厚生労働科学研究費補助金

循環器疾患・糖尿病等生活習慣病対策総合研究事業

内臓脂肪蓄積を簡便に推定できる評価モデル式の開発とそのリスク評価に関する縦断研究

（ H23　-循環器等（生習）-　一般-006 ）

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研究代表者

松　下　由　実　国立国際医療研究センター　臨床研究支援部

分担研究者

中　川　　徹　日立製作所　日立健康管理センタ

山　本　修一郎　日立製作所　日立健康管理センタ

溝　上　哲　也　国立国際医療研究センター　疫学予防研究部

野　田　光　彦　国立国際医療研究センター　糖尿病研究部

高　橋　義　彦　岩手医科大学　糖尿病・代謝内科学分野

西　　信　雄　国立健康・栄養研究所　国際産学連携センター

大　庭　志　野　国立保健医療科学院　生涯健康研究部

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厚生労働科学研究費補助金(循環器疾患・糖尿病等生活習慣病対策総合研究事業)

総括報告書
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研究代表者　松下　由実
国立国際医療研究センター　臨床研究支援部　臨床研究推進室長

研究要旨

日本のメタボリックシンドローム診断基準の内臓脂肪蓄積の簡易指標として、ウエスト周囲径が使われているが、研究代表者らは、CT測定による内臓脂肪面積に比べ、ウエスト周囲径はメタボリックシンドロームのリスク重複を女性では5割、男性では7割しか検出することができず、ウエスト周囲径を簡易指標として用いることには限界があることを明かにした。しかし、CTによる内臓脂肪面積測定はX線の被曝の問題、さらには高コストの面などの問題点があり、健診現場での汎用性に欠ける面もある。そこで、内臓脂肪の簡易指標として効果的、効率的、経済的でかつ簡便な評価モデル式の横断的、縦断的検討が必要であり、さらに、アディポサイトカインなどの要因も評価モデル式に入れる必要があるかどうかの検討も必要である。

そこで、研究代表者らが今開発中である内臓脂肪の蓄積をより鋭敏に反映する効果的、効率的、経済的で簡便に測れる評価モデル式を身体計測値、バイオマーカー、生活習慣要因から検討し、推定能力の高いものにし、また、その式が循環器疾患リスクを予測できるかどうかについて追跡調査により明らかにすることを目的として本研究を行った。

本研究のコホートでは、CTによる内臓脂肪の計測データに加え、生活習慣病に関する詳細な検査データなどを多数蓄積し、かつそれらを経時的に観察できる集団を対象としている。このような検討は世界的にも類がなく、本研究から科学的エビデンスに基づく質の高い内臓肥満を反映する評価モデル式の作成が可能である。このことにより、強化型保健指導が必要な対象者の絞込みに役立ち、保健資源の効率的な運用を可能とする。また、特定保健指導評価としても我々が作成する評価モデル式は適応可能である。以上を通じて、メタボリックシンドロームに関連した諸疾病群の発症リスクを低減し、国民の健康寿命の延伸に貢献する。

分担研究者

中川徹
日立製作所　日立健康管理センタ
副センタ長
山本修一郎
日立製作所　日立健康管理センタ
主任医長
溝上哲也
国立国際医療研究センター
疫学予防研究部長
野田光彦
国立国際医療研究センター
糖尿病研究部長
高橋義彦
岩手医科大学
糖尿病・代謝内科学分野
特任講師
西信雄
国立健康・栄養研究所
国際産学連携センター
センター長
大庭志野
国立保健医療科学院
生涯健康研究部
特命上席主任研究官

A. 研究目的

研究代表者らが今開発中である内臓脂肪の蓄積をより鋭敏に反映する効果的、効率的、経済的で簡便に測れる評価モデル式を身体計測値、バイオマーカー、生活習慣要因から検討し、推定能力の高いものにする。また、その式が循環器疾患リスクを予測できるかどうかについて追跡調査により明らかにすることを目的とする。

B. 研究方法

対象

日立製作所日立健康管理センタで通年行っている人間ドック成績のうち、腹部ＣＴ検査が導入された平成16年度以降を分析対象とする。さらに、平成20年度以降の受診者には同意を得た上で研究用の追加採血を行った。本研究は同社の産業医との共同研究として進めることで合意しており、倫理審査で承認済みである。

同センタ人間ドックでは、中性脂肪、HDLコレステロール、血圧、空腹時血糖、腹囲といったメタボリックシンドローム診断に必要な項目に加え、インスリンや高感度CRPを受診者全員に測定している。腹部CTによる内臓脂肪面積の計測は希望者に行っているが、人間ドック受診者17,000人の約3分の1にあたる6,000人が毎年、腹部CTを受診している。平成16年から平成25年度までのCT受診者(少なくとも1回以上の検査)12628人を対象として解析を行った。なお、人間ドック受診者における男女比は6:1であった。心電図も測定した。

方法

1. 採血およびアディポサイトカインの測定（同意書の得られた人のみ）

人間ドック受付時に研究用採血についての説明・依頼文書と同意書を渡し、書面で同意を得た。同意の得られた人から静脈血5mlを採取し、同施設にて7343名のアディポネクチンを測定した。残検体は健診施設内の冷凍庫（−80℃）に一時保管し、3ヶ月ごとに国立国際医療研究センターへ低温で輸送し、凍結保管（−80℃）した。

2. 既存データ（平成 16 年度～平成 24 年度）のデータベース化

1) 人間ドックデータ（腹部 CT、肺部 CT を含む）をデータベース化した。
2) 各疾病の ICD-10 コード化を行った。
3) 心電図データのミネソタコード化を行った。
4) 糖尿病・高血圧・高脂血症・脳心血管疾患発症の把握
糖尿病、高血圧、高脂血症、脳心血管疾患の発症、既往歴、治療の有無は人間ドック成績、調査票および欠勤時の診断書より把握した。

3. データの解析

内臓脂肪の蓄積をより鋭敏に反映する効果的、効率的、経済的で簡便に測れる評価モデル式を身体計測値、バイオマーカー、生活習慣要因から再検討し、妥当性の検討を横断解析で行った。さらに心血管疾患イベントをエンドポイントとした縦断解析を行い、作成した評価モデル式の妥当性を確認した。

（倫理面への配慮）

本研究の実施計画は「疫学研究に関する倫理指針」に則って作成し、研究実施前に、研究代表者及び実施する会社の分担研究者は研究計画書をそれぞれが所属する機関の倫理委員会に諮り、承認を得た。通常に行われている健診データに使用にあたっては、個別にインフォームドコンセントをとらず、社内の掲示にて研究の目的と意義を説明した。また研究用採血に関して、調査内容をわかりやすく示したパンフレットを用いて、自由意志に基づく参加であることや、個人情報の保護対策を含め人間ドックスタッフが対象者に説明した後に、本人から署名入りの同意書を得た上で実施した。人間ドック検査成績と採取した血液は匿名化（連結可能）した上で、鍵のかかるロッカー、-80℃の冷凍庫にそれぞれ保管した。結果の公表に際しては個人が特定できない形式で行った。

