

Format for ANSWERING REVIEWERS



February 10, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: **8460-review.doc**).

Title: Clinical significance of visceral adiposity assessed by computed tomography: A Japanese perspective

Author: Miwa Ryo, Ken Kishida, Tadashi Nakamura, Tohru Yoshizumi, Tohru Funahashi, Iichiro Shimomura

Name of Journal: *World Journal of Radiology*

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The manuscript has been improved according to the suggestions of reviewers:

Reviewer No. 02664607

This is a very important topic, as obesity is an epidemic in the United States and the incidence is increasing in other developed countries. The ability to quantitatively assess visceral adiposity using CT and risk-stratify patients may prove to be useful clinically. The authors detail a low-dose, reliable method for doing so. This may also be helpful for CT scans obtained for other reasons. Hopefully, we as radiologists can in the future standardize the way we describe obesity in our reports and use a quantitative approach (such as measuring VFA at the level of L4) for every case we read.

We appreciate your helpful comments.

Reviewer No. 02664527

The authors present a detailed review of the estimation of visceral fat. This is an uncommon subject. The author's institute nevertheless has considerable expertise in the topic. No major comments. Few typos like in table 1 (umbilicus is misspelt) should be corrected.

As the reviewer suggested, we revised totally our manuscript. The revised manuscript was edited by a professional Australian medical editor (www.word-medex.com.au).

Reviewer No. 02785233

In the present study, Ryo et al review the current status and the clinical significance of visceral adiposity assessment by computed tomography (CT). They also describe the technical details regarding image acquisition and post-processing. The subject is interesting and clinically relevant. Nevertheless, there are some issues that merit consideration:

1- The authors state that there is a significant association between the magnitude of visceral adiposity and the number of metabolic/cardiac risk factors. However, they do not present any data about the relationship between visceral adiposity and patients' prognosis. Are there studies demonstrating that the magnitude of visceral adiposity is associated with worse patient survival? If so, has it been demonstrated that visceral adiposity is an independent predictor of adverse events? On the other hand, if there aren't any studies demonstrating a relationship between visceral adiposity and patients'

prognosis, what do the authors believe is the reason? This should be discussed.

2- Is there any association between visceral adiposity and the Framingham risk score, or between visceral adiposity and other markers of subclinical atherosclerosis, such as calcium score, carotid intima-media thickness, C-reactive protein, etc? Maybe the authors could discuss that also.

We appreciate the valuable and helpful comments.

Many studies support a potential link between visceral adiposity and biological pathways important in the pathogenesis of multiple disease outcomes. Adipocytokines are key component of these pathways and include inflammatory cytokines, angiogenic factors, lipid metabolites, and extracellular matrix component (Ouchi N. et al, *Nat Rev Immunol.* 2011; 11: 85-97). We reported that plasma adiponectin, anti-atherogenic adipocytokine, levels correlated negatively with visceral adiposity and metabolic syndrome [Ryo M, et al. *Circ J.* 2004; 68: 975-981].

Indeed, visceral adiposity measured by CT correlates with the US-measured carotid intima-media thickness (IMT), plaque area, and total area (IMT area plus plaque area) after adjusting for demographics, family history, smoking, and percent body fat (Lear SA, et al. *Stroke.* 2007; 38: 2422-2429). Framingham study, showed a significant correlation between visceral adiposity and cardiovascular diseases and cancer after adjustment for clinical risk factors and BMI. In contrast, the amount of subcutaneous adipose tissue did not correlate with atherosclerotic cardiovascular diseases (ACVD) (Britton KA, et al *J Am Coll Cardiol.* 2013; 10: 921-925). In our Amagasaki Visceral Fat Study, a significant decrease was observed in the cumulative incidence of cardiovascular events in subjects who showed visceral fat reduction, compared to those who showed increase in visceral fat [Okauchi Y, et al. *Atherosclerosis.* 2010; 212: 698-700]. Therefore, we described in the revised manuscript as follows;

(Page 8, line 162)

“Using a different approach, other investigators showed that ACVD can be predicted by measuring the carotid intima-media thickness (IMT) by ultrasonography (US) [18]. Interestingly, however, the Multicultural Community Health Assessment Trial (M-CHAT) demonstrated that visceral adiposity measured by CT correlates with the US-measured carotid IMT, plaque area, and total area (IMT area plus plaque area) after adjusting for demographics, family history, smoking, and percent body fat [19].

