Statistical methods

Correlation between values obtained by Dual BIA and CT were evaluated using Pearson's correlation analysis. Weekly values of Dual BIA-IAFA, BW, and WC were compared with the baseline values of day 0 by Student's paired *t*-test. Analysis of covariance was applied for comparison of Dual BIA-IAFA, BW, and WC at week 3.

Results

In 67 patients with obesity and related conditions, Dual BIA-IAFA correlated well with CT-IAFA ($r = 0.821$, $P < .0001$) (Figure 1B).

Thirty-five (17 males and 18 females) out of 67 patients were monitored with Dual BIA for longer than 3 weeks, and 19 (10 males and 9 females) out of 35 patients achieved weight loss of more than 5% of the initial BW. In order to elucidate the change in IAFA during weight loss, Dual BIA-IAFA, BW, and WC of the 19 patients were analyzed. Baseline characteristics of the 19 patients were (mean ± SD); age, 49.0 ± 14.4 years, height 163.0 ± 10.5 cm, BMI 33.2 ± 7.3 kg/m^2, and CT-IAFA 143.6 ± 47.4 cm^2. BW, WC, and Dual BIA-IAFA at baseline and at week 3 were: 89.2 ± 26.2 kg and 84.5 ± 25.1 kg, 110.6 ± 14.1 cm and 106.0 ± 14.2 cm, and 150.4 ± 73.7 cm^2 and 124.3 ± 70.3 cm^2, respectively.

Figure 1C shows the weekly change of Dual BIA-IAFA, BW, and WC in 19 patients whose BW decreased more than 5% during the 3 weeks of monitoring. Dual BIA-IAFA, BW and WC showed a significant reduction after 1 week during the calorie restriction compared with the baseline values ($P < .05$). Dual BIA-IAFA decreased every week for the initial 3 weeks and the average reduction in Dual BIA-IAFA was 18.9%, which was larger than in BW (5.3%) and WC (3.8%) (ANCOVA, $P < .05$).

Discussion

The present study demonstrates that the weekly change in IAFA can be detected with the Dual BIA instrument during the calorie restriction. Due to the practical limitations such as instrumentation and cost, CT and MRI are unsuitable for weekly monitoring of change in IAFA. There is also a problem of X-ray exposure in CT scanning. Consequently, it has been impractical to monitor IAFA weekly or frequently, in clinical follow-up period with CT or MRI. There have been several attempts to evaluate the IAFA by BIA (9-13). They include calculation from whole body impedance and from measuring abdominal impedance by the electrodes placed on the abdomen (9,10). Some of the estimates of IAFA incorporate gender and age of the subject in order to attain high correlation with CT (9,10). In contrast, Dual BIA, which is a method that is not dependent on external variables, such as gender or age, had shown a good correlation between Dual BIA-IAFA and CT-IAFA (11-13). In the present study, we confirmed the good correlation of Dual BIA-IAFA and CT-IAFA in obese patients. The correlation coefficient for the Dual BIA-IAFA and CT-IAFA was 0.821 ($n = 67$) with our subjects whose average BMI was 29.3. This indicates that Dual BIA produced reliable measurements with obesity patients and the result was comparable to the correlation coefficient of 0.888 obtained with subjects whose average BMI was around 25 (13). It must be noted that CT-IAFA and Dual BIA-IAFA was not measured on the same day in the present study, unlike the previous report in which Dual BIA- and CT-IAFA was taken on the same day (13), and therefore direct comparison has its limitations. By applying Dual BIA to monitoring the weekly change of individual body component during the calorie restriction, we could detect the characteristic change of IAFA. The significant decrease in Dual BIA-IAFA, BW, and WC at week 1 supports the suitability of selecting 5% of BW change at week 3 as a criterion for including in weekly analysis of these parameters.

On average, IAFA showed a larger reduction than BW and WC during the initial 3 weeks of calorie restriction. The rapid response of intra-abdominal adipose tissue to calorie restriction has been suggested in an ultrasonography study that examined a portion of peritoneal fat thickness (15). The larger decrease of Dual BIA-IAFA observed is also in agreement with a study which showed larger reduction in IAFA evaluated with MRI than that of BW up to 12 weeks on very low calorie diet (16). Together with these results, the present study established that the intra-abdominal fat decreases rapidly in the initial period of calorie restriction by measuring Dual BIA-IAFA, and demonstrates the usefulness of monitoring the change in IAFA during the treatment of obesity and its related disorders.

Weakness of our study is that its design was not of a prospective weight reduction where every participant was prescribed daily calorie that could produce predetermined level of weight loss within the study period. Instead we selected participants that had their weight decreased by at least 5% in order to illustrate the change in abdominal adiposity on weekly basis. It is also of note that the BW and Dual BIA-IAFA at week 1 may be affected by salt restriction and loss of body water that is observed early in calorie restriction. Because of the small sample size, the observed change in Dual BIA-IAFA could be larger than actual change. It also depends on the precision of the instrument. In a separate population, the coefficient of variation was 7.6% (Ida, M. manuscript in preparation).

In conclusion, the present study demonstrated that Dual BIA instrument can be used to measure IAFA in obese patients, allows frequent measurement, and is useful for detecting the early change in IAFA during calorie restriction. Information thus obtained along with other changes in metabolic parameters will be indispensable for understanding the role of abdominal adiposity, and especially useful as a diagnostic marker for monitoring obesity and its related disorders (1). In addition, the instrument's safety and convenience could be suitable for large population studies.

Acknowledgments

Authors thank all the volunteers who took part in the study, and Research and Development Department of Omron Healthcare Corporation for use of the Dual BIA instrument.

References

1. Matsuzawa Y. The role of fat topology in the risk of disease. *Int J Obes* 2008;32: S83-S92.

2. Miyawaki T, Hirata M, Moriyama K, et al. Metabolic syndrome in Japanese diagnosed with visceral fat measurement by computed tomography. *Proc Jpn Acad Ser B* 2005;81:471-479.
3. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature* 2006; 444:881-887.
4. Ferland M, Després JP, Trembly A, et al. Assessment of adipose tissue distribution by computed axial tomography in obese women: association with body density and anthropometric measurements. *Br J Nutr* 1989;61:139-148.
5. Kuk JL, Lee S, Heymsfield SB, Ross R. Waist circumference and abdominal adipose tissue distribution: influence of age and sex. *Am J Clin Nutr* 2005;81: 1330-1334.
6. Cornier MA, Després JP, Davis N, et al. A scientific statement from the American Heart Association. *Circulation* 2011;124:1996-2019.
7. Miyawaki T, Abe M, Yahata K, Kajiyama N, Katsuma H, Saito N. Contribution of visceral fat accumulation to the risk factors for atherosclerosis in non-obese Japanese. *Intern Med* 2004;43:1138-1144.
8. Isbess JM, Tamboli RA, Hansen EN, et al. The importance of caloric restriction in the early improvements in insulin sensitivity after Roux-en Y gastric bypass surgery. *Diabetes Care* 2010;33:1438-1442.
9. Ryo M, Maeda K, Onda T, et al. A new simple method for the measurement of visceral fat accumulation by bioelectrical impedance. *Diabetes Care* 2005;8:451-453.
10. Nagai M, Komiya H, Mori Y, Ohta T, Kasahara Y, Ikeda Y. Development of a new method for estimating visceral fat area with multi-frequency bioelectrical impedance. *Tohoku J Exp Med* 2008;214:105-112.
11. Shiga T, Oshima Y, Kanai H, Hirata M, Hosoda K, Nakao K. *A simple measurement method of visceral fat accumulation by bioelectrical impedance analysis*, In: *IFMBE Proceedings*, Vol. 17/14: 13th International Conference on Electrical Bioimpedance and the 8th Conference on Electrical Impedance Tomography; Scharfetter H, et al., eds., Springer-Verlag; 2007, pp 687-690.Available at: http://link.springer.com/chapter/10.1007%2F978-3-540-73841-1_177?LI=true.
12. Yoneda M, Tasaki H, Tsuchiya N, et al. A study of bioelectrical impedance analysis methods for practical visceral fat estimation. In: IEEE International Conference on Granular Computing (GCR 2007), Lin TY, et al., eds., IEEE Computer Society Press; 2007, pp 622-627. Available at: http://ieeexplore.ieee.org/xpl/login.jsp?tp=&arnumber=4403174&url=http%3A%2F%2Fieeexplore.ieee.org%2Fxpls%2Fabs_all.jsp%3Farnumber%3D4403174.
13. Shiga T, Hamaguchi T, Oshima Y, et al. *A new simple measurement system of visceral fat accumulation by bioelectrical impedance analysis*. In *IFMBE Proceedings* Vol. 25/7: World Congress on Medical Physics and Biomedical Engineering, Döossel O, et al., eds., Springer-Verlag; 2009, pp 338-341.
14. Matsuzawa Y. Metabolic syndrome—definition and diagnostic criteria in Japan. *J Atheroscler Thromb* 2005;12:301.
15. Li Y, Bujo H, Takahashi K, et al. Visceral Fat: higher responsiveness of fat mass and gene expression to calorie restriction than subcutaneous fat. *Exp Biol Med (Maywood)* 2003;228:1118-1123.
16. Colles SL, Dixon JB, Marks P, et al. Preoperative weight loss with a very-low-energy diet: quantitation of changes in liver and abdominal fat by serial imaging. *Am J Clin Nutr* 2006;84:304-311.