C. 研究結果

1) 内臓脂肪面積の変化がメタボリックシンドロームの各要因の発症に及ぼす影響

2004 年度、2007 年度の腹部 CT 受診者のうち、高血圧、高脂血症、糖尿病の現在治療中の人を除外した男性 1,106 人を対象とした。3 年間の内臓脂肪面積の変化量により 7 群に分け、±10 cm^2 以内の群を基準とした。①中性脂肪高値②HDL コレステロール低値③血圧高値④糖代謝異常、および⑤メタボリックシンドローム（①-④のうち 2 項目以上あり）の 3 年後の発症オッズ比を求めた。⑤のオッズ比は 50cm^2 以上内臓脂肪面積が増加した人で有意な上昇がみられた。②、④でも同様の結果が得られた。①は－50cm^2 以下の群でオッズ比が有意に下がり、30cm^2 以上の群で有意に上昇していた。内臓脂肪の増加を抑制することがメタボリックシンドロームの解消につながる可能性が示唆された。（Matsushita Y, et al. Obesity 2013; 21(10):2126-9.）

2) アディポネクチン・内臓脂肪面積がメタボリックシンドロームのリスク重積に及ぼす影響

男性6221名、女性775名、合計6996名を対象とし、アディポネクチン、内臓脂肪面積別にそれぞれ4分位、16群に群分けし、アディポネクチン最高値・内臓脂肪面積最低値

群を基準（1.0）とした時のメタボリックシンドロームのリスク重積の調整オッズ比を求めた。アディポネクチン最低値・内臓脂肪面積最高値群が最も高いオッズ比（95%信頼区間）であった（男性：12.7（9.7-16.6）、女性：13.5（6.0-30.2））。さらに、内臓脂肪面積とアディポネクチンは、独立してメタボリックシンドロームに影響を及ぼしていることが明かになった。

（Matsushita Y, et al. Obesity 2014; 22(1):287-91.）

3）ウエスト周囲長と体格組成との関係

ウエスト周囲長、BMI は、内臓脂肪面積の簡易指標として用いられているが、性、年齢別の内臓脂肪面積とウエスト周囲長、BMI との関連はいまだ明らかにされていない。そこでわれわれは、ウエスト周囲長の意味を明らかにするため、CT 画像より算出した内臓脂肪、皮下脂肪、筋肉、筋肉内脂肪、骨、内臓面積とウエスト周囲長の関連を検討した。

2004～2009 年度に日立健康管理センタにおいて腹部 CT 検査を受検した 20 歳から 76 歳の男性 9874 名、女性 1696 名を対象とした。身長、体重の測定から BMI を算出し、ウエスト周囲長、内臓脂肪面積、皮下脂肪面積は CT 検査から計測した。CT 画像から筋肉、筋肉内脂肪、骨、内臓領域を分離する技術はこれまでなかったが、私共は、新しく解析ソフトを開発し、これらの面積を算出した。

解析は、性、年齢別（～39、40-49、50-59、60-69、70 歳～）に分け、内臓脂肪面積と他の体格指数（皮下脂肪面積、ウエスト周囲長、BMI）の相関係数、皮下脂肪面積と他の体格指数（ウエスト周囲長、BMI）の相関係数を求めた。回帰分析により、ウエスト周囲長と内臓脂肪面積および内臓脂肪面積と皮下脂肪面積の和との関係を表す回帰係数と切片を求めた。

男女ともに内臓脂肪面積は年齢が高くなるにしたがって増加するが、ウエスト周囲長は、女性は年齢ともに増加するが、興味深いことに、男性は年齢とともに減少していた（$P<0.001$）。内臓脂肪面積とウエスト周囲長の関係が男女で異なることが明らかになった。その原因を解明するため、さらに体格構成につき、男女合計 11570 名からランダムで各年齢層別に抽出した約 1500 名を対象とし、詳細に検討を行った。内臓脂肪面積と皮下脂肪面積の和は、ウエスト周囲長の年齢別の動きと似ていることが明らかになった（相関係数：男性 0.901、女性 0.945）。このことより、ウエスト周囲長は、内臓脂肪面積ではなく、内臓脂肪と皮下脂肪面積の和を反映していることが示唆され、さらに男女で比較すると、男性は筋肉量が多いという特徴が認められた（$P<0.001$）。同じ内臓脂肪面積に相当するウエスト周囲長は、年齢の高いグループは年齢の低いグループに比べ、低くなっていた。

年齢層が高くなるに従って、内臓脂肪面積は男女ともに大きくなる傾向が認められた。しかしながら、ウエスト周囲長は内臓脂肪面積ではなく内臓脂肪面積と皮下脂肪面積の和を表していることが明らかになった。現在は、メタボリックシンドロームの診断基準では、全年齢で同じウエスト周囲長のカットオフを用いているが、若い世代

ではメタボリックシンドロームの人を見落とす可能性があることが明らかになった。各年齢層に適したウエスト周囲長のカットオフを設定する必要があると考えられる。

4) 内臓脂肪の蓄積をより鋭敏に反映する効果的、効率的、経済的で簡便に測れる評価モデル式の作成と妥当性の検討

既存の肥満指標（内臓脂肪面積、ウエスト周囲長、BMI）と我々が作成した新しい体格指標（BSI; Body Shape Index）を用い、どの体格指標が心筋梗塞および心電図異常を予測うる能力が最も高いかを 10811 人を対象として ROC 曲線を描き、検討した。ROC 曲線の曲線下面積を比較したところ、男女とも BSI が最も大きかった。男性では、BSI は内臓脂肪面積、ウエスト周囲長、BMI よりも有意に ROC の曲線下面積が大きくなっており、女性では、BSI は内臓脂肪面積とほぼ同等で、ウエスト周囲長、BMI よりは有意に大きかった。

さらに BSI を用い、虚血性心疾患の発症のハザード比を求めた（追跡期間：8 年)。女性は発症数が低かったため、解析できず、男性のみ（2632 名）解析を行った。BSI で 2 分位に分け、BSI が低いグループを基準としたハザード比は、1.3 であった。

D. 考察

縦断解析により、内臓脂肪蓄積が多いほど、メタボリックシンドロームのリスクが高まることが明らかになった。内臓脂肪面積の 3 年間の増加量を 50 cm^2 未満に抑制することにより、メタボリックシンドロームのリスク重積の解消につながる可能性が示唆された。

ウエスト周囲長の年代別の変化は、内臓脂肪面積の年代別変化を特に男性においては正確に反映していないことが明らかになった。メタボリックシンドローム診断のためのウエストカットオフは、年齢別に定める必要があることが示唆された。

また、脂肪細胞から放出されるホルモン（アディポネクチン）は、内臓脂肪面積とは独立してメタボリックシンドロームに影響を及ぼしていることが明らかとなった。

CT で測定した内臓脂肪面積に比べて男性ではより鋭敏に、女性では同等に心筋梗塞と心電図異常を検出でき、なおかつ効果的、経済的で簡便に測れる評価モデル式の作成に成功した。虚血性心疾患発症をエンドポイントとした縦断解析では、男性では BSI が高くなるとオッズ比の上昇がみられ、妥当性が認められた。