The importance of CT-based adiposity indexes in ACVD was further confirmed in the Framingham Heart study (n=3,086; men=1,574, women=1,512; mean age 50.2 years; median follow-up 5.0 years), which showed a significant correlation between visceral adiposity and cardiovascular diseases (hazard ratio: 1.44; 95% confidence interval: 1.08 to 1.92; p=0.01) and cancer (hazard ratio: 1.43; 95% confidence interval: 1.12 to 1.84; p=0.005), even after adjustment for clinical risk factors and BMI. In contrast, the amount of subcutaneous adipose tissue did not correlate with ACVD [20].”

(Page 12, line 259)

“During 4-year follow-up of cardiovascular events in 3,228 employees (men 2,486, women 742), providing risk factor-oriented “Hokenshido” to subjects with visceral fat accumulation, resulted in a significant decrease in the cumulative incidence of cardiovascular events in subjects who showed visceral fat reduction (-20.7 ± 16.1 cm²), compared to those who showed increase in visceral fat (12.7 ± 14.6 cm²) (p =0.0049) [39]”

3- Maybe the authors could discuss the issue of radiation. What is the usual radiation dose used in the standard protocol for visceral adiposity assessment?

Authors described in the revised version as follows; (Page 7, line 136) "With regard to the radiation dose, the dose-length product (mGy·cm) is determined by multiplying CT dose index volume (mGy) by scan length (cm) [13]. The effective dose (0.015 mSv / mGy·cm) is computed by multiplying the dose-length product by a conversion factor for the abdomen [13]. The mean±standard deviation of the radiation dose used in the standard protocol for assessment of abdominal fat measured in 37 subjects (men 20, women 17) was 26.6±4.4 for men and 25.6±4.2 mGy/slice for women, while the respective effective dose was 0.42±0.07 and 0.41±0.06 mSv/slice."

4- The description of the "Hokenshido" technique is very interesting. However, I wasn't able to fully understand it. What does this "Health education guidance Hokenshido" consist of? Is it a dietary education? Does it include regular physical exercise? What other aspects of health education does it include? Maybe the authors could describe the "Hokenshido" in greater detail, in particular for the non-Japanese readership.

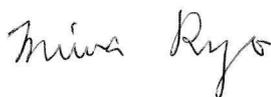
We appreciate helpful comments. After the annual medical examinations, health promotion program was performed by medical staff. The medical staff picked up the high risk persons who had multiple risk factors with visceral fat accumulation, and perform the health promotion "Hokenshido" program aiming to encourage scientific understanding on visceral fat accumulation to ACVD. It consists of education about the relationship between visceral fat accumulation and ACVD, and interviews, including counseling, about eating habits, alcohol intake, and physical activity. Through "Hokenshido", the guided subjects image their own condition of vascular damage and identify problematic habits that need to be changed. It doesn't include demonstration of physical exercise.

Authors described in the revised version as follows; (Page 10, line 228) "Public health nurses and/or dietitians provide "Hokenshido" to subjects at high risk in a group setup and/or one-to-one meetings. "Hokenshido" consists of education about the relationship between visceral fat accumulation and ACVD, and interviews, including counseling, about eating habits, alcohol intake, and physical activity. Through "Hokenshido", the guided subjects image their own condition of vascular damage and identify problematic habits that need to be changed."

5- I suggest that, if possible, the manuscript undergo a formal language review by a native English speaker.

As you suggested, the revised manuscript was edited by a professional Australian medical editor (www.word-medex.com.au).

Sincerely yours,



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