III. 肥満・肥満症の診断と評価

最新の測定機器による腹腔内脂肪量および体組成の測定

井田みどり　平田雅一　細田公則　中尾一和

Abdomen specific bioelectrical impedance analysis (BIA) methods for evaluation of abdominal fat distribution

Midori Ida, Masakazu Hirata, Kiminori Hosoda, Kazuwa Nakao
Department of Medicine and Clinical Science,
Kyoto University Graduate School of Medicine

Abstract

Two novel bioelectrical impedance analysis (BIA) methods have been developed recently for evaluation of intra-abdominal fat accumulation. Both methods use electrodes that are placed on abdominal wall and allow evaluation of intra-abdominal fat area (IAFA) easily without radiation exposure. Of these, "abdominal BIA" method measures impedance distribution along abdominal anterior-posterior axis, and IAFA by BIA method (BIA-IAFA) is calculated from waist circumference and the voltage occurring at the flank. Dual BIA method measures impedance of trunk and body surface at the abdominal level and calculates BIA-IAFA from transverse and antero-posterior diameters of the abdomen and the impedance of trunk and abdominal surface. BIA-IAFA by these two BIA methods correlated well with IAFA measured by abdominal CT (CT-IAFA) with correlation coefficient of 0.88 ($n=91$, $p<0.0001$) for the former, and 0.861 ($n=469$, $p<0.01$) for the latter. These new BIA methods are useful for evaluating abdominal adiposity in clinical study and routine clinical practice of metabolic syndrome and obesity.

Key words: abdominal adiposity, intra-abdominal fat area, bioelectrical impedance analysis

はじめに

腹腔内脂肪蓄積を特徴とする腹部肥満はメタボリックシンドロームや肥満症の成因と病態に密接にかかわりがあり[1]，腹部肥満の診療にはその定量的な評価が重要である．現在，腹腔内脂肪蓄積の評価方法として，MRI，CT，DEXA，超音波を用いた画像診断および生体インピーダンス法（bioelectrical impedance analysis: BIA），ウエスト周囲長測定が利用されている．CTによる定量的評価は腹腔内脂肪蓄積評価のゴールドスタンダードとされているが，X線被曝やコスト面で，集団健診などにおけるスクリーニング検査としては適さない．MRIは測定可能な施設が限られ，コストの問題もある．DEXAでは，体脂肪量の測定の中で，腹部に相当する部位の

京都大学大学院医学研究科 内分泌代謝内科

0047-1852/13/¥60/頁/JCOPY

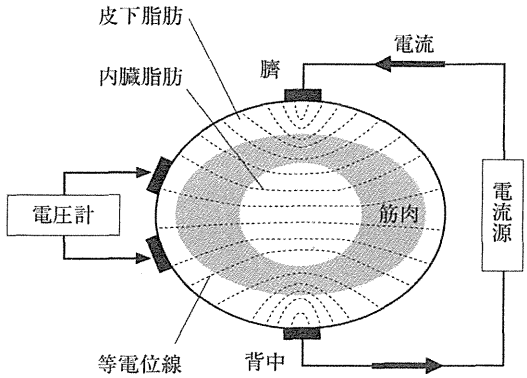

図1 体幹前後軸方向のインピーダンス測定法の原理

臍レベルで腹部前面と背面に設置した電極に電流を流した場合の体幹前後軸方向の等電位分布の模式図.
(文献[4]より引用)

腹腔内脂肪を定量することは原理的に不可能である. 超音波画像診断を応用する方法では, 体表から近い限られた部位での測定に限定され, 測定方法は未確立である. ウエスト周囲長測定は非常に簡便に測定が可能であり, 特定健診でも導入されているが, 腹部皮下脂肪の影響を大きく受けるため, 必ずしも腹腔内脂肪量を反映できるわけではない. 近年, BIA法が開発され, X線被曝なく簡便に腹腔内脂肪蓄積を定量的に評価できるようになった.

1. BIA法とは

インピーダンスとは電流と電圧の比を表しており, 生体に一定の電流を流した場合, 脂肪組織は骨組織以外の生体組織に比べて高いインピーダンス特性を示す[2]. BIA法は, この特性を利用して, 体組成に関する情報を獲得する方法であり[3], 既に一般の健康管理機器として体重計と併用した体脂肪計などが広く普及している. しかしながら, 今までのBIA法は, 皮下脂肪を含む全体の脂肪量の中から, 腹腔内脂肪量そのものを定量的に評価することは困難であった. 近年, BIA法を腹部に応用しCTでの腹腔内脂肪面積(intra-abdominal fat area: IAFA)に相当する値を算出する腹部BIA法が開発されている.

2. 腹部BIA法

BIA法による腹腔内脂肪蓄積評価法として我が国で開発された2つの方法につき概説する.

1) 体幹前後軸方向のインピーダンス測定による腹腔内脂肪量の測定[4,5]

大阪大学内分泌代謝内科と花王株式会社により共同開発された腹腔内脂肪量測定装置は, 臍レベルの腹部前面と背面との間(体幹の前後軸方向)に電流を流したときに側腹部の表面に生じる電位差が腹腔内脂肪量を反映することを利用している. この原理では, 電流を流したレベルにおける等電位線の概要は**図1**の破線のようになるが, このとき腹腔内脂肪を通過した等電位線は体表面上の側腹部に導出され, 側腹部表面に発生した電圧Vは腹腔内脂肪量を反映する. 電流は人体をほぼ最短距離で横断するため, 側腹部の皮下脂肪にはほとんど電流が流れず, 側腹部の皮下脂肪は測定電圧に影響を与えることが少ない. 脂肪組織のインピーダンスは筋肉組織などの他組織よりも大きいため, 電流を一定とした場合, 腹腔内脂肪量の蓄積が多いほど側腹部での電位差は大きくなり, 側腹部電極で測定した電圧が相対的な腹腔内脂肪量を反映する. 側腹部の電極間距離を一定とした場合, BIAによる腹腔内脂肪面積(BIA-IAFA)の推定値は

$$BIA\text{-}IAFA = a + bV/Wc^3$$

(V: 側腹部電圧, Wc: ウエスト周囲長, a, bは定数)

という式で表すことができる.

この測定方法により算出された推定BIA-IAFAはCT-IAFAと高い相関を認めた($r=0.88$, $p<0.0001$, $n=91$)[5]. また, この方法による腹腔内脂肪量測定装置を大規模集団検診に導入し保健指導を行った結果, 1年後の健診において腹腔内脂肪量の減少に伴いメタボリック危険因子の有意な減少を認めたと報告されている[6].

2) Dual BIA法による腹腔内脂肪量の測定[7-10]

京都大学内分泌代謝内科とオムロンヘルスケア株式会社はDual BIA法による腹腔内脂肪量

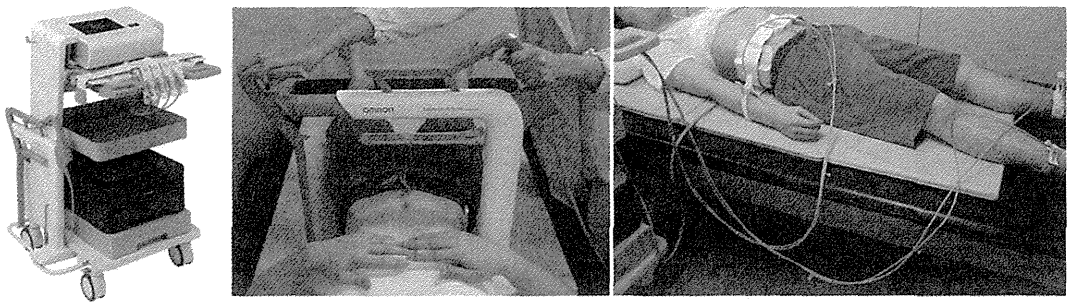

図2　Dual BIA法による腹腔内脂肪量測定機器と測定風景
HDS-2000　DUALSCAN(Omron Healthcare Co., Ltd)と測定風景.