E. 結論

得られたデータは、前向きコホート研究による発症率調査及び糖尿病・メタボリックシンドロームの曝露要因としての役割の検討の際、基礎データとして活用する。

今後は、研究代表者らが開発した内臓脂肪の蓄積をより鋭敏に反映する効果的、経済的で簡便に測れる評価モデル式（BSI）が循環器疾患発症を予測できるかどうかについて、さらに追跡期間を延ばし、発症率の低い女性についても検討する。

F. 健康危険情報

なし

G. 研究発表

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3) 2型糖尿病患者における内因性インスリン分泌の指標による治療選択と将来の治療効果予測への有効性
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H. 知的財産権の出願・登録状況

1. 特許取得
なし

2. 実用新案登録
なし

3. その他

研究成果の刊行に関する一覧表

書籍

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Iwata M, Matsushita Y, Fukuda K, Wakura T, Okabe K, Koshimizu Y, Fukushima Y, Kobashi C, Yamazaki Y, Honoki H, Suzuki H, Tobe K.	Secretory units of islets in transplantation index (SUIT)is a useful predictor of insulin requirement in Japanese type 2 diabetic patients.	J Diabetes Investigation.			in press
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Original Article
EPIDEMIOLOGY/GENETICS

Obesity

Effect of Longitudinal Changes in Visceral Fat Area on Incidence of Metabolic Risk Factors: the Hitachi Health Study

Yumi Matsushita[1], Toru Nakagawa[2], Shuichiro Yamamoto[2], Yoshihiko Takahashi[3], Tetsuji Yokoyama[4], Tetsuya Mizoue[5] and Mitsuhiko Noda[6,7]

Objective: To examine the incidences of metabolic risk factors according to changes in visceral fat area (VFA) in a large Japanese population.

Design and Methods: The subjects were 973 men who received a computed tomography (CT) examination in health checkups twice (2004-2005 and 2007-2008), and not having two or more of metabolic risk factors (except for the waist circumference) in 2004-2005. VFA was measured using CT. To assess the potential influence of changes in VFA for the 3-year incidences of each metabolic risk factor and clustering metabolic risk factors, logistic regression analyses were used.

Results: A significant association was observed between the change in VFA and the components of the metabolic risk factors. Incidences of the components of the metabolic risk factors were significantly higher among subjects with a larger increase in VFA and were significantly lower among subjects with a larger decrease in VFA (trend $P < 0.001$). Significant increases in the odds ratios for the incidences of high triglycerides and low high-density lipoprotein cholesterol level were observed among subjects with $\geq$50 cm^2 VFA increase.

Conclusions: The adoption of a lifestyle that does not increase the VFA is important for preventing metabolic syndrome.

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Introduction

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality in the world (1). Previous reports have shown that obesity plays a significant role in increasing cardiovascular risk (2). Some indicators of obesity, such as the visceral fat area (VFA), or visceral adipose tissue, are more strongly associated with the risk of CVD than other indicators of obesity, such as waist circumference, body mass index (BMI) (3,4), or subcutaneous fat area (SFA) (2,3). A larger VFA is strongly related to a higher prevalence of impaired fasting glucose levels (5), diabetes (5), insulin resistance (5), hypertension (6), abnormality of lipid metabolism (7), and metabolic risk factors (7,8). Several cross sectional and other types of studies have examined the association between VFA and metabolic risk factors. For instance, in some prospective studies, VFA was measured at baseline and its correlation between risk factors for diabetes (plasma insulin level, homeostasis model assessment for insulin resistance, etc.) was evaluated (9-11). However, no study has measured the longitudinal change in VFA among the same subjects twice, at baseline and at follow-up, to examine its relation to the incidences of metabolic risk factors in a large cohort study. Thus, whether an increase in VFA leads to an increase in the risk of CVD or whether a decrease in VFA leads to a decrease in the risk of CVD remain uncertain. Clarifying this point could be useful for preventing CVD in clinical settings.

Therefore, we examined the incidences of the clustering of metabolic risk factors and its components among subjects who did not have each of the risk factors or the clustering of metabolic risk factors at baseline according to the aforementioned changes in VFA.

[1] Department of Clinical Research, National Center for Global Health and Medicine, Tokyo, Japan. Correspondence: Yumi Matsushita (ymatsushita@ri.ncgm.go.jp) [2] Hitachi, Ltd., Hitachi Health Care Center, Ibaraki, Japan [3] Division of Diabetes and Metabolism, Iwate Medical University, Iwate, Japan [4] Department of Health Promotion, National Institute of Public Health, Saitama, Japan [5] Department of Epidemiology and Prevention, National Center for Global Health and Medicine, Tokyo, Japan [6] Department of Diabetes and Metabolic Medicine, Center Hospital, National Center for Global Health and Medicine, Tokyo, Japan [7] Department of Diabetes Research, Diabetes Research Center, National Center for Global Health and Medicine, Tokyo, Japan

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Methods and Procedures

Overall, a total of 13,965 male employees and their spouses who, after more than 12 h of fasting, underwent health checkups during the baseline survey performed in 2004 and 2005 at the Hitachi Health Care Center in Ibaraki Prefecture. Of them, 3,119 men received a computed tomography (CT) scan. We studied 1,106 men who also participated in a 3-year follow-up survey performed in 2007 and 2008 (aged 30-72 years in 2004 and 2005) in the final analysis. Subjects without each metabolic risk factor (except for the waist circumference) or clustering of risk factors were included into the analysis of the incidence. Numbers of subjects in each group are shown in Table 1. Informed consent was obtained from each examinee regarding the use of his or her data for research purposes. The present study was approved by the ethics review committee of the National Center for Global Health and Medicine.

In this study, subjects with two or more of the four risk factors (high blood pressure, high triglyceride, low high-density lipoprotein (HDL) cholesterol, and hyperglycemia) defined in the criteria of the National Cholesterol Education Program's Adult Treatment Panel III guidelines in 2005 (12), except for waist circumference, were defined as having the clustering of metabolic risk factors. Subjects currently receiving treatment for hyperlipidemia, hypertension, or diabetes were deemed as having the respective risk factors, regardless of the biochemical values. Subjects with metabolic risk factor and/or who were screened for diabetes, hypertension, hyperlipidemia, and obesity at the health check received brief recommendation on life style modification verbally and/or were advised to consult a doctor, if necessary.

