2007

Original Article

Relationship between Visceral Fat and Cardiovascular Disease Risk Factors: The Tanno and Sobetsu Study

Yu CHIBA[1], Shigeyuki SAITOH[1], Satoru TAKAGI[1], Hirofumi OHNISHI[1], Nobuo KATOH[1], Junichi OHATA[1], Motoya NAKAGAWA[1], and Kazuaki SHIMAMOTO[1]

We assessed the amount of visceral fat using ultrasonography (US) and studied its relationship to cardiovascular disease risk factors, particularly blood pressure. The subjects in the first study were 45 male and 61 female outpatients. We measured the visceral fat area (VFA) of each subject using abdominal CT and waist circumference (WC), and visceral fat distance (VFD) using US. The subjects in the second study were 353 male and 457 female inhabitants of a rural community, for whom VFD and WC were measured. We divided subjects into tertiles based on VFD and WC, and studied the relationship between each group and individual risk factors. In an analysis of outpatient subjects, the correlation coefficient between VFA and VFD was satisfactory: r=0.660 for men and r=0.643 for women. In the analysis of the rural subjects, the high VFD group had a significantly higher odds ratio than the low VFD group in high blood pressure (HBP) and hypertriglyceridemia (HTG) for men and, in HBP, HTG and low high-density lipoprotein cholesterolemia (LHDL) for women. Moreover, adjusting VFD for body mass index revealed that, in comparison to WC, VFD was significantly related to risk factors. VFD was used as an independent variable in multiple regression analysis with blood pressure level as a dependent variable; no significant association between WC and blood pressure was obtained. Visceral fat assessment by US may be useful for epidemiological study and for clinics with no abdominal CT equipment for identifying high-risk individuals, such as those with metabolic syndrome. (*Hypertens Res* 2007; 30: 229–236)

Key Words: ultrasonography, visceral obesity, cardiovascular disease risk factors, waist circumference, hypertension

Introduction

Obesity is often complicated by arteriosclerotic diseases such as hypertension, ischemic heart disease and cerebrovascular disease as well as by their risk factors (*1, 2*). Since the late 1980s, these complications have been explained by the concept of a multiple risk factor syndrome such as syndrome X (*3*), the deadly quartet (*4*), and visceral fat syndrome (*5*). More recently, the term metabolic syndrome (MS) has been adopted by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) (*6*). Visceral obesity, in which fat markedly accumulates in the peritoneal mesentery and around the greater omentum, is thought to be a fundamental pathology for MS in particular. The incidence of cardiovascular disease is high even in non-obese individuals with a body mass index (BMI) within the normal range who have an accumulation of visceral fat (*7*), and accurate assessment of both body fat distribution and visceral fat accumulation is critical for assessing the risk of arteriosclerotic disease.

Previous studies have shown that waist-to-hip ratio, waist-to-height ratio, waist circumference (WC), and visceral fat

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assessed by abdominal CT are relatively good indicators of the risk of cardiovascular disease (*8–13*). Abdominal CT enables quantification of the visceral fat area (VFA) and therefore serves as the gold standard for visceral fat assessment. On the other hand, WC measurement is recommended as a simpler and easier screening method (*14*). However, abdominal CT has drawbacks, including exposure to radiation, lack of ease and simplicity, and high cost. WC includes subcutaneous fat, and WC measurement therefore has drawbacks such as an inability to account for an individual's height and a low level of reproducibility in the case of marked obesity.

Simple methods for assessing visceral fat accumulation using ultrasonography (US) have been studied in recent years (*15–20*). In addition, previous studies have indicated a relationship between hypertension and visceral fat assessed by abdominal CT and WC, but US was not used in any of those studies (*21–24*). Thus, in the present study, we assessed the usefulness of visceral fat assessment by US in outpatients. Then, based on the results of a cross-sectional study, we assessed the relationships between abdominal obesity determined by US and cardiovascular disease risk factors, particularly blood pressure levels.

Methods

Study 1

The subjects were 45 men and 61 women outpatients (mean ages: 55.4±19.4 years for men and 67.5±10.8 years for women). Individuals with cardiovascular disease, renal disease or a severe debilitating disease were excluded from participation. Height, body weight, WC, VFA and total fat area (TFA) were determined by abdominal CT, and visceral fat distance (VFD) was determined by US. The subcutaneous fat area (SFA) was calculated by subtracting VFA from TFA.

Informed consent was obtained from each outpatient, who completed a form consenting to testing. Height, body weight and visceral fat levels were measured on the same day, and BMI was calculated. Correlations between VFA, SFA, VFD, BMI and WC were investigated.

Measurement of Visceral Fat Levels

CT equipment from Toshiba Medical Systems (Tokyo, Japan) was used for abdominal CT. Imaging was done at the end of expiration at the umbilical level. Tracing in cross-sectional images was done using a trackball; the total cross-sectional area was determined by automatic calculation of portions with a CT number of −200 to 1,000 Hounsfield units (HU) using the method of Grauer *et al.* (*25*). In addition, portions with a CT number of −200 to −10 HU were separated as adipose tissue and their areas were automatically calculated.

WC was measured with non-stretchable measuring tape while subjects bared the circumference of the abdomen. The umbilical circumference was measured in increments of 0.1 cm during expiration while standing (*14*).

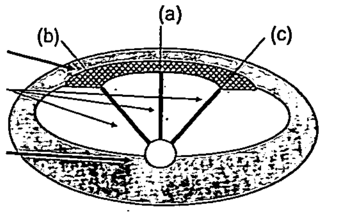

Fig. 1. *VFD was measured between the peritoneum and the lumbar spine, and which was taken as the average value. VFD = (a + b + c)/3. Each subject assumed a supine position, and at the end of expiration the distance from the peritoneum to the front of the vertebral body was measured perpendicularly three times with a 3.5 MHz linear probe while making the slightest contact possible, and the average value was used as the VFD.*

VFD was measured using VF-750XT portable ultrasonography equipment (Fukuda Electrical, Tokyo, Japan) by the method of Stolk *et al.* (*18, 19*). That is, each subject assumed a supine position, and at the end of expiration the distance from the peritoneum to the front of the vertebral body was measured perpendicularly three times with a 3.5 MHz linear probe while making the least possible amount of contact, and the average value was used as the VFD (Fig. 1). All measurements were performed by the same investigator.