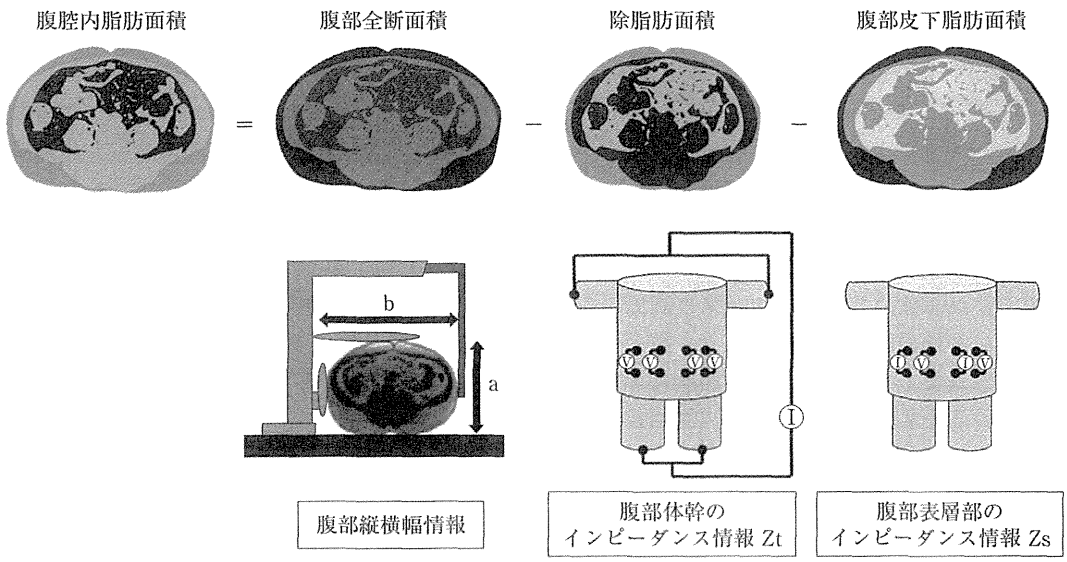

図3　Dual BIA法の測定原理
腹部の全断面積から，除脂肪面積および腹部皮下脂肪面積を除くことで，腹腔内脂肪面積を算出する.

測定装置(DUALSCAN® Omron Healthcare Co., Ltd)を共同開発し[7-10]，2011年夏には医療機器として承認された(**図2**)．四肢電極に通電して得られる電圧から腹部全体のインピーダンスを算出し，腹部電極に通電して得られる電圧から腹部表層のインピーダンスを測定している．2つのインピーダンス値と臍レベルにおける腹部断面の横径と縦径から腹腔内脂肪面積値(Dual BIA-IAFA)を算出する方法である(**図3**)．腹部全体の脂肪から腹部皮下脂肪量を除することで腹腔内脂肪面積値を算出しており，

$$\text{Dual BIA-IAFA} = \alpha_1 a^2 + \alpha_2 b - \alpha_3 (a^2 + b^2)^{1/2} Zs - \alpha_4 / Zt + \alpha_5$$

($\alpha_1 - \alpha_5$は定数，a: 腹部縦幅，b: 腹部横幅，Zt: 腹部体幹のインピーダンス，Zs: 腹部表層のインピーダンス)

という式で表される．著者らの解析では，Dual BIA法とCTにより腹腔内脂肪量測定を受けた469人(男性273人，女性196人，平均年齢47.4±14.0歳，BMI 25.6±4.6 kg/m^2)において，Dual BIA-IAFAとCT-IAFAの相関係数はr=0.861であり，ウエスト周囲長とCT-IAFAの相

関(r=0.760)よりも高い相関を認め，男女別の検討でも同様の結果であった[9]．著者らの施設で，減量治療のため入院した67例(男性36人，女性31人，平均年齢54.7±14.7歳，BMI 29.3±6.5kg/m^2)の解析では，Dual BIA-IAFAとCT-IAFAの相関係数はr=0.821で，肥満症を多く含む群においても高い相関を確認した．食事制限による減量治療における腹腔内脂肪蓄積の変化について，毎週の経過を追うことも可能であった[10]．

おわりに

腹腔内脂肪蓄積を正確に評価することは，健康診断やメタボリックシンドローム・肥満症の診療や研究において重要である．近年，新たに開発・実用化された腹部BIA法による腹腔内脂肪量測定装置は，X線の被曝なく，簡便に，高い精度で腹腔内脂肪量の定量的評価が可能であり，経時的な観察も容易である．今後，保健指導や診療，臨床研究分野において，大きな役割を果たすことが期待されている．

文　献

1) Matsuzawa Y: The role of fat topology in the risk of disease. Int J Obes **32**: S83-S92, 2008.
2) Geddes LA, Baker LE: The specific resistance of biological material—a compendium data for the biomedical engineer and physiologist. Med Biol Eng **5**: 271-293, 1967.
3) Foster KR, Lukaski HC: Whole-body impedance—what does it measure? Am J Clin Nutr **64** (Suppl): 388S-396S, 1996.
4) 梁　美和ほか：腹部生体インピーダンス法による内臓脂肪測定法の開発．肥満研究 **9**: 136-142, 2003.
5) Ryo M, et al: A new simple method for the measurement of visceral fat accumulation by bioelectrical impedance. Diabetes Care **8**: 451-453, 2005.
6) Okauchi Y, et al: Reduction of visceral fat is associated with decrease in the number of metabolic risk factors in Japanese men. Diabetes Care **30**: 2392-2394, 2007.
7) 志賀利一：インピーダンス法による新規の内臓脂肪測定法．最新医学 **61**: 615-624, 2006.
8) Shiga T, et al: A simple measurement method of visceral fat accumulation by bioelectrical impedance analysis. In: ICEBI 2007, IFMBE Proceedings, vol 17(ed by Scharfetter H, Merva R), p687-690, Springer, Berlin Heidelberg, 2007.
9) 井田みどり ほか：Dual Bioelectrical Impedance法を用いた内臓脂肪量測定装置のスクリーニング機器としての有用性．糖尿病 **55**(Suppl 1): S351, 2012.
10) 井田みどり ほか：Dual生体インピーダンス法による減量治療における経時的腹部内臓脂肪蓄積と代謝パラメータ変化における意義．糖尿病 **52**(Suppl 1): S105, 2009.

I. 概　論

肥満・肥満症の概念と分類

中尾一和　孫　徹

Concept and classification of obesity

Kazuwa Nakao, Chiyoru Son
Department of Medicine and Clinical Science,
Kyoto University Graduate School of Medicine

Key words: obesity, concept, classification

はじめに

過食や運動不足などを背景に，近年世界の多くの国で肥満とそれに伴う健康障害の増加が大きな問題となっている．日本肥満学会は2000年に‘新しい肥満の判定と肥満症の診断基準’[1]，2006年に‘肥満症治療ガイドライン2006’[2]，2011年に‘肥満症診断基準2011’[3]を発表し肥満・肥満症の診断と治療に指導的役割を果たしてきた．本稿では松澤祐次 日本肥満学会前理事長と斎藤 康 肥満症診断基準検討委員会前委員長の下にまとめられた‘肥満症診断基準2011’における肥満・肥満症の概念と分類について概説し，今後の肥満・肥満症診療における課題について述べる．

1. 肥　満

1）肥満の概念と分類

日本肥満学会では‘肥満は脂肪組織に脂肪が過剰に蓄積した状態’と定義している．

したがって，本来肥満の判定には，全身の脂肪量を直接定量的に測定することが期待される．肥満の通常の診断には，身長と体重を用いて簡便に計算でき，浮腫やるいそうなどの特殊な病態を除き脂肪量をよく反映する，body mass index(BMI)：体重(kg)/身長(m)^{2}が用いられる．

WHOの診断基準では，BMI 25以上をoverweight，BMI 30以上をobeseと定義し，18.5≦BMI<25をnormal rangeとしたうえで，25≦BMI<30をpre-obese，30≦BMI<35をobese class I，35≦BMI<40をobese class II，BMI≧40をobese class IIIと分類している(**表1**)．このように国際的には，肥満の診断にBMIのカットオフ値として30を用いる．我が国においては，日本人の相対リスクのエビデンスに基づき，BMI 25以上を肥満としている[4]．すなわち，我が国におけるエビデンスでは，肥満関連疾患がBMI 25あたりから有意に増加し，25≦BMI<30でそれらの疾患のオッズ比が2を超えることより，BMI 25をカットオフ値として設定している．これに伴い日本肥満学会の肥満の分類では，18.5≦BMI<25を正常領域たる‘普通体重’としたうえで，25≦BMI<30を肥満1度，30≦BMI<35を肥満2度，35≦BMI<40を肥満3度，BMI≧40を肥満4度としている(**表1**)．

なお，このようにBMIのカットオフ値を30より低く設定しているのは日本だけではない．

京都大学大学院医学研究科 内科学講座 内分泌代謝内科

0047-1852/13/¥60/頁/JCOPY

表1 日本とWHOの肥満の分類

BMI	日本	WHO
<18.5	低体重	underweight
18.5≦-<25	普通体重	normal range
25≦-<30	肥満(1度)	pre-obese
30≦-<35	肥満(2度)	obese class I
35≦-<40	肥満(3度)	obese class II
40≦	肥満(4度)	obese class III

表2 東アジア各国における肥満判定・診断のBMIカットオフ値

日本		韓国		台湾		中国*	
<18.5	underweight	<18.5	underweight	<18.5	underweight		
18.5-24.9	normal	18.5-22.9	normal	18.5-24	normal		
25-29.9	obesity grade 1	23-24.9	at-risk of obesity	24-27	overweight	24-27.9	overweight
30-34.9	obesity grade 2	25-29.9	obesity	27-30	mild obesity	28-	obesity
35-39.9	obesity grade 3	30-	severe obesity	30-35	moderate obesity		
40-	obesity grade 4			35-	severe obesity		

*Bei-Fan Z, et al: Asia Pac J Clin Nutr 11(Suppl 8): S685-693, 2002. より引用.