TABLE 1 Characteristics of subjects at baseline

	Subjects with 0–1 metabolic risk factor	Subjects with ≥2 metabolic risk factors
n	973	659
Age (years)	52.7[a] (8.4)	55.1[a] (7.8)
Height (cm)	168.9[a] (6.2)	168.2[a] (5.9)
Weight (kg)	66.7[a] (9.1)	70.4[a] (9.2)
BMI (kg/m^2)	23.3[a] (2.6)	24.8[a] (2.7)
VFA (cm^2)	113.2[a] (52.1)	149.1[a] (50.5)
SFA (cm^2)	118.2[a] (51.9)	136.8[a] (50.4)
VFA/SFA	1.0[a] (0.4)	1.2[a] (0.6)
Waist circumference (cm)	84.6[a] (7.8)	89.2[a] (8.3)
SBP (mmHg)	120.1[a] (11.7)	130.6[a] (10.0)
DBP (mmHg)	76.1[a] (8.3)	82.7[a] (7.2)
Triglycerides (mg/dL)	113.4[a] (62.3)	193.6[a] (133.5)
HDL-cholesterol (mg/dL)	59.1[a] (13.6)	51.8[a] (14.7)
Fasting glucose (mg/dL)	103.2[a] (16.1)	121.2[a] (27.9)
High blood pressure	261[b] (26.8)	520[b] (78.9)
Hyperglycemia	132[b] (13.6)	458[b] (69.5)
High triglycerides	154[b] (15.8)	451[b] (68.4)
Low HDL cholesterol	17[b] (1.7)	142[b] (21.5)
VFA ≥ 100cm^2	584[b] (60.0)	549[b] (83.3)

[a]Values are mean (SD)
[b]Values are number (percentage)

The 3-year change in the participants' VFA (designated as ΔVFA) was categorized into seven groups (Group 1, ≤ −50 cm^2; Group 2, > −50 cm^2 and ≤ −30 cm^2; Group 3, > −30 cm^2 and ≤ −10 cm^2; Group 4, > −10 cm^2 and <10 cm^2; Group 5, ≥ 10 cm^2 and < 30 cm^2; Group 6, ≥ 30 cm^2 and < 50 cm^2; Group 7, ≥ 50 cm^2). Odds ratios (95% confidence intervals (CI)) of the 3-year incidence of each metabolic risk factor and/or clustering of metabolic risk factors according to the seven groups of ΔVFA were estimated with the use of a multiple logistic regression analysis, where adjustments were made for the following potential confounders: age, VFA, and each parameter of the metabolic risk factors (high blood pressure, hyperglycemia, high triglycerides, or low HDL cholesterol) at baseline. *P* value for trend across the seven groups was calculated by applying consecutive integers to the categories in the logistic regression model. Similarly, odds ratios for incidences of four risk factors for metabolic syndrome were calculated. All analyses were performed using SPSS (Version 15.0, SPSS, IL).

Results

Characteristics of subjects at baseline are shown in Table 1. The mean values of age, the waist circumference, VFA, SFA, and BMI of the subjects who were without clustering of metabolic risk factors at baseline were 52.7 ± 8.4 years, 84.6 ± 7.8 cm, 113.2 ± 52.1 cm^2, 118.2 ± 51.9 cm^2, and 23.3 ± 2.6 kg/m^2, respectively. The incidences of the metabolic risk factors at the 3-year follow-up survey are shown in Figure 1. The odds ratios for the incidences of the clustering of metabolic risk factors according to the ΔVFA groups were 0.45, 0.63, 0.74, 1.00 (ref.), 0.70, 1.04, and 3.91, respectively (trend $P < 0.001$). These results did not change after further adjustments for lifestyle factors (smoking and alcohol drinking) or lifestyle factors and ΔSFA. The odds ratios (95% CI) of the incidences of hyperglycemia, high triglycerides, and low HDL cholesterol for the group with the largest increase in ΔVFA (50 cm^2 or more) were 2.98 (1.33-6.68), 4.88 (2.51-9.47), and 3.36 (1.26-8.91), respectively. The odds ratios (95% CI) of the incidences of high blood pressure, hyperglycemia, high triglycerides, and low HDL cholesterol for the group with the largest decrease in ΔVFA (−50 cm^2 or less) were 0.83 (0.34-2.04), 1.16 (0.42-3.15), 0.19 (0.06-0.59), and 0.42 (0.13-1.39), respectively. In subjects with a decrease in ΔVFA, the incidences were low for high triglycerides and low HDL cholesterol, but did not change for high blood pressure and hyperglycemia. Of the components of the metabolic syndrome, especially the incidences of high triglycerides and low HDL-cholesterol paralleled with ΔVFA (trend $P < 0.05$).

Discussion

This study investigated the change in metabolic risk factors between a baseline examination and a 3-year follow-up examination among subject groups divided according to the change in VFA, as measured using CT. We calculated the odds ratios for the incidences of metabolic risk factors and found that the risks of hyperglycemia, high triglycerides, low HDL cholesterol, and clustering of metabolic risk factors were significantly greater for the ΔVFA ≥ 50 cm^2 group, compared with the stable ΔVFA groups. For subjects with a decrease in ΔVFA, the incidences of high triglycerides and low HDL cholesterol levels were low, but the incidences of high blood pressure and hyperglycemia did not change.