Study 2

The subjects were 353 men and 457 women (mean ages: 62.8±12.2 years for men and 57.8±12.6 years for women) out of 1,455 individuals who underwent screening for local residents of a rural community; individuals being treated for hypertension, diabetes or hyperlipidemia were excluded. The study was approved by the Ethics Committee of Sapporo Medical University, and written informed consent was obtained from each subject.

For all subjects, height and body weight were measured after fasting for 8 h or longer since their last meal, blood pressure levels were measured and blood samples were taken. The blood samples were used to measure high-density lipoprotein (HDL)–cholesterol levels (HDL-c), triglyceride levels (TG), fasting plasma glucose levels (FPG) and serum insulin levels. Afterwards, WC and VFD were measured. Height and body weight were measured at intervals of 0.1 cm and 0.1 kg, respectively, with subjects lightly dressed and shoes removed. Blood pressure was measured twice consecutively on the upper arm using an automated sphygmomanometer (HEM-907, Omron Instruments, Tokyo, Japan) with subjects in a seated resting position, and the average was used for systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Table 1. Characteristics of the Subjects for Study 1

	Men (n=45)	Women (n=61)	p-value
Age (years)	55.4±19.4	67.5±10.8	<0.001
Body weight (kg)	67.1±11.8	56.4±8.8	<0.001
BMI (kg/m^2)	24.2±3.2	24.7±3.9	0.462
Lean: BMI<22	11/45 (24%)	14/61 (23%)	
Overweight: 22≤BMI<25	17/45 (38%)	23/61 (38%)	
Obese: 25≤BMI	17/45 (38%)	24/61 (39%)	
WC (cm)	84.9±8.8	85.6±10.1	0.787
VFD (cm)	5.2±1.2	4.9±1.43	0.459
SFA (cm^2)	147.0±63.8	221.2±132.4	<0.001
VFA (cm^2)	137.0±62.6	128.9±51.8	0.606

All values are mean±SD. BMI, body mass index; WC, waist circumference; VFD, visceral fat distance; SFA, subcutaneous fat area; VFA, visceral fat area.

Table 2. Correlation between Adipose Tissue Measured by CT and Other Anthropometric Parameters

	Adipose tissue measured by CT	
	SFA	VFA
Men (n=45)		
BMI	0.763*	0.565*
WC	0.861*	0.646*
VFD	0.237	0.660*
Women (n=61)		
BMI	0.591*	0.571*
WC	0.595*	0.499*
VFD	0.289**	0.643*

Values are Pearson's correlation coefficients. *p<0.001, **p<0.05. SFA, subcutaneous fat area; VFA, visceral fat area; BMI, body mass index; WC, waist circumference; VFD, visceral fat distance.

Measurement Methods

HDL-c was measured by the enzymatic method (homogenous), TG was measured by the enzymatic colorimetric method (free glycerol elimination), FPG was measured by the GOD immobilized oxygen electrode maximum reaction acceleration method, and serum insulin level was measured by the enzyme immunoassay method. In addition, homeostasis model assessment index (HOMA-IR) was calculated on the basis of FPG and serum insulin levels (*26*).

Diagnostic Criteria for Cardiovascular Disease Risk Factors

Diagnostic criteria for cardiovascular disease risk factors followed the NCEP ATPIII criteria for MS (*6*). High blood pressure (HBP) was defined as SBP ≥130 mmHg and/or DBP ≥85 mmHg or higher, hypertriglyceridemia (HTG) was defined as TG ≥150 mg/dl, low HDL cholesterolemia (LHDL) was defined as HDL-c <40 mg/dl for men and <50 mg/dl for women, and high fasting plasma glucose (HFPG) was defined as FPG ≥110 mg/dl.

Statistical Analysis

Statistical analysis was done using Windows SPSS version 11.5J. Numerical values are shown as means (mean)±SD. The correlation between two variables was evaluated using Pearson's correlation coefficient. Comparison between two groups was done with an unpaired t-test. For logistic regression analysis, subjects were divided into tertiles based on VFD and WC, adjusted for age (model 1) and then adjusted for age and BMI (model 2); with the low VFD and low WC groups as a reference, odds ratios (OR) and individual cardiovascular disease risk factors were examined. Comparison of three groups was done by multiple comparisons after one-way ANOVA. For multiple regression analysis, blood pressure level served as a dependent variable, and the relationships between cardiovascular disease risk factors with VFD and WC were studied. In all instances, the level of significance was p<0.05.

Results

Study 1

Table 1 shows characteristics of the 45 male and 61 female outpatient subjects whose visceral fat levels were measured by abdominal CT. No significant difference between the male and female subjects was found in BMI, WC, VFD or VFA. SFA was significantly larger for women than for men.

The correlations between SFA and VFA determined by abdominal CT and BMI, VFD and WC are shown in Table 2. The correlation coefficients between VFA and VFD were r=0.660 (p<0.001) for men and r=0.643 (p<0.001) for women. In addition, VFA had a stronger correlation to VFD than to BMI or WC. Moreover, BMI and WC had stronger

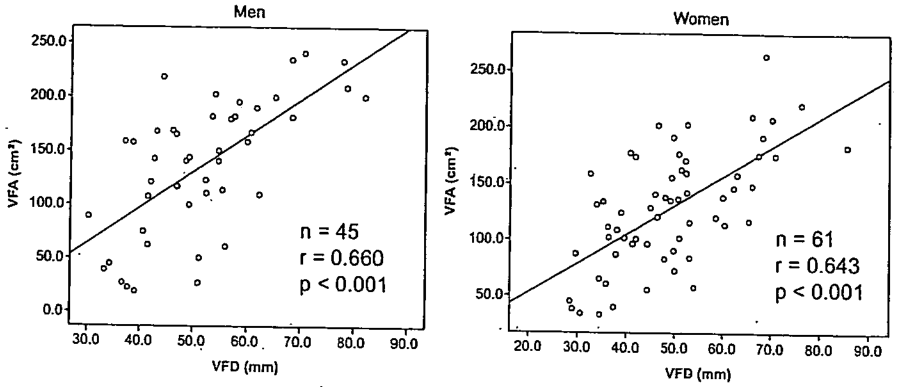

Fig. 2. *Scattergrams of relationship between VFD and VFA for men and women. VFD, visceral fat distance assessed by ultrasonography; VFA, visceral fat area assessed by CT. There were significant positive correlations between VFD and VFA in both men and women.*