表2に東アジアにおける肥満判定・診断におけるBMIのカットオフ値のまとめを示すが，韓国では25以上，台湾では27以上，中国では28以上を肥満とみなしている．

2) ハイリスク肥満

'肥満症診断基準2011'では，'肥満体型と疾病発生率との関係から，内臓脂肪蓄積を中核におく'とし，ハイリスク肥満を定義している．ハイリスク肥満は内臓脂肪型肥満と同義で用いられている．すなわち，診断時には健康障害がなくても，将来的に健康障害を起こす可能性が高い肥満で，健康障害の合併がなくても肥満症(後述の肥満症の定義参照)として扱う．ハイリスク肥満のスクリーニングのカットオフ値にはウエスト周囲長：男性85 cm，女性90 cmを設定し，確定診断のカットオフ値には臍レベルCT断面像による内臓脂肪面積100 cm^2が定められている．

3) 高度肥満

'肥満症診断基準2011'ではBMI≧35の肥満が高度肥満として新たに定義された．我が国では高度肥満者の比率は，男性で0.2%，女性で0.3%と少ないが，一般的には'高度肥満者は治療が困難で，重篤な合併症や心理・精神的問題を有することが多い'とされており，診断と治療法の選択には注意を要する．

2. 肥 満 症

1) 肥満症の概念

'肥満症診断基準2011'では，肥満症は'肥満に起因ないしは関連して発症する健康障害の予防および治療に医学的に減量が必要である状態'と定義され，疾患単位として扱う．この定義は，肥満者の中から医学的に減量を必要とする者を選別することを意図している．

2) 肥満症の診断

'肥満症診断基準2011'では，肥満症の診断においてBMIに基づく肥満の判定とともに腹腔内の脂肪蓄積である内臓脂肪蓄積に基づく判定を取り入れている．**図1**に示すようにBMI

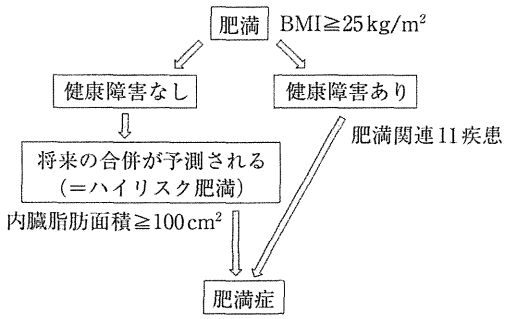

図1 肥満症診断の流れ

25以上で判定される肥満に11の肥満関連疾患(耐糖能障害，脂質異常症，高血圧，高尿酸血症・痛風，冠動脈疾患，脳梗塞，脂肪肝，月経異常および妊娠合併症，睡眠時無呼吸症候群・肥満低換気症候群，整形外科的疾患，肥満関連腎臓病)を有する場合が肥満症と診断される．この11疾患のうち肥満関連腎臓病は，'肥満症診断基準2011'で新たに追加された疾患である．更に，BMI 25以上で診断時には健康障害すなわち肥満関連疾患がなくても，CTにおける内臓脂肪面積が100 cm²を超える場合は，将来的に肥満関連疾患を起こす可能性が高いハイリスク肥満として，疾患たる肥満症と診断する．

3. 今後の課題

1) 肥満判定における今後の課題

日本の診断基準では普通体重と肥満との間に境界域を設けていない．一方，WHOの基準，東アジア各国の基準では名称は様々であるが，正常と肥満との間に境界領域を設定している．多くの臨床疫学研究で，肥満度と肥満関連疾患保有との関係は連続的かつ直線的である．すなわち，正常と異常を明確に区別する特異点がないことを示しており，我が国における診断基準の検討においても，境界域の設定について議論することは今後の課題の一つである．また，日本肥満学会は淡路宣言2011で'アジアの肥満症研究と連携し，肥満症を代表とする生活習慣病対策における指導的役割を使命とする'という方向性を示しており[5]，東アジアにおける肥満の統一的なBMIカットオフ値に関する議論・検討を行うことも重要であろう．肥満判定におけるウエスト周囲長や内臓脂肪面積のカットオフ値の継続的な検討も今後の課題である．

2) 肥満症診断における今後の課題

ここまで述べてきたように，日本肥満学会の肥満症の診断には，内臓脂肪蓄積が重要な位置を占めてきた伝統がある．'肥満は脂肪組織への脂肪の過剰蓄積である'との定義を考えると，腹腔内の脂肪量を直接反映している内臓脂肪面積による診断には，BMIやウエスト周囲長とは異なる利点があろう．ただし，現在の診断基準ではBMI 25以上が前提となっているので，'内臓脂肪面積はBMI ≧25のときにだけ診断価値をもつのか'，という疑問が出てくる．**図2**は，CTによる内臓脂肪面積測定を実施された1,380人を対象に，我が国のメタボリックシンドローム診断における3構成因子すなわち，血圧高値(収縮期血圧≧130，または拡張期血圧≧85)，耐糖能異常(空腹時血糖110 mg/dL以上)，脂質代謝異常(血中中性脂肪値≧150 mg/dL，かつ/または血中HDLコレステロール値≦40 mg/dL)のない正常者が，その後どれか1つの構成因子を有するようになる相対ハザード値と内臓脂肪面積との関係を縦断的に解析した研究成果を示したものである[6]．ここで示されるように，内臓脂肪蓄積を反映する内臓脂肪面積の程度から予想される相対ハザード比の上昇は，BMI 25未満の群とBMI 25以上の群で統計学的な有意差がない．すなわち，内臓脂肪蓄積は，BMI 25未満であっても，メタボリックシンドロームの3構成因子のどれか1つを有するようになることの予測因子として意義があることを示している．

'肥満症診断基準2011'の肥満症診断のフローチャートでは，内臓脂肪蓄積があり，肥満症関連疾患を有している患者群は，BMI 25未満では，肥満に起因ないし関連して起こった病態である可能性が考慮されていない．前述したように，肥満度と肥満関連疾患保有との関係は，連続的かつ直線的で，肥満と非肥満を明確に区別する特異点はない．したがって，これらの患者群では，BMI 25未満でも内臓脂肪蓄積に伴

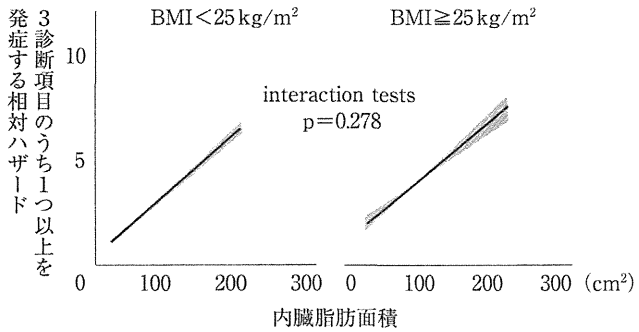

図2　メタボリックシンドロームの3診断項目のうち1つ以上を発症する相対ハザード比と内臓脂肪面積との関係
（文献[6]より引用）

い肥満関連疾患が発症している可能性があり，肥満症と同様に，過食や運動不足などの生活習慣の改善による減量が有効な可能性が考えられる．更には，このような患者群は前述の肥満判定における課題で述べた境界領域の患者とオーバーラップしている可能性が高いので，これらの患者群をどのように扱うかに関して今後検討していくべきと思われる．

文　献

1）松澤佑次ほか：新しい肥満の判定と肥満症の診断基準．肥満研究 **6**(1)：18-28，2000.
2）松澤佑次ほか：肥満症治療ガイドライン 2006．肥満研究 **12**(臨増)：1-91，2006.
3）斎藤　康ほか：肥満症診断基準 2011．肥満研究 **17**(臨増)：1-78，2011.
4）吉池信男ほか：Body Mass Index に基づく肥満の程度と糖尿病，高血圧，高脂血症の危険因子との関連 多施設共同研究による疫学的検討．肥満研究 **6**(1)：4-17，2000.
5）日本肥満学会：淡路宣言 2011．(http://wwwjassoorjp/data/data/pdf/awaji2011pdf)
6）Nakao YM, et al: Intra-abdominal fat area is a predictor for new onset of individual components of metabolic syndrome: MEtabolic syndRome and abdominaL ObesiTy(MERLOT study). Proc Jpn Acad Ser B Phys Biol Sci **88**(8)：454-461，2012.