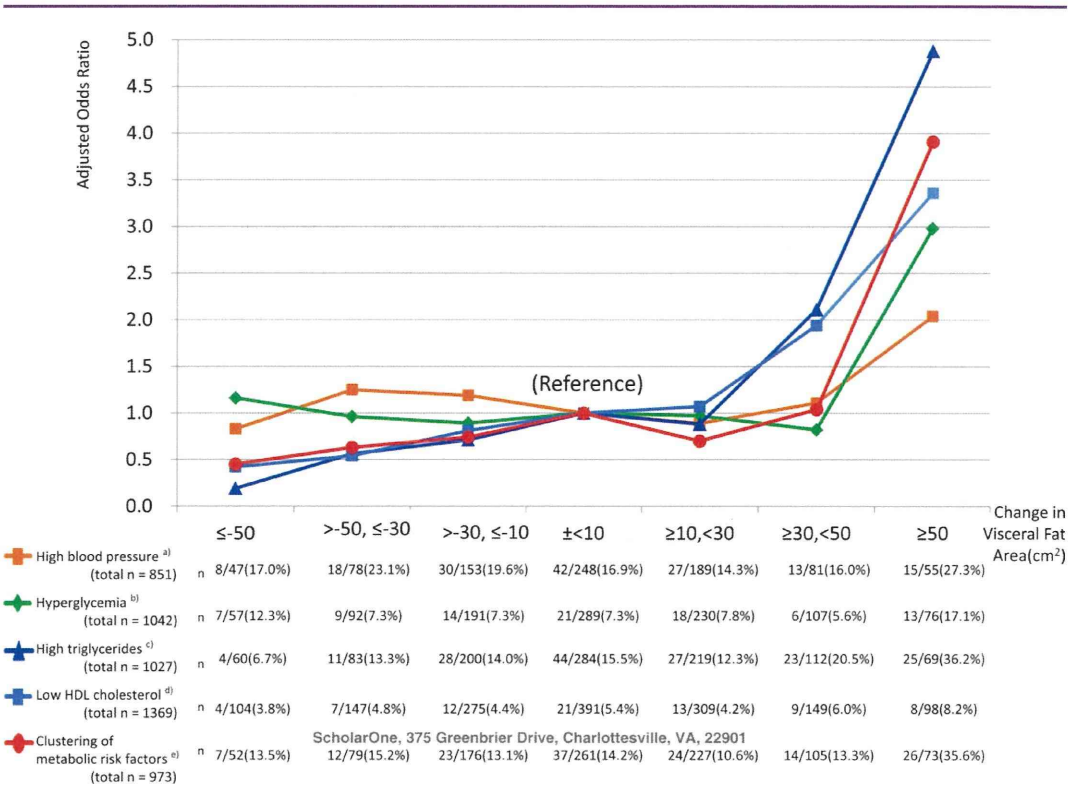

FIGURE 1 Odds ratio of metabolic risk factors (defined by NCEP-ATPIII) at the 3-year follow-up survey. Values are odds ratio (95% CI) adjusted for age, visceral fat area at baseline in 2004 and 2005, and the baseline value of each risk factor, i.e., (**a**) mean blood pressure ((systolic blood pressure + diastolic blood pressure × 2)/3), (**b**) glucose levels, (**c**) triglyceride levels, (**d**) HDL-cholesterol levels, and (**e**) mean blood pressure, glucose, triglyceride, and HDL-cholesterol in 2004 and 2005. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

In previous cross-sectional studies, significant and positive correlations between VFA measured using CT and systolic blood pressure, serum triglycerides were shown (7). In previous longitudinal studies, the effects of changes in VFA (13), BMI (14), weight (15), and waist circumference (16-18) on the metabolic risk factors have been examined. One of those reports studied 1,106 men and showed that changes in the VFA were associated with changes in metabolic risk factors (13). Another report showed a strong linear trend between increasing BMI and a worsening of various variables of metabolic risk factors, including blood pressure and lipid profiles (14). Similarly, another report showed that weight changes were linearly related to all measurements of each component of metabolic risk factors (15). Other studies have shown that a reduction in waist circumference achieved through lifestyle modifications is closely linked to an improvement in metabolic risk factors (17,18). These studies suggest that the changes in VFA, BMI, weight, and waist circumference are related to risk factors for CVD. However, the impact of the change in VFA (measured twice in the same person), which is regarded as the strongest indicator of a risk of CVD, has remained uncertain. To our knowledge, this is the first study to analyze the relationship between the incidences of metabolic risk factors and changes in VFA by measuring VFA twice.

Our findings clearly showed that changes in VFA were significantly associated with the incidences of metabolic risk factors.

When the odds ratios of the incidences of the metabolic risk factors for the ΔVFA $\geq$ 50 cm^2 were compared with those for the stable ΔVFA group (ΔVFA $>$ -10 cm^2, $<$ 10 cm^2) as a reference group, the highest odds ratio was seen for a high triglycerides level. The odds ratios for the incidences of high triglycerides and low HDL cholesterol levels, which are indicators of hyperlipidemia, were significantly higher among subjects with a larger increase in VFA and were significantly lower among subjects with a larger decrease in VFA (trend $P < 0.05$). In previous studies (14), the mean value of each component of metabolic risk factors or the prevalence of metabolic risk factors and its components were compared according to changes in BMI, body weight, and waist circumference. To our knowledge, however, no other studies have compared the strength of the association among metabolic risk factors to the change in VFA. Our study is the first to clarify the risk of each disease by calculating comparable odds ratios.

In conclusion, this study of Japanese men showed that changes in VFA were associated with the incidences of metabolic risk factors, with a significant increase in the odds ratios observed with a ΔVFA $\geq$ 50 cm^2. This association was most pronounced for the risk of high triglycerides and low HDL cholesterol levels. The adoption of a lifestyle that does not result in an increase in VFA is important for preventing metabolic syndrome. O

Acknowledgments

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Original Article
EPIDEMIOLOGY/GENETICS

Obesity

Adiponectin and Visceral Fat Associate with Cardiovascular Risk Factors

Yumi Matsushita[1], Toru Nakagawa[2], Shuichiro Yamamoto[2], Takanori Kato[2], Takanori Ouchi[2], Nobuko Kikuchi[2], Yoshihiko Takahashi[3], Tetsuji Yokoyama[4], Tetsuya Mizoue[5] and Mitsuhiko Noda[6]

Objective: To examine the combined effect of CT-measured visceral fat area (VFA) and adiponectin level against the clustering of metabolic risk factors.
Design and Methods: The subjects were 6,996 Japanese. The subjects were divided according to the combinations of VFA and adiponectin level quartiles and the odds ratio for multiple risk factors of metabolic syndrome were calculated (adjusted for age and lifestyle factors using logistic regression analyses). Group with the lowest VFA and the highest adiponectin level was used as a reference. The correlation between adiponectin level and each metabolic risk factor was evaluated.
Results: The strongest correlation was observed between adiponectin level and high-density lipoprotein cholesterol levels (r = 0.369 and 0.439 for men and women). Both VFA and adiponectin level were independently associated with the clustering of metabolic risk factors (interaction P = 0.58 and 0.11 for men and women). The odds ratio for the clustering of metabolic risk factors in the group with the highest VFA and the lowest adiponectin level, compared with the group with the lowest VFA and the highest adiponectin level, was 12.7 (9.7-16.6) for men and 13.5 (6.0-30.2) for women.
Conclusion: The ability to detect metabolic syndrome could be improved by examining adiponectin level in conjunction with VFA.

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Introduction

The prevalence of metabolic syndrome has been growing globally with clusters of obesity, high blood pressure, impaired lipid metabolism, and hyperglycemia. Individuals with metabolic syndrome have a higher risk of cardiovascular disease and a subsequent increase in disease mortality or morbidity (1-3). Several criteria for the diagnosis of metabolic syndrome are used worldwide. The visceral adipose tissue is regarded as an endocrine organ, partly because it secretes adipocytokines and other vasoactive substances that can influence the risk of developing traits of metabolic syndrome (4). We recently demonstrated that measuring the visceral fat area (VFA) is superior in predicting the accumulation of multiple risk factors, compared with the subcutaneous fat area (SFA), BMI, and waist circumference (WC) measurements (5). Regarding the multiple risk factors of metabolic syndrome, the odds ratios for the VFA quintiles were 1.0 (ref.), 2.4, 3.4, 5.0, and 9.7 for men and 1.0 (ref.), 1.5, 2.6, 4.6, and 10.0 for women (P < 0.001 for trends in both sexes) (5).

Adiponectin is predominantly secreted by adipocytes, and the adiponectin level is reduced in individuals with obesity, insulin resistance, and type 2 diabetes (6-10). Low plasma adiponectin levels have recently been shown to predict the risk of developing type 2 diabetes in humans (9,11). The adiponectin level is also inversely associated with other traditional cardiovascular risk factors, such as blood pressure, total and low-density lipoprotein (LDL) cholesterol, and triglyceride (TG) levels (12,13), and is positively related to high-density lipoprotein (HDL) cholesterol levels (12,14).

Some previous studies reported the impact of adiponectin levels on metabolic syndrome and its components (15); however, the sample sizes were insufficient. In addition, the combined effect of the VFA and adiponectin level has not been examined in an epidemiological study. Thus, we have examined the combined effect of the VFA and adiponectin level on the clustering of metabolic risk factors.