Table 3. Characteristics of the Study Subjects of Residents of a Rural Community

	Men (n=353)	Women (n=457)	p-value
Age (years)	62.8±12.2	57.8±12.6	<0.001
Body weight (kg)	63.9±10.1	53.7±7.6	<0.001
BMI (kg/m²)	23.7±3.2	23.0±3.2	0.002
Lean: BMI<22	107/353 (30%)	177/457 (39%)	
Overweight: 22≤BMI<25	143/353 (41%)	171/457 (37%)	
Obese: 25≤BMI	103/353 (29%)	109/457 (24%)	
WC (cm)	84.7±9.1	82.6±9.9	0.002
VFD (cm)	5.5±1.7	4.7±1.3	<0.001
SBP (mmHg)	131.9±20.1	127.0±21.2	0.001
DBP (mmHg)	75.5±11.6	71.9±10.6	<0.001
HDL-c (mg/dl)	51.3±11.7	59.3±14.5	<0.001
TG (mg/dl)	115.1±75.2	88.3±49.2	<0.001
FPG (mg/dl)	96.8±15.7	94.4±17.7	0.041
Serum insulin levels (μU/ml)	4.5±4.7	4.4±2.9	n.s.
HOMA-IR	1.13±1.38	1.04±0.72	n.s.

All values are mean±SD. BMI, body mass index; WC, waist circumference; VFD, visceral fat distance; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein-cholesterol; TG, triglyceride; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment index; n.s., not significant.

correlations to SFA than to VFA (Table 2).

Figure 2 shows scattergrams of the relationships between VFD and VFA for men and women. There were significant positive correlations between VFD and VFA in both sexes.

Study 2

Table 3 shows the characteristics of the subjects in Study 2. Average VFDs were 5.5±1.7 cm for men and 4.7±1.3 cm for women; and average WCs were 84.7±9.1 cm for men and 82.6±9.9 cm for women.

The subjects were divided into tertiles based on VFD and WC; OR for cardiovascular disease risk factors with individual low-tertile groups as a reference are shown in Table 4. Adjusted only for age (model 1); OR increased significantly for the male VFD group in comparison to that for the low VFD group in HBP (OR: 3.45 [95% CI: 1.83–5.77]; $p<0.001$) and HTG (OR: 3.74 [1.72–8.12]; $p<0.05$), and it increased significantly for the female group in HBP (OR: 2.31 [1.37–3.92]; $p<0.05$), HTG (OR: 13.3 [3.02–58.5]; $p\leq 0.05$) and LHDL (OR: 4.62 [2.47–8.62]; $p<0.001$). Similarly, OR increased significantly for the male WC group in comparison to that for the low WC group in HBP (OR: 2.00 [1.15–3.45]; $p<0.05$), HTG (OR: 3.09 [1.41–6.75]; $p<0.05$) and LHDL (OR: 8.82 [1.98–39.3]; $p<0.05$), and it increased significantly for the female group in HBP (OR: 1.95 [1.18–3.23];

Table 4. Odds Ratios and 95% CIs of CAD Risk Factors by Tertile of VFD and WC

	HBP	HTG	HFPG	LHDL
Men (n=353)				
Model 1				
VFD				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.79 (1.04–3.09)*	2.31 (1.04–5.16)*	1.04 (0.4–2.44)	1.95 (0.83–4.59)
Upper tertile	3.45 (1.83–5.77)†	3.74 (1.72–8.12)*	0.80 (0.32–2.00)	2.02 (0.85–4.77)
WC				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	2.10 (1.22–3.59)*	3.41 (1.56–7.44)*	0.79 (0.32–1.99)	16.4 (3.79–71.1)†
Upper tertile	2.00 (1.15–3.45)*	3.09 (1.41–6.75)*	1.26 (0.54–2.96)	8.82 (1.98–39.3)*
Model 2				
VFD				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.67 (0.95–2.95)	2.21 (0.97–5.04)	0.88 (0.36–2.13)	1.71 (0.71–4.14)
Upper tertile	2.75 (1.37–5.50)*	3.35 (1.35–8.32)*	0.52 (0.17–1.62)	1.44 (0.52–4.04)
WC				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.60 (0.86–2.96)	3.09 (1.31–7.31)*	0.71 (0.25–1.96)	17.6 (3.77–82.2)†
Upper tertile	1.15 (0.51–2.59)	2.54 (0.87–7.41)	1.00 (0.29–3.46)	10.1 (1.75–58.1)*
Women (n=457)				
Model 1				
VFD				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.76 (1.04–2.98)*	6.28 (1.38–28.6)*	0.52 (0.16–1.72)	2.32 (1.23–4.38)*
Upper tertile	2.31 (1.37–3.92)*	13.3 (3.02–58.5)*	1.82 (0.71–4.69)	4.62 (2.47–8.62)†
WC				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.05 (0.63–1.76)	3.79 (1.21–11.8)*	1.10 (0.43–2.82)	2.72 (1.52–4.86)*
Upper tertile	1.95 (1.18–3.23)*	5.79 (1.93–17.4)*	0.93 (0.37–2.34)	2.46 (1.36–4.43)*
Model 2				
VFD				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.27 (0.73–2.22)	4.59 (0.99–21.3)	0.56 (0.16–1.92)	1.91 (0.99–3.70)
Upper tertile	1.06 (0.55–2.04)	6.36 (1.30–31.3)*	2.16 (0.67–6.92)	2.94 (1.40–6.17)*
WC				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	0.65 (0.37–1.15)	2.37 (0.73–7.73)	0.90 (0.32–2.47)	1.78 (0.95–3.33)
Upper tertile	0.74 (0.37–1.45)	2.06 (0.56–7.57)	0.60 (0.17–2.05)	0.97 (0.45–2.09)

Model 1: adjusted for age; Model 2: adjusted for age and BMI. Significantly different from the Lower tertile: *$p<0.05$, †$p<0.001$. CI, confidence interval; CAD, cardiovascular disease; HBP, high blood pressure; HTG, hypertriglyceridemia; HFPG, high fasting plasma glucose; LHDL, low high-density lipoprotein cholesterolemia; VFD, visceral fat distance; WC, waist circumference.