Intra-abdominal fat area is a predictor for new onset of individual components of metabolic syndrome: MEtabolic syndRome and abdominaL ObesiTy (MERLOT study)

By Yoko M. NAKAO,[*1,*2] Takashi MIYAWAKI,[*3] Shinji YASUNO,[*2] Kazuhiro NAKAO,[*1] Sachiko TANAKA,[*2] Midori IDA,[*1] Masakazu HIRATA,[*1] Masato KASAHARA,[*2] Kiminori HOSODA,[*1] Kenji UESHIMA[*2] and Kazuwa NAKAO[*1,*2,†]

(Communicated by Masanori OTSUKA, M.J.A.)

Abstract: **Objective**: To investigate the significance of intra-abdominal fat area (IAFA) on new onset of individual components of the metabolic syndrome: high blood pressure, dyslipidemia, or hyperglycemia. **Methods**: We conducted a longitudinal study using checkup data of a hospital from 1994 to 2010. Of 25,255 subjects, we examined 1,380 Japanese, who underwent computed tomography to measure IAFA and had no metabolic syndrome components at baseline. **Results**: During 3.6 years of the mean follow-up period, one of metabolic syndrome components occurred in 752 subjects. Of three components, high blood pressure was more prevalent. The multiple Cox regression analysis disclosed that IAFA is significantly associated with onset of metabolic syndrome components (HR: 1.05 per 10 cm^2, 95%CI: 1.03–1.07). This finding was independent of BMI, and significant even in non-obese individuals with body mass index $<25\,kg/m^2$. **Conclusions**: MERLOT study demonstrates that IAFA is an independent predictor for new onset of individual components of the metabolic syndrome, even in non-obese healthy Japanese.

Keywords: intra-abdominal fat area, abdominal obesity, metabolic syndrome, cohort study

Introduction

Metabolic syndrome is a cluster of abdominal obesity and metabolic abnormalities including high blood pressure, dyslipidemia, and hyperglycemia.[1] This constellation of metabolic disturbances is associated with an increased risk of cardiovascular mortality,[2] and the increase in risk begins with the presence of just one metabolic syndrome component.[3]

Although there are several definitions for the metabolic syndrome, abdominal or visceral obesity is an essential element in Japanese definition.[1] Evidence accumulated indicates that intra-abdominal fat area (IAFA) measured by computed tomography (CT) is the most accurate parameter for assessing abdominal obesity.[4] Several cross-sectional analyses suggest a possible association of higher amounts of IAFA with increased prevalence of metabolic syndrome,[5,6] even in normal weight men and women.[7] To date, however, there are no longitudinal studies to assess the association between IAFA measured by CT and the new onset of one metabolic syndrome component in the population without any metabolic syndrome components. Thus, it is unclear whether abdominal obesity precedes the onset of one of these metabolic syndrome components in Japanese healthy population.

The objective of the present study (MEtabolic syndRome and abdominaL ObesiTy: MERLOT) was to investigate the significance of IAFA measured by CT reflecting abdominal obesity on the new onset of

[*1] Department of Medicine and Clinical Science, Kyoto University Graduate School of Medicine, Kyoto, Japan.
[*2] EBM Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan.
[*3] Health Administration Center, NTT West Kyoto Hospital, Kyoto, Japan.
[†] Corresponding should be addressed: K. Nakao, Department of Medicine and Clinical Science, Kyoto University Graduate School of Medicine, 54 Shogoinkawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan (e-mail: nakao@kuhp.kyoto-u.ac.jp).

Abbreviations: IAFA: intra-abdominal fat area; CT: computed tomography; SFA: subcutaneous fat area; BMI: body mass index; HRs: hazard ratios; CIs: confidence intervals.

doi: 10.2183/pjab.88.454

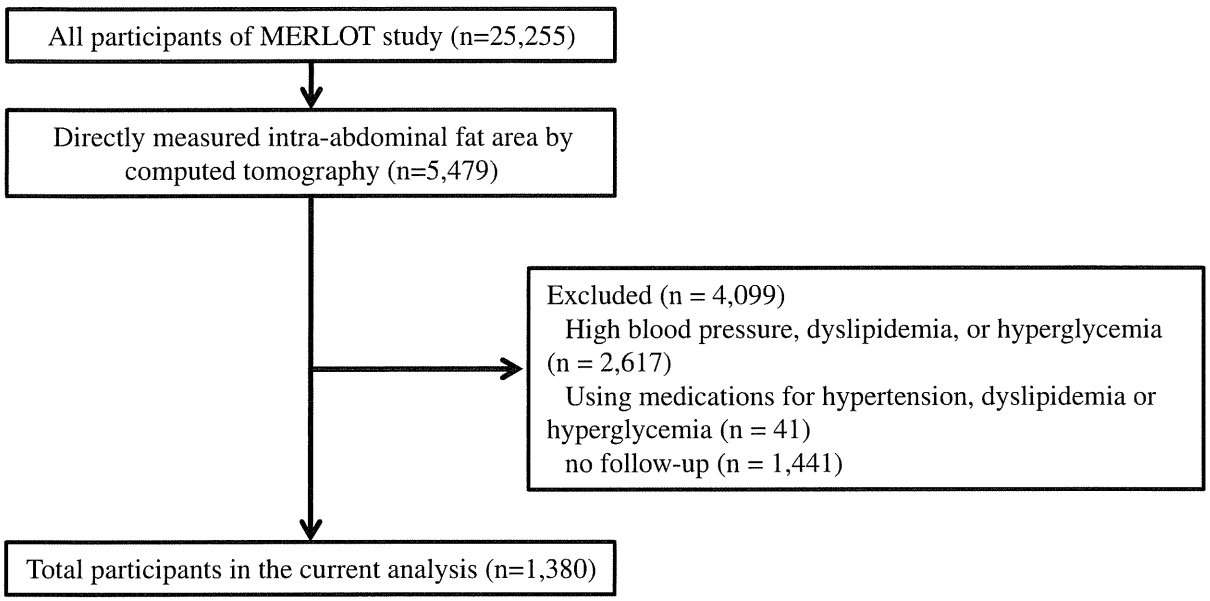

Fig. 1. Study flow chart.

metabolic syndrome components in Japanese. We also studied the role of IAFA as a predictor for the new onset of metabolic syndrome components in non-obese individuals with body mass index (BMI) $<25\,kg/m^2$.

Materials and methods

MERLOT study is a single-center, hospital-based non-concurrent prospective cohort study designed to investigate the significance of abdominal obesity on components of the metabolic syndrome, high blood pressure, dyslipidemia, and hyperglycemia.[1)]

The study included 25,255 subjects, aged 21 and 70 years old, from employees of telecommunication company, NTT West who lived in Kinki area of Japan. The cohort members underwent a corporate subsidized general health check program annually offered to the employees at Health Administration Center, NTT West Kyoto Hospital (Kyoto, Japan) from 1994 to 2010. MERLOT study included a part of subjects who participated in MONK study that we conducted.[5)]

The checkups were included consulting with physicians, physical examinations and a set of biochemical analyses of blood samples. All subjects voluntarily chose to be examined by CT for the IAFA and subcutaneous fat area (SFA). Registered nurses or physicians recorded information on current medication use and lifestyle using standard questionnaires, from which we identified those taking antihypertensive, lipid-regulating, or glucose-lowering drugs, and smoking status. An average blood pressure was calculated from two consecutive measurements over two days in a sitting position. IAFA and SFA were examined at an umbilical level in the supine position using CT, and were determined using a commercial software (Fat Scan, N2 System, Osaka, Japan). The details of measurements have been described previously.[5)]

We used data from MERLOT study to assess the new onset of metabolic syndrome components in association with IAFA, as well as potential role of IAFA in non-obese individuals with BMI $<25\,kg/m^2$. Of the 25,255 cohort members, 5,479 subjects underwent the measurement of IAFA by CT (Fig. 1). We excluded 4,099 subjects with high blood pressure (blood pressure $\geq$130/85 mmHg); dyslipidemia (triglycerides $\geq$150 mg/dl or HDL-cholesterol $<$40 mg/dl); hyperglycemia (fasting plasma glucose $\geq$110 mg/dl); medications including antihypertensive, lipid-regulating, or glucose lowering agents; no follow-up. Data from the remaining 1,380 subjects (1,053 men and 327 women) who had no metabolic syndrome components at baseline were analyzed in the present study.