Methods and Procedures

Survey

Among the 17,606 employees of the same company and their spouses who underwent a health examination in Japan between 2008 and 2009, we analyzed 6,996 subjects ranging in age from 25 to 75 years (6,221 men and 775 women) who had undergone a computed

[1] Department of Clinical Research, National Center for Global Health and Medicine, Tokyo, Japan, Correspondence: Yumi Matsushita (ymatsushita@ri.ncgm.go.jp) [2] Hitachi, Ltd., Hitachi Health Care Center, Ibaraki, Japan [3] Division of Diabetes and Metabolism, Iwate Medical University, Iwate, Japan [4] Department of Health Promotion, National Institute of Public Health, Saitama, Japan [5] Department of Epidemiology and Prevention, National Center for Global Health and Medicine, Tokyo, Japan [6] Department of Diabetes and Metabolic Medicine, National Center for Global Health and Medicine, Tokyo, Japan

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TABLE 1 Characteristics of the subjects

	Men		Women	
	Mean	(SD)	Mean	(SD)
N	6,221		775	
Age, years	52.8	(10.2)	57.4	(9.7)
Body mass index, kg/m^2	24.1	(3.0)	23.0	(3.4)
Visceral fat area, cm^2	121.7	(53.4)	81.6	(46.3)
Subcutaneous fat area, cm^2	133.6	(56.4)	182.8	(76.9)
Adiponectin, log μg/mL	0.83	(0.20)	1.05	(0.21)
High blood pressure, %	38.9		34.1	
High triglyceride, %	35.4		23.7	
Low HDL cholesterol, %	11.0		17.8	
Hyperglycemia, %	57.8		40.8	
Multiple risk factors of metabolic syndrome, %	45.5		34.2	

tomography (CT) examination and answered a questionnaire on lifestyle factors and current treatments for metabolic conditions (hyperlipidemia, hypertension, or diabetes). The VFA was measured using a CT scanner and was calculated using a software application (fatPointer; Hitachi Medico, Tokyo, Japan) according to a protocol described elsewhere (11). Briefly, single slice imaging at the umbilical level was performed using a CT machine (Redix turbo; Hitachi Medico) while the subject was in a supine position. The imaging conditions were 120 kV, 50 mA, using a 5 mm thick slice. Height, weight, and body fat were measured using an automated scale (BF-220; Tanita, Tokyo, Japan) with the patient wearing a light gown. The BMI was defined as the weight (kg) divided by the square of the height (m^2). A blood sample was collected from each subject after more than 12 hours of fasting. The glucose level was measured using the glucose oxidase enzyme-electrode method (A&T, Tokyo, Japan). TG and HDL cholesterol levels were measured using an enzymatic colorimetric method (Cholestest TG; Sekisui Medical, Tokyo, Japan) and a nonsettling enzymatic method (Cholestest NHDL; Sekisui Medical), respectively. Adiponectin levels were measured using an immunoturbidimetric method (Adiponectin Latex Kit for humans; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan). Blood pressure was measured using an automated sphygmomanometer (Kentaro ADVANCE BP-203RV III A/B; Colin, Tokyo, Japan). This study was approved by the ethics review committee of the National Center for Global Health and Medicine. Written informed consent was obtained from all the subjects.

Definition of the state of risk factor clustering

In this study, subjects were defined using the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines (6) published in 2005: [1] high TG (TG $\geq$ 150 mg/dL), [2] low HDL cholesterol (HDL cholesterol <40 mg/dL in men and <50 mg/dL in women), [3] high blood pressure (systolic blood pressure $\geq$130 mm Hg or diastolic blood pressure $\geq$85 mm Hg), [4] hyperglycemia (fasting glucose $\geq$100 mg/dL), and [5] multiple risk factors (having two or more of components [1-4] listed above). Subjects currently receiving treatment for hyperlipidemia, hypertension, or diabetes were deemed as having the respective risk factor, regardless of the biochemical value.

Statistical analyses

We calculated the Pearson's correlation coefficients between the adiponectin level and each metabolic risk factor. We divided the subjects according to quartiles of the adiponectin level and calculated the odds ratio for multiple risk factors of metabolic syndrome. We adjusted for age, smoking habits (never, past, current), alcohol consumption (nondrinker, drinker consuming less than 2 go per day [the go is a conventional unit of alcohol intake in Japan and contains approximately 23 g of ethanol], or drinker consuming more than 2 go per day), and regular fitness habit (based on a single yes/no question in the questionnaire) using a logistic regression analysis, with the highest adiponectin level group used as a reference. We calculated the odds ratio for the multiple risk factors of metabolic syndrome for a +1 SD increment in the quintile categories of VFA and a +1 SD increment in the quintile categories of adiponectin levels. Furthermore, we divided the subjects according to combinations of VFA and adiponectin level quartiles and calculated the odds ratio for multiple risk factors of metabolic syndrome adjusted for the above-mentioned variables, using the category with the lowest VFA and the highest adiponectin level as the reference. VFA, adiponectin levels, and their interaction term (VFA $\times$ adiponectin levels) were included as independent variables in the logistic regression model to examine the interaction effect between VFA and adiponectin levels on the risk of clustering of metabolic risk factors. The stepwise procedure was used to select variables in the multiple logistic regression model with $P < 0.1$ for entry and $P < 0.05$ for removal. All the analyses were performed using SPSS for Windows, Version 15.0 (SPSS Inc., Chicago. IL, USA).

Results

The characteristics of the subjects are shown in Table 1. The mean (SD) age of the subjects was 52.8 $\pm$ 10.2 years for men and 57.4 $\pm$ 9.7 years for women. The mean VFA was 121.7 $\pm$ 53.4 cm^2 in men and 81.6 $\pm$ 46.3 cm^2 in women. The mean BMI was 24.1 $\pm$ 3.0 kg/m^2 in men and 23.0 $\pm$ 3.4 kg/m^2 in women. The mean log adiponectin level was 0.83 $\pm$ 0.20 μg/mL in men and 1.05 $\pm$ 0.21 μg/mL in women. The prevalence of multiple risk factors of metabolic syndrome was 45.5% in men and 34.2% in women.

Table 2 shows the partial correlations between adiponectin level and each metabolic risk factor. The HDL cholesterol level positively correlated with adiponectin level ($P < 0.001$). Other metabolic risk factors negatively correlated with the adiponectin level ($P < 0.001$).