$p<0.05$); HTG (OR: 5.79 [1.93–17.4]; $p<0.05$) and LHDL (OR: 2.46 [1.36–4.43]; $p<0.05$).

When additionally adjusted for BMI (model 2), OR increased significantly for the male VFD group in comparison to that for the low VFD group in HBP (OR: 2.75 [1.37–5.50]; $p<0.05$) and HTG (OR: 3.35 [1.35–8.32]; $p<0.05$). However, no significant association was found between WC and HBP or between WC and HTG. In addition, OR increased significantly for the female high VFD group in comparison to that for the low VFD group in HTG (OR: 6.36 [1.30–31.3]; $p<0.05$) and LHDL (OR: 2.94 [1.40–6.17]; $p<0.05$). However, no significant association was found between WC and any of the factors.

Table 5 shows the results of multiple regression analysis with SBP and DBP as dependent variables. For men, VFD was selected as a significant independent variable for both SBP and DBP. However, there was no significant association between WC and SBP or between WC and DBP.

Table 5. Results of Multiple-Regression Analysis Related to SBP and DBP

	Independent	Dependent			
		SBP		DBP	
		β	p-value	β	p-value
Men (n=353)	VFD	2.093	0.015	1.049	0.047
	WC	0.287	0.226	0.163	0.265
Women (n=457)	VFD	1.422	0.118	0.739	0.154
	WC	0.110	0.425	−0.057	0.466

Dependent variables: systolic blood pressure (SBP) or diastolic blood pressure (DBP). Independent variables: visceral fat distance (VFD) or waist circumference (WC) and additionally adjusted for age, triglyceride (TG), high-density lipoprotein-cholesterol (HDL-c), fasting plasma glucose (FPG), body mass index (BMI). β: standardized regression coefficient.

Although the data are not shown, when VFD was divided into tertiles, HOMA-IR increased significantly in the higher tertiles. Moreover, in multiple regression analysis using HOMA-IR as a dependent variable and using age, SBP, TG and VFD as independent variables, VFD was found to be a significant indepeńdent variable of HOMA-IR for both men and women.

Discussion

The significance of visceral obesity has been noted in recent years, and the accumulation of visceral fat must be accurately assessed. However, abdominal CT is not a simple technique, and WC also has the drawback of leading to an assessment that includes subcutaneous fat. In contrast, US involves no radiation exposure, the technique can be quickly learned, it is typically completed in less than 5 min, and it has been reported to have a good level of reproducibility (*15–20*). In the present study we therefore investigated whether US can be used as an easy screening method for the accurate estimation of the accumulation of visceral fat in Japanese as well.

When the correlations between VFA, SFA, BMI, VFD and WC were examined, VFD was found to have a stronger positive correlation with VFA than with SFA for both men and women. Additionally, BMI and WC each had a stronger positive correlation with SFA than with VFA. This is because measurements of BMI and WC are assessment methods that include elements of subcutaneous fat. The present study indicated that VFD measurement is a simple method for assessing visceral fat that does not include elements of subcutaneous fat and that VFD measurement is a useful means of assessing visceral fat in a large number of subjects.

The relationships between visceral fat and cardiovascular disease risk factors were then assessed in a study using US performed on inhabitants of a rural community who were not being treated for hypertension, diabetes or hyperlipidemia. The data presented in Table 4, obtained after adjustment for age and BMI (model 2), showed that VFD was significantly correlated with HBP, HTG and LHDL in men and with HTG and LHDL in women. On the other hand, WC was correlated with LHDL in men but showed only weak correlations with risk factors in women.

What eliminated the relationship between WC and cardiovascular disease risk factors in women subjects in particular was the effect of subcutaneous fat. Subcutaneous fat has less of an effect on arteriosclerosis than visceral fat and instead has antiarteriosclerotic action (*27*). In general, visceral obesity, a condition in which visceral fat readily accumulates, affects men more than women; women are affected by female sex hormones and exhibit body types that feature subcutaneous obesity (*28, 29*). Thus, in assessment by BMI and WC, the effects of subcutaneous fat are more intensely reflected in women than in men. This fact is supported by the stronger correlation of BMI and WC to SFA than to VFA in the study of outpatient cases (Study 1).

We could not find a significant association between FPG and a rise in VFD or WC for either men or women. The reasons are threefold. First, individuals on medication for type 2 diabetes were excluded in this study and, second, the study was conducted in a homogenous population with a relatively low FPG. Third, we could not find participants with impaired glucose tolerance (IGT) because we did not conduct oral glucose tolerance test (OGTT) in this study. Thus, there was a small number of participants with high FPG and there was no significant relationship between FPG and VFD for either men or women.

The results of multiple regression analysis showed that VFD was an independent explanatory variable of blood pressure in men. No significant relationship was found between WC and blood pressure in men or women. VFD may be a good indicator of blood pressure in men. Moreover, VFD may also be a useful index for the management of blood pressure in men with metabolic syndrome.

In a state of visceral fat accumulation, it is thought that free fatty acid produced by the decomposition of TG flows into the liver and induces insulin resistance. Moreover, substances that induce insulin resistance such as tumor necrosis factor (TNF)-α are produced from visceral fat. Studies have indicated the possibility that elevation of blood pressure is induced in a state of insulin resistance by various mechanisms *via* adipocytokines (*30*). It has also been reported that compensatory hyperinsulinemia, which occurs in a state of insulin resistance, plays a role in blood pressure elevation *via* renal mechanisms (*31*).