Our endpoint was the new onset of one of three metabolic syndrome components with the definition by the Examination Committee of Criteria for the Metabolic Syndrome in Japan (blood pressure $\geq$130/

Table 1. Baseline characteristics

	All (n = 1,380)	Male (n = 1,053)	Female (n = 327)
Age (yr)	47.3 ± 7.4	46.9 ± 7.7	48.6 ± 6.3
BMI (kg/m^2)	22.8 ± 2.5	23.0 ± 2.4	22.0 ± 2.7
IAFA (cm^2)	71.6 ± 36.5	79.5 ± 35.5	46.4 ± 27.3
SFA (cm^2)	132.0 ± 55.3	123.4 ± 49.2	159.7 ± 64.3
Obesity (BMI ≥25 kg/m^2)	243 (17.6%)	196 (18.6%)	47 (14.4%)
Systolic blood pressure (mmHg)	115.3 ± 8.9	116.3 ± 8.6	112.0 ± 9.2
Diastolic blood pressure (mmHg)	72.2 ± 6.4	73.1 ± 6.1	69.1 ± 6.5
HDL-cholesterol (mg/dl)	61.0 ± 13.3	59.2 ± 12.8	66.7 ± 13.3
Triglycerides (mg/dl)	85.3 ± 29.6	89.3 ± 29.4	72.6 ± 26.6
Fasting plasma glucose (mg/dl)	97.1 ± 6.4	97.9 ± 6.1	94.7 ± 6.5
HbA1c (NGSP, %)	5.4 ± 0.3	5.4 ± 0.3	5.4 ± 0.3
Past or current smoker	50.8%	62.1%	17.0%

BMI: body mass index; IAFA: intra-abdominal fat area; SFA: subcutaneous fat area; NGSP: National Glycohemoglobin Standardization Program.

85 mmHg; dyslipidemia, triglycerides ≥150 mg/dl or HDL-cholesterol <40 mg/dl; fasting plasma glucose ≥110 mg/dl; new medications for hypertension, dyslipidemia, or hyperglycemia).[1] The subjects without event were censored at last clinical follow-up.

MERLOT study was approved by the ethics committee of Kyoto University Graduate School of Medicine and NTT West Kyoto Hospital (E1159).

Statistical analysis. We assessed IAFA, SFA, and BMI in relation to the endpoint. We generated Kaplan-Meier curves for quartiles of each obesity parameter. We used Cox proportional hazard regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Multivariate models were adjusted for age, gender, smoking status, systolic blood pressure, triglyceride, HDL-cholesterol, hemoglobin A1c (HbA1c), BMI, and SFA. We calculated the prediction from a linear regression of relative hazard on IAFA and showed the resulting line along with a 95%CI by BMI categories. A potential effect modification by BMI categories (BMI <25 or ≥25 kg/m^2) was evaluated by testing a statistical significance of multiplicative interaction terms in models.[8] We used multiple imputation in the validation cohort to replace missing values for smoking status. All statistical analyses were carried out with STATA (version 12.1, STATA, College Station, TX, USA).

Results

Table 1 showed characteristics of 1,380 subjects (1,053 men and 327 women) at baseline. The mean age was 47.3 ± 7.4 years ranged from 23 to 64 years. The mean BMI was 22.8 ± 2.5 kg/m^2 and mean IAFA was 70.6 ± 36.5 cm^2. Of the 1,380 subjects, 243 (17.6%) were BMI ≥25 kg/m^2. Figure 2 showed the correlation matrix among IAFA, SFA, and BMI. All parameters showed good correlations ($p < 0.001$), although the range of IAFA levels varied widely among subjects with the same BMI.

During 3.6 years of the mean follow-up period (maximum 9.7 years), one of metabolic syndrome components occurred in 752 subjects (54.5%) which consisted of 615 men and 137 women. These were 58.4% of men and 41.9% of women, respectively. Of three metabolic syndrome components, high blood pressure was more prevalent (395/615 [64.2%] in men, 79/137 [57.7%] in women) than dyslipidemia (332/615 [54.0%] in men, 59/137 [43.1%] in women) and hyperglycemia (144/615 [23.4%] in men, 36/137 [26.3%] in women). The Kaplan–Meier curves showed the unadjusted incident rate increased in a stepwise fashion across increasing quartiles (Fig. 3; Log-rank test, $p < 0.001$; p for trend, $p < 0.001$). This pattern of an increased incidence according to quartiles remained significant for other obesity parameters including BMI and SFA, although quartiles 2–4 of BMI and quartiles 2–4 of SFA were nearly overlapping (Fig. 1A in the Supplementary Appendix at http://japanlinkcenter.org/DN/JST.JSTAGE/pjab/88.454).

Multivariate Cox proportional hazards analysis for the endpoint showed that IAFA, SFA and BMI were significant predictors after adjusting for age, gender (Table 2–Model 1). After adjusting for age, gender, and baseline other factors (Model 2), HRs

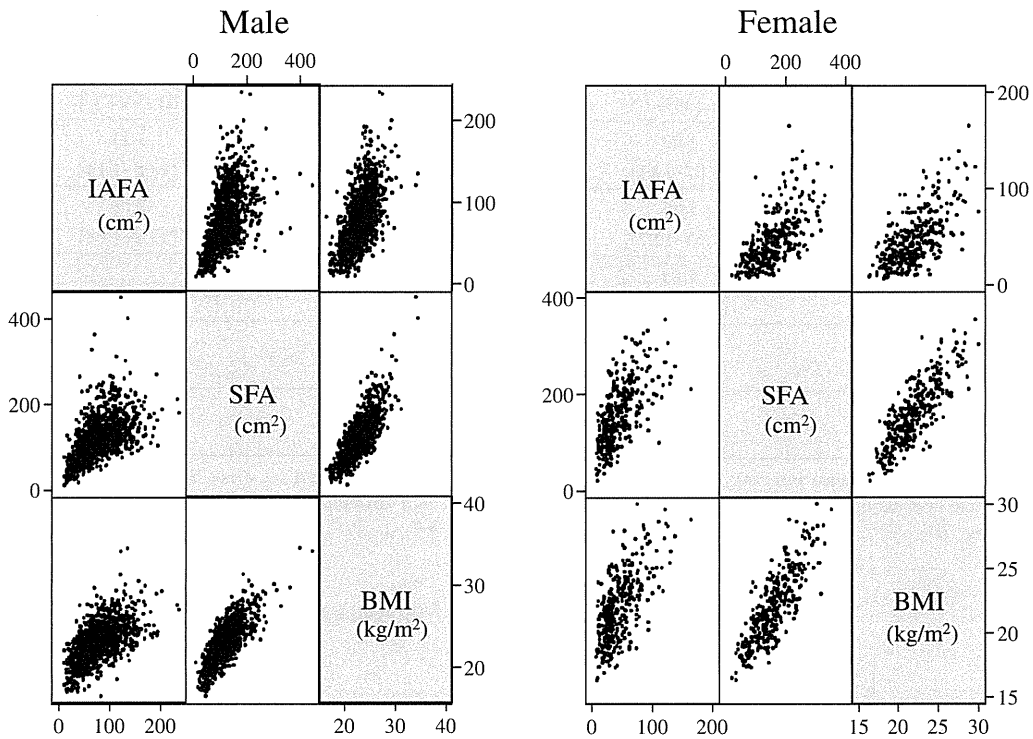

Fig. 2. Correlation matrix. The Pearson's correlation coefficient between IAFA and SFA (r = 0.536 in male, r = 0.629 in female); IAFA and BMI (r = 0.600 in male, r = 0.658 in female); SFA and BMI (r = 0.792 in male, r = 0.825 in female). IAFA: intra-abdominal fat area; SFA: subcutaneous fat area; BMI: body mass index.

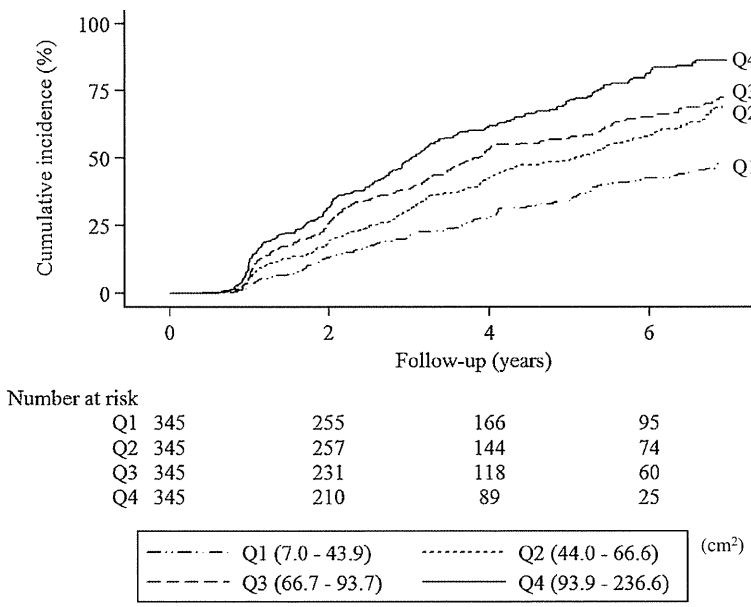

Fig. 3. Kaplan-Meier curves for new onset of components of metabolic syndrome according to intra-abdominal fat area.