The odds ratios for each component of metabolic syndrome according to the adiponectin level are shown in Figure 1. The odds ratios for a high TG level, a low HDL cholesterol level, high blood pressure, and hyperglycemia decreased with increasing quartile categories of adiponectin levels. For the multiple risk factors of metabolic syndrome, the odds ratios (95% confidence intervals [CI]) of the Q1, Q2, Q3, and Q4 adiponectin level categories were 3.4 (3.0-4.0), 2.1 (1.8-2.5), 1.5 (1.3-1.7), and 1.0 (ref.) for men and 4.3 (2.7-6.9), 2.5 (1.6-4.1), 1.5 (0.9-2.4), and 1.0 (ref.) for women. The odds ratio (95% CI) of the lowest (Q1) adiponectin level category for a high TG level was 3.9 (3.4-4.6) in men and that for a low

TABLE 2 Partial correlation between adiponectin level and each metabolic risk factor

	Men	Women
VFA	−0.364	−0.428
SFA	−0.220	−0.234
BMI	−0.281	−0.237
log TG	−0.340	−0.342
HT	−0.104	−0.153
HDL cholesterol	0.369	0.439
FG	−0.103	−0.177

VFA, visceral fat area; SFA, subcutaneous fat area; BMI, body mass index; TG, triglyceride; HT, hypertension; FG, fasting glucose.
P-values are all less than 0.001.
Values are partial correlation coefficients adjusted for age, smoking habits (never, current, past), alcohol consumption (nondrinker, drinker consuming 2 go or less per day [a go is a conventional unit of alcohol intake in Japan and contains ~23 g of ethanol], or consuming more than 2 go per day), and regular fitness habit (yes/no).

HDL cholesterol level was 5.8 (4.4-7.8) in men and 9.9 (4.8-20.1) in women.

In Table 3, the odds ratios of adiponectin and VFA levels for the clustering of multiple risk factors of metabolic syndrome are shown according to the VFA and adiponectin quartiles, respectively. For men, the increased adiponectin levels were significantly related to reduced clustering of metabolic risk factors, regardless of the VFA category ($P = 0.58$ for interaction VFA × adiponectin). For women, however, the odds ratio for a +1 SD in the VFA slightly weakened according to the increment of adiponectin level category ($P = 0.11$ for interaction of VFA × adiponectin). The odds ratio for multiple risk factors of metabolic syndrome according to combined groups of VFA and adiponectin are depicted in Figure 2. The odds ratio for the multiple risk factors of metabolic syndrome in the category with the highest VFA and the lowest adiponectin levels were 12.7 (9.7-16.6) for men and 13.5 (6.0-30.2) for women. We conducted stepwise logistic regression analyses among the largest quartile group of VFA, with hypoadiponectinemia (lowest vs. highest quartile group) as the independent variable. The result revealed that smoking, high TG, low HDL cholesterol, and older age were associated with hypoadiponectinemia in men. Low HDL cholesterol and age were associated with hypoadiponectinemia in women (data not shown).

Discussion

We observed a strong association between the combined effect of an increasing VFA and a decreasing adiponectin level and the prevalence of multiple risk factors of metabolic syndrome. Both the VFA and the adiponectin level were independently associated with the clustering of metabolic risk factors. Among the components of metabolic syndrome, the adiponectin level had a particularly strong impact on a high TG level in men and a low HDL cholesterol level in both men and women.

Only one previous report, studying 68 obese Korean subjects, demonstrated an association between the adiponectin level and VFA. The adiponectin level was inversely correlated with the VFA ($r = -0.691$, $P = 0.009$ in men, $r = -0.319$, $P = 0.002$ in women). Levels of a high molecular weight adiponectin also negatively correlated with the VFA ($r = -0.650$, $P = 0.016$ in men, $r = -0.370$, $P = 0.005$ in women) but not with the BMI or SFA, suggesting hypoadiponectinemia may represent a dysfunction of adipose tissue during obesity (16).

It was unknown whether adiponectin levels were correlated with disease, even when the VFAs were the same. Therefore, we compared the prevalence of multiple risk factors of metabolic syndrome with combinations of the VFA and adiponectin level. We found a markedly increased risk of clustering of metabolic syndrome among individuals who had a low adiponectin level and a high VFA. It was revealed that even when VFAs were the same, hypoadiponectinemia was associated with older age, smoking, and lipid metabolism (high TG and low HDL cholesterol) in men. In women, hypoadiponectinemia was associated with older age and low HDL cholesterol. Thus, it was confirmed that adiponectin correlated with lipid metabolism independent of VFA; from this, we concluded that adiponectin correlated with the clustering of metabolic risk factors. However, even

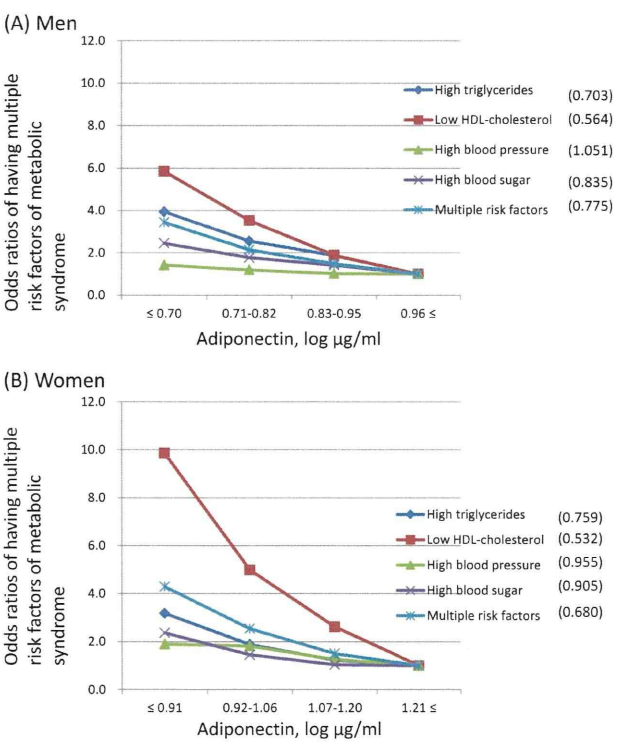

FIGURE 1 Odds ratios for clustering of metabolic risk factors according to the quartiles of adiponectin. The definition of metabolic risk factors is based on the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines published in 2005. Subjects with two or more of the metabolic risk factors (except for waist circumference) were defined as having multiple risk factors. Odds ratios for clustering of metabolic risk factors according to the quartiles (Q1-Q4) of adiponectin adjusted for age, smoking habits (never, current, past), alcohol consumption (nondrinker, drinker consuming 2 go or less per day [a go is a conventional unit of alcohol intake in Japan and contains ~23 g of ethanol], or consuming more than 2 go per day), and regular fitness habit (yes/no). Values in the case arcs are odds ratios for +1 SD increments of adiponectin. (Multiple risk factors; multiple risk factors of metabolic syndrome.) [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 3 Odds ratios for clustering of metabolic risk factors

		n			Odds ratios of +1 SD increment of adiponectin
Men					
VFA (cm^2)	≤84.80	1,557	Q1	0.8	(0.7-0.9)
	84.81-120.10	1,559	Q2	0.8	(0.7-0.9)
	120.11-156.90	1,553	Q3	0.8	(0.7-0.9)
	156.91≤	1,552	Q4	0.8	(0.7-0.9)
Women					
VFA (cm^2)	≤44.30	194	Q1	0.7	(0.4-1.2)
	44.31-77.90	195	Q2	0.5	(0.3-0.9)
	77.91-113.10	193	Q3	0.8	(0.6-1.2)
	113.11≤	193	Q4	0.6	(0.4-0.9)
		n			Odds ratios of +1 SD increment of VFA
Men					
Adiponectin (log μg/mL)	≤0.70	1,620	Q1	2.1	
	0.71-0.82	1,556	Q2	2.2	(1.8-2.3)
	0.83-0.95	1,518	Q3	1.9	(1.9-2.5)
	≤0.96	1,527	Q4	2.1	(1.7-2.2)
Women					(1.9-2.4)
Adiponectin (log μg/mL)	≤0.91	198	Q1	2.6	(1.7-3.9)
	0.92-1.06	191	Q2	2.5	(1.6-3.8)
	1.07-1.20	193	Q3	2.1	(1.3-3.3)
	1.21≤	193	Q4	1.7	(1.1-2.5)