In multiple regression analysis, no relationship was found between VFD and blood pressure in women. Possible reasons for this are the influence of an autocorrelation due to the addition of BMI to the adjusted items and both the small mean value and the low distribution of VFD in female subjects.

WC measurement is a very useful screening method for assessing visceral fat because it is simple and cheap. It does, however, have drawbacks, such as an inability to assess tall individuals differently than short ones and a low level of reproducibility in the case of marked obesity, since WC includes subcutaneous fat. Therefore, the Japanese criteria of MS recommend assessing real visceral fat accumulation by CT when we find individuals with WC ≥85 cm in men and ≥90 cm in women. Although abdominal CT is the gold standard for visceral fat assessment, it entails exposure to radiation, lack of ease and simplicity, and high cost. General practitioners may have a good deal of opportunity to assess individuals with MS, but very few physicians have CT equipment in their clinics. Assessment by US is a simpler technique than abdominal CT and allows general practitioners to assess visceral fat accumulation in their clinics. When we find high-risk individuals with an accumulation of risk factors and without abdominal obesity (WC <85 cm in men, WC <90 cm in women), it is important to confirm their fat distribution by other methods than WC. In such cases, the US method may be useful simply assessing the accumulation of visceral fat.

One limitation of the present study is that all of the subjects were Japanese; thus the results may not apply to Westerners or individuals of certain ethnic groups. The female body type in particular differs between Westerners and Japanese. Nevertheless, diagnostic criteria for WC that take into account ethnicity have been incorporated in the International Diabetes Federation (IDF)'s diagnostic criteria for MS. While there are differences in extent, the relationship between visceral fat accumulation and cardiovascular disease risk factors is universal (*32, 33*).

No statistical analysis was performed to evaluate the differences in the measured parameters between premenopausal and postmenopausal women in our study group. In general, postmenopausal women tend toward obesity more than premenopausal women, and their blood pressure levels and visceral fat levels are known to increase (*34, 35*). A study taking this into account is needed in the future. Additionally, the present study involved cross-sectional studies, and additional prospective studies on the relationship between abdominal obesity and elevated blood pressure are needed.

In conclusion, US is a simpler technique than abdominal CT, and its usefulness in visceral fat assessment was demonstrated in the screening of residents of a rural community. VFD is thought to be a good index for assessing not only visceral fat accumulation but also cardiovascular risk factors. Moreover, in men VFD showed a significant correlation with blood pressure. Visceral fat assessment by US may be useful for epidemiological studies and for clinics with no abdominal CT equipment to identify high-risk individuals such as those with metabolic syndrome.

References

1. Kannel WB, Brand N, Skinner JJ Jr, Dawber TR, McNamara PM: The relation of adiposity to blood pressure and development of hypertension. The Framingham study. *Ann Intern Med* 1967; **67**: 48–59.
2. Hubert HB, Feinleib M, McNamara PM, Castelli WP: Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983; **67**: 968–977.
3. Reaven GM: Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988; **37**: 1595–1607.
4. Kaplan NM: The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Arch Intern Med* 1989; **149**: 1514–1520.
5. Fujioka S, Matsuzawa Y, Tokunaga K, Tarui S: Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. *Metabolism* 1987; **36**: 54–59.
6. The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): 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.
7. Nakamura T, Tokunaga K, Shimomura I, *et al*: Contribution of visceral fat accumulation to the development of coronary artery disease in non-obese men. *Atherosclerosis* 1994; **107**: 239–246.
8. Kissebah AH, Vydelingum N, Murray R, *et al*: Relation of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab* 1982; **54**: 254–260.
9. Houmard JA, Wheeler WS, McCammon MR, *et al*: An evaluation of waist to hip ratio measurement methods in relation to lipid and carbohydrate metabolism in men. *Int J Obes* 1991; **15**: 181–188.
10. Pouliot MC, Despres JP, Lemieux S, *et al*: Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* 1994; **73**: 460–468.
11. Hsieh SD, Yoshinaga H: Abdominal fat distribution and coronary heart disease risk factors in men—waist/height ratio as a simple and useful predictor. *Int J Obes Relat Metab Disord* 1995; **19**: 585–589.
12. Hsieh SD, Yoshinaga H: Waist/height ratio as a simple and useful predictor of coronary heart disease risk factors in women. *Intern Med* 1995; **34**: 1147–1152.
13. Hsieh SD, Yoshinaga H, Muto T: Waist-to-height ratio, a simple and practical index for assessing central fat distribution and metabolic risk in Japanese men and women. *Int J Obes Relat Metab Disord* 2003; **27**: 610–616.
14. The Examination Committee of Criteria for 'Obesity Dis-

ease' in Japan, Japan Society for the Study of Obesity: New criteria for 'obesity disease' in Japan. *Circ J* 2002; **66**: 987–992.

