European Journal of Clinical Nutrition (2015) 69, 933–938

www.nature.com/ejcn

ORIGINAL ARTICLE

Storage capacity of subcutaneous fat in Japanese adults

S Sato[1], S Demura[2] and M Nakai[3]

BACKGROUND: On the basis of our previous study, which examined the nonlinear relationship between visceral fat area (VFA) and percent regional fat mass in the trunk, we hypothesise the presence of some storage capacity of subcutaneous fat. This study aimed to examine the storage capacity of subcutaneous fat on the basis of subcutaneous fat area (SFA) and VFA in 791 Japanese adult males and 563 females.

METHODS: Regression analyses by using SFA as a dependent variable and VFA as an independent variable were performed for each group classified by visceral fat obesity (VO): VO (VFA $\geqslant 100\,cm^2$) and the no-VO (NVO) groups. To statistically identify an optimal critical point for subcutaneous fat accumulation, we changed the cutoff point for the VO group from 50–150 cm^2 in 10-cm^2 increments and confirmed the significance of the correlation between SFA and VFA for each obesity group, the statistical difference in correlations between NVO and VO groups, and the goodness of fit for the two regression lines using the standard error of estimation values. These analyses were conducted for each sex and age (<65 and $\geqslant 65$ years) group.

RESULTS: The critical point for subcutaneous fat accumulation appears at the following cutoff points of VFA: 130 cm^2 in <65-year-old males, 110 cm^2 in $\geqslant 65$-year-old males and 100 cm^2 in both female groups.

CONCLUSIONS: These results suggest the presence of some storage capacity of subcutaneous fat. As a further application, these findings may serve to improve the risk assessment of obesity-related diseases.

European Journal of Clinical Nutrition (2015) **69,** 933–938; doi:10.1038/ejcn.2014.292; published online 4 February 2015

INTRODUCTION

Various studies have indicated a close relationship between the accumulation of visceral fat and the risk of obesity-related diseases.[1–4] Recently, the effects of subcutaneous fat accumulation on metabolic health were examined; these studies showed that a defect in adipogenesis and the storage capacity of subcutaneous adipose tissue was strongly associated with insulin resistance and type 2 diabetes mellitus.[2–4] In studies examining the effects of the surgical removal of subcutaneous abdominal fat on metabolic health and/or obesity-related diseases, the improvement in metabolic parameters was not consistent.[5–8] In contrast, Kim *et al.*[9] reported that total fat mass increased by expansion of the amount of subcutaneous fat, whereas relative visceral fat and triglycerides in the liver and skeletal muscle decreased. This finding suggests that massive expansion of subcutaneous fat is not harmful but may be beneficial for the action of insulin by preventing ectopic and visceral fat deposition.[1,10] Although these studies reported inconsistent results, they indicated new possibilities for correlating subcutaneous fat assessment with obesity-related disease prevention.

In our previous study,[11] a significant nonlinear relationship was confirmed between the visceral fat area (VFA) at L4–5 and percent regional fat mass (%RFM: regional fat mass ((g)/total fat mass (g)) in the trunk. These parameters proportionally increased at a low obesity level; however, %RFM in the trunk did not increase in individuals with visceral fat obesity (VO). Thus, even if the abdominal visceral fat increases, subcutaneous fat in the trunk does not increase, suggesting the presence of a critical point at which the characteristics of subcutaneous and visceral fat accumulation are altered. If a critical point where visceral fat accumulation becomes more pronounced actually exists, it may relate to the storage capacity of subcutaneous fat (the amount of subcutaneous fat that the body is capable of accumulating) and may become available as a useful indicator to screen for obesity-related diseases.

Accumulation of intra-abdominal visceral fat is closely associated with metabolic disorders such as diabetes, hypertension and hyperlipidemia.[2–4] However, specific imaging techniques such as computed tomography or magnetic resonance imaging are essential for direct and non-invasive measurement of the amount of visceral fat. Recent studies have shown how genes influence the storage capacity requirements of human subcutaneous adipose tissue.[2,12,13] Furthermore, it has been shown that visceral fat or abnormal ectopic fat accumulation is facilitated if subcutaneous fat exceeds this capacity.[12] Shiderman *et al.* (2007)[13] proposed the adipose tissue overflow hypothesis, in which the superficial subcutaneous adipose tissue compartment has some storage capacity that is closely related to the metabolic health. These findings suggest the potential of the storage capacity of subcutaneous fat as a useful indicator to screen for excess accumulation of visceral fat or the risk of obesity-related disease without direct measurement of the amount visceral fat. However, these hypotheses have not been examined in a field setting. Furthermore, in previous studies of the risk assessment of visceral fat accumulation, there was a considerable interest in developing simple techniques to estimate the amount of visceral fat. However, no reports have attempted to quantify the storage capacity of subcutaneous fat as a risk-assessment procedure for obesity-related diseases. Subcutaneous fat can be non-invasively, simply, economically and accurately measured in the field setting, possibly leading to the development of a simple and versatile risk-assessment method for obesity-related diseases.

[1]Kanazawa Institute of Technology, Nonoichi, Ishikawa, Japan; [2]Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Kanazawa, Ishikawa, Japan and [3]Houju Memorial Hospital, Warani Medical Corporation, Nomi, Ishikawa, Japan. Correspondence: Dr S Sato, Kanazawa Institute of Technology, Ohgigaoka 7-1, Nonoichi, Ishikawa, Japan.
E-mail: sssato@neptune.kanazawa-it.ac.jp
Received 26 June 2014; revised 14 November 2014; accepted 13 December 2014; published online 4 February 2015

This study aimed to examine the storage capacity of subcutaneous fat accumulation on the basis of the relationship between abdominal visceral and subcutaneous fat.