Table 2. Hazard ratios for incidence of metabolic syndrome components according to baseline obesity parameters

	IAFA, per 10 cm^2		SFA, per 10 cm^2		BMI, per 1 kg/m^2	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Model 1: Age and gender-adjusted model.	1.09 (1.07–1.11)	<0.001	1.04 (1.03–1.06)	<0.001	1.11 (1.08–1.14)	<0.001
Model 2: Multivariate model. (Model 1 + other factors*)	1.05 (1.03–1.07)	<0.001	1.02 (1.01–1.04)	0.003	1.05 (1.02–1.08)	0.003
Model 3: BMI-adjusted model. (Model 2 + BMI)	1.04 (1.01–1.07)	0.003	1.01 (0.99–1.04)	0.275	—	—
Model 4: SFA-adjusted model. (Model 2 + SFA)	1.04 (1.01–1.07)	0.002	—	—	1.03 (0.98–1.08)	0.318
Model 5: Multivariate model 2. (Model 2 + BMI + SFA)	1.04 (1.01–1.07)	0.004	—	—	—	—

HR: hazard ratio; CI: confidence interval; BMI: body mass index; IAFA: intra-abdominal fat area; SFA: subcutaneous fat area.
* Smoking status, systolic blood pressure, log-triglyceride, HDL-cholesterol, and HbA1c.

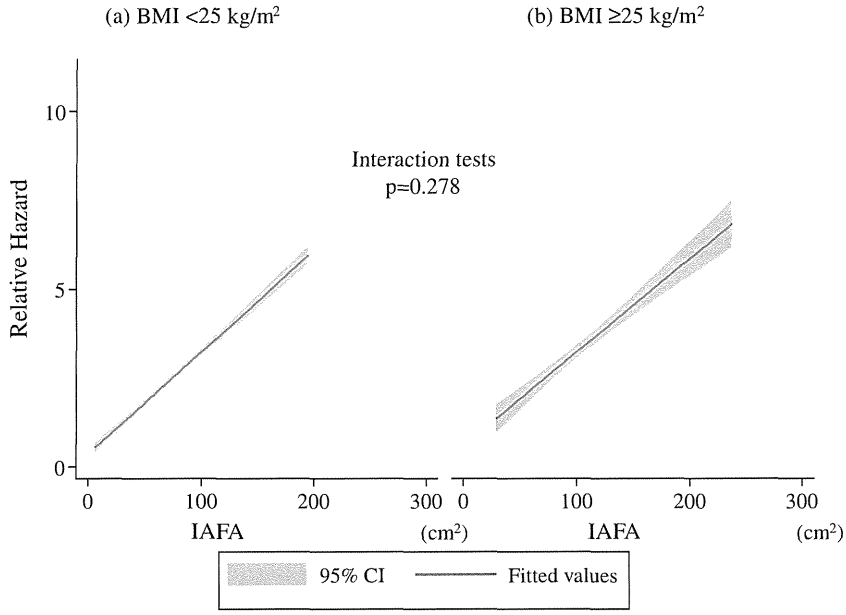

Fig. 4. Relative hazard and intra-abdominal fat area. Relative hazards were calculated on the basis of female gender and baseline data including mean intra-abdominal fat area, mean systolic blood pressure, mean triglyceride, mean HDL-cholesterol, and mean HbA1c in subjects with lower quartile of intra-abdominal fat area. IAFA: intra-abdominal fat area; BMI: body mass index; CI: confidence interval.

were reduced substantially, but broadly similar (IAFA, HR 1.05 per 10 cm^2, 95%CI 1.03–1.07; SFA, HR 1.02 per 10 cm^2, 95%CI 1.01–1.04; BMI, HR 1.05 per 1 kg/m^2, 95%CI 1.02–1.08). After further adjusting for BMI, IAFA remained an independent predictor for the new onset of metabolic syndrome components (HR 1.04, 95%CI 1.02–1.07; Table 2–Model 3), but SFA did not (HR 1.01, 95%CI 0.99–1.04). In SFA-adjusted model and multivariate model including SFA and BMI, IAFA was still an independent predictor of the endpoint.

In subgroup analyses, we documented 159 cases of the endpoint in obese subjects (BMI $\geq$25 kg/m^2), while 593 cases in non-obese (BMI <25 kg/m^2). In

the multiple Cox regression analysis, obese and non-obese subjects showed the same HRs for the endpoint (HR, 1.05; 95% CI, 1.03–1.09 in non-obese: HR 1.05; 95% CI, 1.00–1.10 in obese). There was no significant difference in test for interaction between obese (BMI $\geq 25\,kg/m^2$) or non-obese (BMI $<25\,kg/m^2$) and IAFA in predicting the endpoint ($p = 0.278$; Fig. 4).

Discussion

MERLOT study is the first report of a large-number, long-term follow-up longitudinal analysis on clinical significance of IAFA measured by CT in the metabolic syndrome. MERLOT study demonstrates that IAFA is an independent predictor for the new onset of individual components of the metabolic syndrome in Japanese. In addition, the present study also demonstrates that the finding is significant even in non-obese individuals with BMI $<25\,kg/m^2$.

Our findings are in line with previous cross-sectional studies in Japanese that examine the relationship between IAFA measured by CT and metabolic syndrome components.[5),6),9),10)] Longitudinal studies from a small number of ($n = 300$–457) Japanese Americans included patients with high blood pressure, dyslipidemia, and high blood glucose showed that greater abdominal adiposity increased the risk of hypertension,[11)] insulin resistance,[12)] and coronary heart disease.[13)] While a substudy from the Diabetes Prevention Program for averaged 3.2 years showed IAFA predicted the development of diabetes,[14)] this study was limited subjects with BMI $\geq 24\,kg/m^2$ (≥ 22 for Asian Americans). MERLOT study includes larger number of subjects with no limits in subjects' BMI, which ranged from 16.3 to $34.5\,kg/m^2$.

MERLOT study, using a larger cohort with a long-term follow-up period, verified these preliminary findings observed in a limited number of Japanese-Americans[11)–13)] and in a relatively short follow-up subgroup study of the Diabetes Prevention Program[14)] showing that IAFA is a predictor of the new onset of metabolic syndrome components and further expanded these findings in Japanese without any metabolic syndrome components.

Since another previous study from Japanese Americans showed that the association between IAFA and the future development of the metabolic syndrome appeared to be independent of SFA,[15)] the important question is whether or not the association is independent of BMI. MERLOT study documented, for the first time, that the new onset of individual components of the metabolic syndrome is predicted by IAFA, independently of BMI, in healthy Japanese. There have been debates and research progress on the relative importance of body weight, BMI and abdominal obesity in predicting cardiometabolic disorders.[7),16)] Although BMI is widely used to classify obesity and identify population at increased risk of obesity-related adverse health outcomes at population level, BMI is an indirect and imperfect measurement of abnormal or excessive body fat accumulation, because it does not distinguish fat mass and lean body mass components. IAFA reflecting abdominal obesity is proposed to be the essential clinical parameter for the metabolic syndrome.[17)] MERLOT study demonstrates that IAFA can be a better predictor than BMI for the new onset of individual components of the metabolic syndrome in Japanese.

The results of MERLOT study showed that the important role of IAFA among parameters in rational cardiometabolic risk stratification of Japanese, especially in normal BMI. The "metabolically obese, but normal weight" persons are a subgroup of individuals who have normal weight and BMI but display a cluster of obesity-related abnormalities.[18)] These individuals can display premature signs of insulin resistance, hyperinsulinemia, and dyslipidemia that may eventually increase their risk for the development of cardiovascular diseases. In general, the presence of these metabolic abnormalities could go undetected for years due to the normal body weight, which may mask the need for early detection and intervention.[19)] The previous study reported that abdominal obesity is a good indicator of risk for the metabolic syndrome for non-obese individuals in Western countries (BMI $<30\,kg/m^2$).[20)] In other study from Nurses' Health Study, abdominal obesity speculated by waist circumference and waist-hip ratio which is essentially limited to apply to differentiate the subcutaneous and intra-abdominal fat is strongly associated with increased coronary heart disease risk among women even with BMI $<25\,kg/m^2$.[21)] Our results in MERLOT study using IAFA measured more accurately with CT in Japanese population are consistent with prior findings by using waist circumference in Western population and extended these findings to a large, community-based sample in that we showed that IAFA is associated with a significantly higher prevalence of the metabolic syndrome components in normal-weight subjects (BMI $<25\,kg/m^2$). Furthermore, in MERLOT study, the interaction test for the new onset of metabolic syndrome components between BMI $<25\,kg/m^2$ and $\geq 25\,kg/m^2$ was not statistically

significant, supporting the risk for the new onset of metabolic syndrome components in non-obese individuals with BMI $<25\,kg/m^2$ can increase in a similar way compared in obese subjects with $\geq 25\,kg/m^2$. Thus, MERLOT study strongly indicates that IAFA can identify persons who are at greater cardiometabolic risk than are those identified by BMI alone.