15. Armellini F, Zamboni M, Robbi R, *et al*: Total and intra-abdominal fat measurements by ultrasound and computerized tomography. *Int J Obes Relat Metab Disord* 1993; **17**: 209–214.
16. Suzuki R, Watanabe S, Hirai Y, *et al*: Abdominal wall fat index, estimated by ultrasonography, for assessment of the ratio of visceral fat to subcutaneous fat in the abdomen. *Am J Med* 1993; **95**: 309–314.
17. Ribeiro-Filho FF, Faria AN, Kohlmann O Jr, *et al*: Ultrasonography for the evaluation of visceral fat and cardiovascular risk. *Hypertension* 2001; **38**: 713–717.
18. Stolk RP, Wink O, Zelissen PM, Meijer R, van Gils AP, Grobbee DE: Validity and reproducibility of ultrasonography for the measurement of intra-abdominal adipose tissue. *Int J Obes Relat Metab Disord* 2001; **25**: 1346–1351.
19. Stolk RP, Meijer R, Mali WP, Grobbee DE, van der Graaf Y: Ultrasound measurements of intraabdominal fat estimate the metabolic syndrome better than do measurements of waist circumference. *Am J Clin Nutr* 2003; **77**: 857–860.
20. Kim SK, Kim HJ, Hur KY, *et al*: Visceral fat thickness measured by ultrasonography can estimate not only visceral obesity but also risks of cardiovascular and metabolic diseases. *Am J Clin Nutr* 2004; **79**: 593–599.
21. Johnson D, Prud'homme D, Despres JP, Nadeau A, Tremblay A, Bouchard C: Relation of abdominal obesity to hyperinsulinemia and high blood pressure in men. *Int J Obes Relat Metab Disord* 1992; **16**: 881–890.
22. Hayashi T, Boyko EJ, Leonetti DL, *et al*: Visceral adiposity and the prevalence of hypertension in Japanese Americans. *Circulation* 2003; **108**: 1718–1723.
23. Hayashi T, Boyko EJ, Leonetti DL, *et al*: Visceral adiposity is an independent predictor of incident hypertension in Japanese Americans. *Ann Intern Med* 2004; **140**: 992–1000.
24. Boyko EJ, Leonetti DL, Bergstrom RW, Newell-Morris L, Fujimoto WY: Visceral adiposity, fasting plasma insulin, and blood pressure in Japanese-Americans. *Diabetes Care* 1995; **18**: 174–181.
25. Grauer WO, Moss AA, Cann CE, Goldberg HI: Quantification of body fat distribution in the abdomen using computed tomography. *Am J Clin Nutr* 1984; **39**: 631–637.
26. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412–419.
27. Yusuf S, Hawken S, Ounpuu S, *et al*: Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet* 2005; **366**: 1640–1649.
28. Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Despres JP: Sex differences in the relation of visceral adipose tissue accumulation to total body fatness. *Am J Clin Nutr* 1993; **58**: 463–467.
29. Kotani K, Tokunaga K, Fujioka S, *et al*: Sexual dimorphism of age-related changes in whole-body fat distribution in the obese. *Int J Obes Relat Metab Disord* 1994; **18**: 207–212.
30. Matsuzawa Y: Pathophysiology and molecular mechanisms of visceral fat syndrome: the Japanese experience. *Diabetes Metab Rev* 1997; **13**: 3–13.
31. Miyazaki Y, Hirata A, Murakami H, *et al*: Effects of aging on the insulin actions for the glucose metabolism and renal function in normotensives and essential hypertensives. *Am J Hypertens* 1998; **11**: 1056–1064.
32. Alberti KG, Zimmet P, Shaw J: The metabolic syndrome—a new worldwide definition. *Lancet* 2005; **366**: 1059–1062.
33. Ford ES: Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. *Diabetes Care* 2005; **28**: 2745–2749.
34. Faria AN, Ribeiro Filho FF, Gouveia Ferreira SR, Zanella MT: Impact of visceral fat on blood pressure and insulin sensitivity in hypertensive obese women. *Obes Res* 2002; **10**: 1203–1206.
35. Reckelhoff JF, Fortepiani LA: Novel mechanisms responsible for postmenopausal hypertension. *Hypertension* 2004; **43**: 918–923.

Original Article

Visceral Obesity in Japanese Patients with Metabolic Syndrome: Reappraisal of Diagnostic Criteria by CT Scan

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To reappraise the cutoff level of abdominal circumference (AC) for diagnosis of visceral obesity in Japanese, we examined the association of visceral fat deposition with other constituents of metabolic syndrome and atherosclerotic cardiovascular disease (ASCD). CT was used for determination of visceral-fat area (VFA), subcutaneous-fat area (SFA) and AC on CT (AC_{CT}) in 420 Japanese patients with (n=180) or without ASCD (n=240). VFA cutoff levels were calculated by receiver operating characteristic (ROC) analysis. AC_{CT} correlated with VFA (r=0.828), SFA (r=0.795), and AC measured with an anthropometric tape (AC_M, r=0.96). The VFA cutoff levels yielding the maximum sensitivity and specificity to predict two or more components of metabolic syndrome were 92 cm^2 in males and 63 cm^2 in females, which correspond to AC_M values of 83 cm and 78 cm, respectively. The male AC_M cutoff level was similar to the AC in current Japanese criteria (85 cm), but the female AC_M cutoff level was considerably smaller than the criteria, and this change in cutoff level increased the prevalence of metabolic syndrome in females three-fold. The cutoff levels of VFA for predicting presence of ASCD were 98 cm^2 in males and 75 cm^2 in females, corresponding to AC_M values of 84 cm and 80 cm, respectively. The present results obtained by CT support the validity of the current Japanese criteria for visceral obesity in males but not in females. AC_M of 78 cm appears to be a cutoff level suitable for diagnosing visceral obesity in Japanese females, though further confirmation is needed. (*Hypertens Res* 2007; 30: 315–323)

Key Words: metabolic syndrome, coronary arterial disease, visceral obesity, aging

Introduction

Clustering of major risk factors (hypertension, diabetes mellitus, and hyper-lipidemia) has been shown to have synergistic effects on the development of atherosclerotic cardiovascular disease (ASCD) (*1, 2*). The contribution of clustered minor risk factors for ASCD has also received attention recently, and attractive clinical concepts (*3–6*) emerged in the 1980s: metabolic syndrome X, insulin resistance syndrome, visceral fat syndrome, and multiple risk factor syndrome. Currently, the cluster of minor metabolic factors for ASCD is referred to as metabolic syndrome, and consists of visceral obesity, glucose intolerance or insulin resistance, dyslipidemia, and raised blood pressure. However, several definitions of metabolic syndrome, which differ in their required combinations of risk factors and cutoff levels for each factor, have been proposed (*7–9*).