VFA, visceral fat area.
Odds ratios of multiple risk factors of metabolic syndrome according to 1 SD increment of VFA or adiponectin adjusted for age, smoking habits (never, current, past), alcohol consumption (nondrinker, drinker consuming 2 go or less per day [a go is a conventional unit of alcohol intake in Japan and contains ~23 g of ethanol], or consuming more than 2 go per day), and regular fitness habit (yes/no).

if the adiponectin levels were the same, weight gain led to a worsening of metabolic risk factors, including lipid. In the largest VFA group, adiponectin itself was related to lipid metabolism and smoking status. Therefore, it was shown that the ability to detect metabolic syndrome would be improved by examining the adiponectin level in conjunction with the VFA, as adiponectin correlated with metabolic risk factors independent of VFA and the correlation was most pronounced between lipid metabolism.

In a case–control study, high plasma adiponectin levels were associated with a lower risk of myocardial infarction (MI) over a follow-up period of 6 years among men without previous cardiovascular disease. After adjustment for matched variables, participants in the highest quintile, compared with the lowest quintile, of adiponectin levels had a significantly decreased risk of MI (relative risk [RR], 0.39; 95% confidence interval [CI], 0.23-0.64; *P* for trend <0.001). Further adjustment for the hemoglobin A1c or C-reactive protein levels had little impact, but additional adjustment for LDL and HDL cholesterol levels modestly attenuated this association (RR, 0.56; 95% CI, 0.32-0.99; *P* for trend =0.02) (17). A multiple logistic regression analysis revealed that hypoadiponectinemia was significantly and independently correlated with coronary artery disease (CAD) ($P < 0.0088$) among 450 Japanese men. The multivariate-adjusted odds ratios for CAD in the first, second, third, and fourth quartiles (95% confidence) were 2.051 (1.288-4.951), 1.221 (0.684-2.186), 0.749 (0.392-1.418), and 1.000, respectively (18). Furthermore, another study showed that BMI, serum TG concentration, and the presence of diabetes or CAD remained significantly related to the plasma adiponectin concentration. Weight reduction significantly elevated the plasma adiponectin levels in diabetic obese Japanese subjects (six men and seven women) and nondiabetic obese Japanese subjects (six men and three women). However, the sample size was very small in this study (6).

This study has several strengths and limitations. As one of its strengths, we directly assessed abdominal fat accumulation using CT scanning. This allowed the role of fat deposition in the development of metabolic syndrome and its components to be examined more closely. Secondly, the sample size of our study was sufficiently large (almost 7,000 subjects), and both sexes were included. Thirdly, we adjusted for alcohol consumption and physical activity, which may confound the association between abdominal fat accumulation and metabolic risk factors. However, the study was limited because of its cross-sectional design, and changes in the metabolic risk profile were not monitored.

In this study, we demonstrated a strong association between the combined effect of an increasing VFA and a decreasing adiponectin level with multiple risk factors of metabolic syndrome. Both the VFA and the adiponectin level were independently associated with the clustering of metabolic risk factors in a large Japanese population, which has a relatively low BMI compared with other

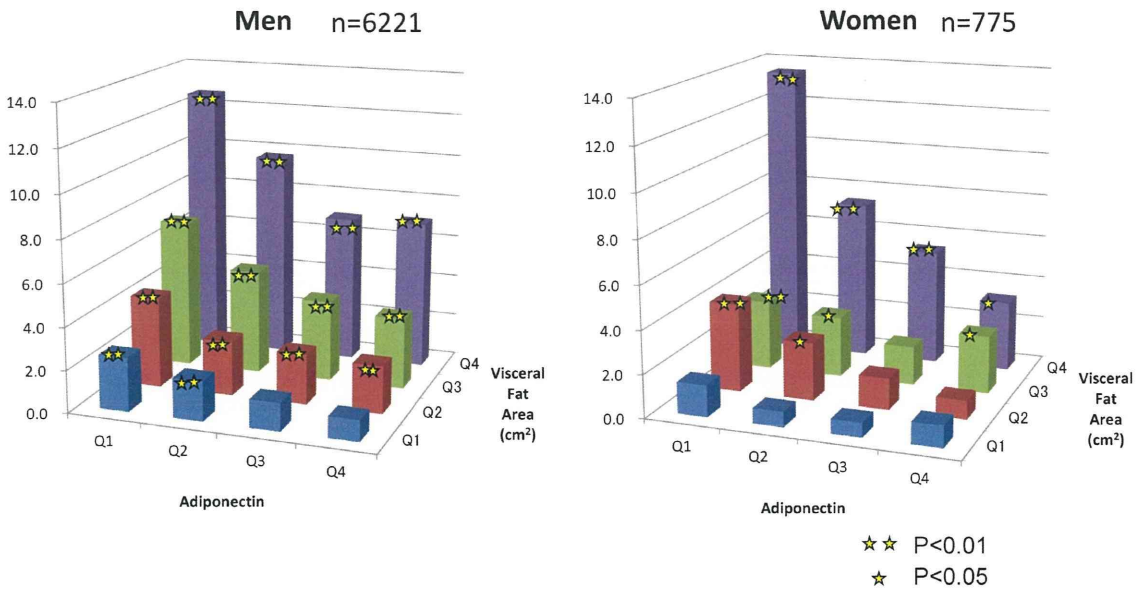

FIGURE 2 Odds ratios for multiple risk factors of metabolic syndrome according to combined groups of VFA and adiponectin. The definition of metabolic risk factors is based on the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines published in 2005. Subjects with two or more of the metabolic risk factors (except for waist circumference) were defined as having multiple risk factors. Odds ratios for multiple risk factors of metabolic syndrome are shown according to combined groups of VFA and adiponectin adjusted for age, smoking habits (never, current, past), alcohol consumption (nondrinker, drinker consuming 2 go or less per day [a go is a conventional unit of alcohol intake in Japan and contains ~23 g of ethanol], or consuming more than 2 go per day), and regular fitness habit (yes/no). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

ethnicities. The present findings have important implications for the prevention of metabolic syndrome. Further prospective studies are needed to assess the impact of the VFA and adiponectin level on the incidence of metabolic syndrome or cardiovascular diseases.O

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