IAFA measured by CT involves considerable radiation exposure to subjects, indicated the limited clinical use of IAFA measured by CT. Recently, using the dual bio-impedance method, we succeeded in developing the new equipment detecting IAFA without X ray exposure.[22),23)]

The limitations of our study include the potential selection bias due to inclusion with subjects who voluntarily chose to be examined by CT. In our study, it was seen in only half of population with IAFA $\geq 100\,cm^2$ (25.6% in men and 5.2% in women) compared with the previous cross-sectional studies, MONK (50.5% in men 11.6% in women)[5)] and VACATION-J (median IAFA was $115.9\,cm^2$ in men and $74.2\,cm^2$ in women),[6)] in Japan. It was consistent that our study includes healthier population without any metabolic syndrome components. Another limitations include the potential unaccounted confounding by lifestyle changes during the follow-up. However, we performed routine screening of metabolic risk factors and adjusted for several potential confounders.

In conclusion, MERLOT study demonstrates that IAFA is an independent predictor of the new onset of individual components of the metabolic syndrome and also indicates that this finding can be applied to non-obese subjects with BMI $<25\,kg/m^2$.

References

1) The Examination Committee of the Criteria for Metabolic Syndrome in Japan (2005) Definition and criteria of the metabolic syndrome in Japan. J. Jpn. Society Intern. Med. **94**, 188–201.
2) Mottillo, S., Filion, K.B., Genest, J., Joseph, L., Pilote, L., Poirier, P., Rinfret, S., Schiffrin, E.L. and Eisenberg, M.J. (2010) The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J. Am. Coll. Cardiol. **56**, 1113–1132.
3) Ho, J.S., Cannaday, J.J., Barlow, C.E., Mitchell, T.L., Cooper, K.H. and FitzGerald, S.J. (2008) Relation of the number of metabolic syndrome risk factors with all-cause and cardiovascular mortality. Am. J. Cardiol. **102**, 689–692.
4) Ross, R. and Janssen, I. (2005) Human Body Composition. Champaign, IL.
5) Miyawaki, T., Hirata, M., Moriyama, K., Sasaki, Y., Aono, H., Saito, N. and Nakao, K. (2005) Metabolic syndrome in Japanese diagnosed with visceral fat measurement by computed tomography. Proc. Jpn. Acad., Ser. B **81**, 471–479.
6) Hiuge-Shimizu, A., Kishida, K., Funahashi, T., Ishizaka, Y., Oka, R., Okada, M., Suzuki, S., Takaya, N., Nakagawa, T., Fukui, T., Fukuda, H., Watanabe, N., Yoshizumi, T., Nakamura, T., Matsuzawa, Y., Yamakado, M. and Shimomura, I. (2012) Absolute value of visceral fat area measured on computed tomography scans and obesity-related cardiovascular risk factors in large-scale Japanese general population (the VACATION-J study). Ann. Med. **44**, 82–92.
7) Goodpaster, B.H., Krishnaswami, S., Harris, T.B., Katsiaras, A., Kritchevsky, S.B., Simonsick, E.M., Nevitt, M., Holvoet, P. and Newman, A.B. (2005) Obesity, regional body fat distribution, and the metabolic syndrome in older men and women. Arch. Intern. Med. **165**, 777–783.
8) Rothman, K.J. (2002) Measuring interactions. *In* Epidemiology; An Introduction. Oxford University Press: New York, NY, pp. 168–180.
9) Oka, R., Kobayashi, J., Yagi, K., Tanii, H., Miyamoto, S., Asano, A., Hagishita, T., Mori, M., Moriuchi, T., Kobayashi, M., Katsuda, S., Kawashiri, M., Nohara, A., Takeda, Y., Hiroshi Mabuchi, H. and Yamagishi, M. (2008) Reassessment of the cutoff values of waist circumference and visceral fat area for identifying Japanese subjects at risk for the metabolic syndrome. Diabetes Res. Clin. Pract. **79**, 474–481.
10) Eguchi, M., Tsuchihashi, K., Saitoh, S., Odawara, Y., Hirano, T., Nakata, T., Miura, T., Ura, N., Hareyama, M. and Shimamoto, K. (2007) Visceral obesity in Japanese patients with metabolic syndrome: reappraisal of diagnostic criteria by CT scan. Hypertens. Res. **30**, 315–323.
11) Hayashi, T., Boyko, E.J., Leonetti, D.L., McNeely, M.J., Newell-Morris, L., Kahn, S.E. and Fujimoto, W.Y. (2004) Visceral adiposity is an independent predictor of incident hypertension in Japanese Americans. Ann. Intern. Med. **140**, 992–1000.
12) Hayashi, T., Boyko, E.J., McNeely, M.J., Leonetti, D.L., Kahn, S.E. and Fujimoto, W.Y. (2008) Visceral adiposity, not abdominal subcutaneous fat area, is associated with an increase in future insulin resistance in Japanese Americans. Diabetes **57**, 1269–1275.
13) Fujimoto, W.Y., Bergstrom, R.W., Boyko, E.J., Chen, K.W., Leonetti, D.L., Newell-Morris, L., Shofer, J.B. and Wahl, P.W. (1999) Visceral adiposity and incident coronary heart disease in Japanese-American men. The 10-year follow-up results of the Seattle Japanese-American Community Diabetes Study. Diabetes Care **22**, 1808–1812.
14) Bray, G.A., Jablonski, K.A., Fujimoto, W.Y., Barrett-Connor, E., Haffner, S., Hanson, R.L., Hill, J.O., Hubbard, V., Kriska, A., Stamm, E. Pi-Sunyer, F.X. and for the Diabetes Prevention Program Research Group (2008) Relation of

central adiposity and body mass index to the development of diabetes in the Diabetes Prevention Program. Am. J. Clin. Nutr. **87**, 1212–1218.
15) Tong, J., Boyko, E.J., Utzschneider, K.M., McNeely, M.J., Hayashi, T., Carr, D.B., Wallace, T.M., Zraika, S., Gerchman, F., Leonetti, D.L., Fujimoto, W.Y. and Kahn, S.E. (2007) Intra-abdominal fat accumulation predicts the development of the metabolic syndrome in non-diabetic Japanese-Americans. Diabetologia **50**, 1156–1160.
16) Klein, S., Allison, D.B., Heymsfield, S.B., Kelley, D.E., Leibel, R.L., Nonas, C. and Kahn, R. (2007) Waist circumference and cardiometabolic risk: a consensus statement from shaping America's health: Association for Weight Management and Obesity Prevention; NAASO, the Obesity Society; the American Society for Nutrition; and the American Diabetes Association. Diabetes Care **30**, 1647–1652.
17) Matsuzawa, Y. (2010) Establishment of a concept of visceral fat syndrome and discovery of adiponectin. Proc. Jpn. Acad., Ser. B **86**, 131–141.
18) Ruderman, N.B., Schneider, S.H. and Berchtold, P. (1981) The "metabolically-obese," normal-weight individual. Am. J. Clin. Nutr. **34**, 1617–1621.
19) Karelis, A.D., St-Pierre, D.H., Conus, F., Rabasa-Lhoret, R. and Poehlman, E.T. (2004) Metabolic and body composition factors in subgroups of obesity: what do we know? J. Clin. Endocrinol. Metab. **89**, 2569–2575.
20) Ascaso, J.F., Romero, P., Real, J.T., Lorente, R.I., Martínez-Valls, J. and Carmena, R. (2003) Abdominal obesity, insulin resistance, and metabolic syndrome in a southern European population. Eur. J. Intern. Med. **14**, 101–106.
21) Rexrode, K.M., Carey, V.J., Hennekens, C.H., Walters, E.E., Colditz, G.A., Stampfer, M.J., Willett, W.C. and Manson, J.E. (1998) Abdominal adiposity and coronary heart disease in women. JAMA **280**, 1843–1848.
22) Shiga, T., Oshima, Y., Kanai, H., Hirata, M., Hosoda, K. and Nakao, K. (2007) A Simple measurement method of visceral fat accumulation by bioelectrical impedance analysis. IFMBE Proceedings **17**, 687–690.
23) Shiga, T., Hamaguchi, T., Oshima, Y., Kanai, H., Hirata, M., Hosoda, K. and Nakao, K. (2009) A new simple measurement system of visceral fat accumulation by bioelectrical impedance analysis. In World Congress on Medical Physics and Biomedical Engineering 2009. IFMBE Proceedings **25**, 338–341.

(Received Dec. 27, 2011; accepted Aug. 24, 2012)