One of the marked differences among the current diagnostic criteria of metabolic syndrome is the method used to assess visceral obesity and its requirement for diagnosis. In the definition of metabolic syndrome by the National Choles-

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Table 1. Clinical Backgrounds in Studied Subjects

	All (n=420)	Male (n=235)	Female (n=185)
Age (years old)	62±15	63±14	61±17
Gender [male/female]	235/185		
Risk factors (n (%))			
Hypertension	275 (66)	163 (69)	112 (61)
Diabetes mellitis	141 (34)	84 (36)	57 (31)
Hyperlipidemia	297 (71)	167 (71)	130 (70)
Hyperuricemia	132 (32)	93 (40)	39 (21)*
Smoking	174 (42)	143 (63)	31 (17)*
Family history	65 (16)	34 (15)	31 (17)
Weight (kg)	60±14	65±14	53±11*
BMI (kg/m^2)	23±4	23±4	22±4*
Systolic blood pressure (mmHg)	134±21	135±20	133±20
Diastolic blood pressure (mmHg)	77±13	77±13	76±13
Major disease (n (%))			
Coronary heart disease	122 (29)	88 (37)	34 (18)
Cardiomyopathy	33 (8)	19 (8)	14 (8)
Valvular disease	40 (10)	15 (6)	25 (14)
Aortic disease	41 (10)	27 (11)	14 (8)
Arrhythmia	61 (15)	38 (16)	23 (12)
Renal disease	56 (13)	27 (11)	29 (16)
Stroke	12 (3)	7 (3)	5 (3)
Others	54 (17)	14 (6)	40 (22)
Medication (n (%))			
Antihypertensive agents	241 (57)	149 (63)	92 (50)*
Antihyperlipidemia agents	112 (26)	49 (21)	63 (34)*
Antidiabetic agents	81 (19)	45 (19)	36 (20)

All the variables are expressed as mean±1 SD. *p<0.05 *vs.* male group, respectively.

terol Education Program Adult Treatment Panel III (NCEP ATP III) (*7*), visceral obesity is not a requisite. However, visceral obesity needs to be present in metabolic syndrome as defined by the International Diabetes Federation (IDF 2005) (*8*) and the Examination Committee of Criteria for Metabolic Syndrome in Japan (Japanese criteria) (*9*). In these definitions, visceral obesity is assessed by abdominal (waist) circumference, but its cutoff level is not the same: abdominal circumferences (ACs) are ≥102 cm in males and ≥88 cm in females in the NCEP ATP III criteria, ≥85–94 cm in males and ≥80–90 cm in females, depending on ethnic groups, in the IDF criteria, and ≥85 cm in males or ≥90 cm in females in the Japanese criteria. These differences in diagnostic criteria of visceral obesity derive from different rationales in each subject population.

In the present study, we used multi-detector-row CT (MDCT) to reappraise visceral obesity criteria for the diagnosis of metabolic syndrome and screening of ASCD in Japanese subjects. Since visceral fat, but not subcutaneous fat, is primarily responsible for the production of cytokines relevant to the development of metabolic syndrome (*10, 11*), the amounts of visceral and subcutaneous fat were separately determined by MDCT together with AC. The relationships between the amount of visceral fat and metabolic syndrome or ASCD were analyzed by use of receiver operating characteristic (ROC) curves, and the results suggest that the current Japanese criterion of visceral obesity in males (AC=85 cm) is valid but that the criterion for females needs to be modified possibly to AC of 78 cm.

Methods

Study Subjects

We enrolled 420 consecutive patients who underwent MDCT at Sapporo Medical University Hospital between January 2001 and December 2003 (Table 1). Informed consent for use of their data in scientific research was obtained from all study subjects. Data from each subject were saved in anonymous formats and securely stored in a computer. Information on coronary risk factors, including data on the blood pressure category, serum triglyceride and high-density lipoprotein (HDL) cholesterol levels and presence/absence of ASCD, was obtained by physical and laboratory examinations. Unless otherwise stated, metabolic syndrome was diagnosed in accordance with the current Japanese criteria (*10*), which

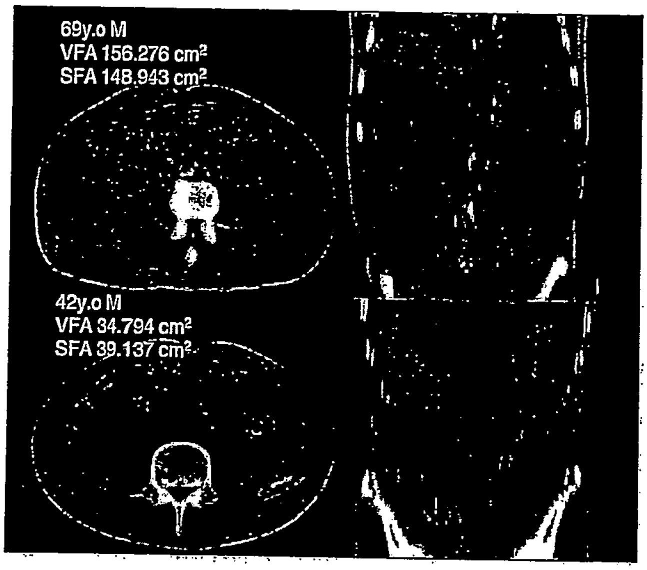

Fig. 1. *Representative MDCT images used for determination of visceral fat area and subcutaneous fat area. CT slices at the level of the umbilicus were used for the determination of areas. VFA, visceral fat area; SFA, subcutaneous fat area. Upper: a case of visceral obesity; Lower: a non-obese case.*

require the presence of visceral obesity (defined as a waist measurement of ≥85 cm in males or ≥90 cm in females) and two or more of the following minor abnormalities; 1) glucose intolerance (fasting blood glucose ≥110 mg/dl) or taking medication for diabetes, 2) serum triglyceride ≥150 mg/dl, 3) HDL cholesterol <40 mg/dl in either males and females, and 4) blood pressure ≥130/85 mmHg. Cases of severe congestive heart failure (NYHA IV), ascites, malignant tumor, thyroidal disease, and the other emaciating disorders were excluded from the study to prevent entry bias. General obesity was determined as body mass index (BMI) ≥25%, following the criteria of the Japanese Society of Obesity (*12*). ASCD in this study included coronary artery disease, cerebrovascular disease, arotic atherosclerotic disease, and atherosclerotic valvular heart disease. The subclinical forms of atherosclerosis, such as thickening of the intima in the carotid artery, were not examined and not included in ASCD in this study.

Determination of Visceral and Subcutaneous Fat Areas by MDCT

All of the MDCT images were obtained either by Aquillion 4DAS (Toshiba Inc., Tokyo, Japan) or Light Speed Ultra 8DAS (General Electrics Japan Co., Tokyo, Japan) with a minimal slice width of 5–7 mm. Data were stored on visual servers and retrospectively analyzed using commercially supplied software without information regarding patients' cardiovascular and biochemical parameters. The fat areas in each subject were determined from an image at the level of the umbilicus (Fig. 1) with Virtual Place (AZE Inc., Tokyo, Japan). Subcutaneous fat was defined as the extraperitoneal fat between skin and muscle, with attenuation ranging from −150 to −50 Hounsfield units. The intraperitoneal part with the same density as the subcutaneous fat layer was defined as visceral fat. The visceral fat area (VFA) and subcutaneous fat area (SFA) were determined by automatic planimetry.

Determination of AC

AC on CT (AC_{CT}) was determined in all subjects from CT images at the umbilical level using a mobile caliper. In 80 randomly selected subjects (37 males and 43 females), abdominal circumference (AC_M) was also measured with an anthropometric tape to confirm its correlation with AC_{CT}.

Statistical Analysis

All numeric variables are expressed as the means±SD. Differences in the incidences between groups were tested by the χ^2 test. Comparison of group mean data was performed by one-way analysis of variance (ANOVA) and Bonferroni's post hoc test. The correlation between two values was evaluated by linear and exponential regression analyses. Difference between regression lines was examined by analysis of covariance. Values of $p<0.05$ were considered statistically significant. ROC analysis was performed to determine cutoff

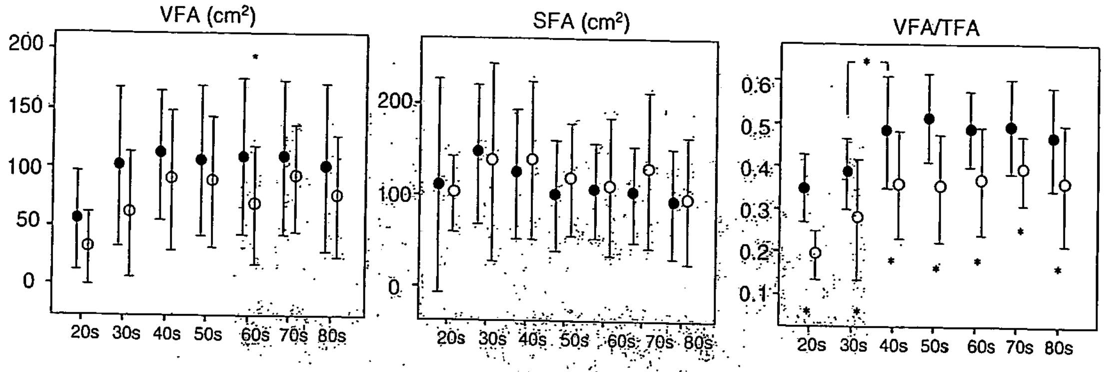

Fig. 2. *Age-related difference in the levels of visceral and subcutaneous fat accumulation. VFA, visceral fat area; SFA, subcutaneous fat area; VFA/TFA, ratio of VFA to total fat areas (VFA+SFA). Closed circles and open circles indicate the data for males and females, respectively. *p≤0.05 vs. males.*

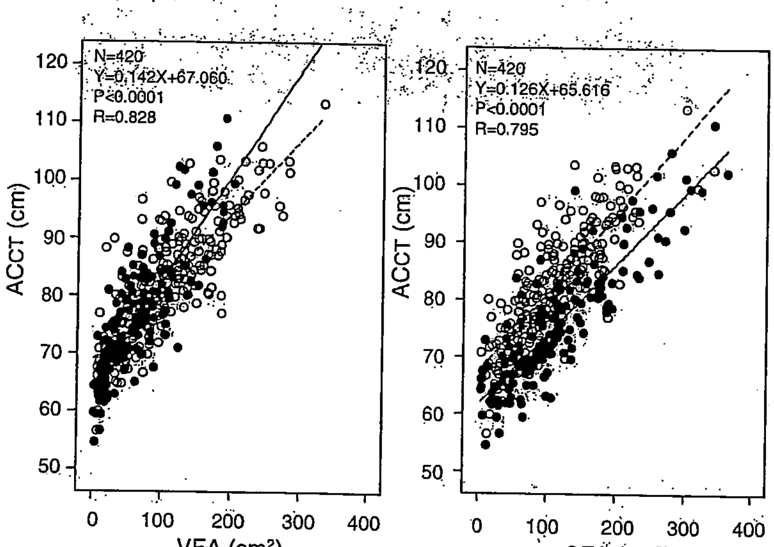

Fig. 3. *Correlation between abdominal circumference (AC_{CT}) and accumulation of visceral (VFA) and subcutaneous fat (SFA). Open circles and closed circles indicate the data for males and females, respectively. There was no significant difference in the regression lines for the AC_{CT}-VFA relationships between males (broken line) and females (solid line). However, the regression line for the AC_{CT}-SFA relationship was shifted upwards in females compared with males.*

points of VFA yielding the maximum sensitivity and specificity for predicting metabolic syndrome and ASCD.

Results

Characteristics of Subjects

As shown in Table 1, we enrolled 420 patients aged 62±15 years old (age range, 14–92 years). The age and incidences of risk factors, except for hyperuricemia and smoking, were comparable in the male and female subjects. Of the 420 patients, 180 (42.9%) had ASCD, and the incidence of coronary artery disease tended to be higher in males than in females, though the difference was not statistically significant. The percentages of subjects on pharmacological treatments for hypertension, hyperlipidemia and diabetes were 57%, 26% and 19%, respectively.

Visceral and Subcutaneous Fat Deposition in Age Subgroups

Figure 2 shows the levels of VFA and SFA and ratio of VFA to total fat area (TFA; TFA=VFA+SFA) in each age group. There was a trend for lower VFA and higher SFA in subjects