METHODS

Participants

In total, 792 Japanese males (mean age, 58.6 ± 13.5 years; range, 23–85 years) and 563 females (mean age, 58.2 ± 12.8 years; range, 21–85 years) who had undergone medical health examinations at a general hospital in Ishikawa prefecture, Japan, participated in this study. The sample included individuals who had undergone medical checkups or received Specific Health Checkups/Guidance as approved by the Ministry of Health, Labour and Welfare, Japan. The physical characteristics of participants for each sex and age group are shown in Table 1. Considering the age composition of the study sample, we classified the participants into two groups of age < 65 and ⩾65 years.

This study was approved by the Ethics Committee on Human Experimentation of the Faculty of Education, Kanazawa University.[14–16] The purpose of this study was thoroughly explained using written materials, and informed consent was obtained in writing from each participant.

Measurement of VFA and subcutaneous fat area

VFA and subcutaneous fat area (SFA) were measured at the umbilical level (L4–L5) using computed tomography (Somatom AR.C; Siemens, Erlangen, Germany) performed on participants in the supine position. VFA and SFA were calculated using a software program (FatScan; N2system, Osaka, Japan) and with a fixed attenuation range from − 190 to − 30 Hounsfield units (HUs).[17] First, a region of the subcutaneous fat layer was defined by tracing its contour on each scan. Then, the range of computed tomography values (in HUs) was calculated for the fat tissue. The total fat area was determined by delineating the surface with a mean computed tomography value plus or minus two standard deviations, and VFA was measured by drawing a line within the muscle wall surrounding the abdominal cavity. SFA was then calculated by subtracting VFA from total fat area.

The first step, calculating computed tomography values from the subcutaneous fat layer, yielded a histogram of computed tomography values (in HUs) for fat tissue. On the basis of mean attenuation plus or minus two standard deviations, total fat area and VFA were calculated.

Statistical analyses

Relationship between VFA and SFA. Correlation coefficients between VFA and SFA were calculated for both the VO (VFA ⩾ 100 cm^2) and no-VO (NVO) groups (VFA < 100 cm^2). In Japan, a VFA cutoff point of 100 cm^2 is used as the threshold for the risk of obesity-related diseases.[18]

Statistical calculation of the critical point for subcutaneous fat accumulation. In our previous study,[11] the relationship between VFA and percent regional fat mass (%RFM, regional fat mass/total fat mass) in the trunk weakened for the VO group (males: r = 0.40, $P < 0.05$; females: − 0.47, $P > 0.05$) compared with the control (BMI < 25 kg/m^2 and VFA < 100 cm^2) group (males: r = 0.68, $P < 0.05$; females: r = 0.45, $P < 0.05$). However, it was not clear whether this cutoff point was optimal, even though the critical point for subcutaneous fat accumulation was as expected. The criterion for VO in Japan was established as an indicator to screen for obesity-related disorders. If a critical point does exist and is associated with a significantly increased risk for visceral fat accumulation, it follows that this point would appear in comparable VFA levels of this diagnosis criterion.

This study attempted to statistically determine the critical point for subcutaneous fat accumulation. The critical point is the point at which the characteristics of subcutaneous and visceral fat accumulation are altered, and SFA accumulation tends to level-off as obesity increases. We defined an optimal cutoff point leading to the critical point as the point at which (a) a significant difference in the SFA–VFA relationships ($r_{SFA-VFA}$) appears between NVO and VO groups, (b) the significance of $r_{SFA-VFA}$ for the VO group disappears and (c) the goodness of fit for the two regression lines for NVO and VO groups is excellent.

To statistically determine the optimal cutoff point for classifying VO that leads to the critical point, we changed the cutoff point for classifying VO from 50–150 cm^2 in 10-cm^2 increments and performed regression analysis using SFA as a dependent variable and VFA as an independent variable for both VO and NVO groups. We then evaluated the significance of $r_{SFA-VFA}$ values for NVO and VO groups, and the difference between these $r_{SFA-VFA}$ values by Fisher's *z* transformation. We evaluated the goodness of fit for the two regression lines by summing the standard errors of estimation values (ΣSEE) for the two regression lines, interpreting lower ΣSEE values as increased goodness of fit. To evaluate sex and age effects, we performed these analyses for each sex and age group.

To calculate the critical point, we calculated the intersection of the two regression lines at the optimal cutoff point of VFA. The *x* and *y* coordinates of this point were taken to be VFA and SFA values at the critical point (SFA_{CP} and VFA_{CP}).

Assessment of clinical implication of the critical point for subcutaneous fat accumulation. To assess the clinical implication of the critical point for subcutaneous fat accumulation, we attempted to calculate waist circumference and BMI values corresponding to this critical point.

To calculate waist circumference and BMI values corresponding to the critical point (WC_{CP} and BMI_{CP}), regression analysis using waist circumference or BMI as a dependent variable and SFA as an independent variable was performed, and the WC or BMI value at SFA_{CP} were calculated. These analyses were conducted for each sex and age group.

These all analyses were performed for each sex and age group by using STATISTICA 10J, StatSoft (Tokyo, Japan). We set the level of statistical significance as $P < 0.05$.

RESULTS

Relationship between VFA and SFA

Figure 1 shows a scatter plot showing the relationship between SFA and VFA for each obesity type. Correlations between SFA and VFA ($r_{SFA-VFA}$) for NVO and VO groups were 0.45 ($P < 0.05$) and 0.41 ($P < 0.05$) for under-65 males, 0.61 ($P < 0.05$) and 0.23

Table 1. The physical characteristics of the participants

	Males						*Females*					
	Age < 65yr (n = 480)			*Age ⩾ 65yr* (n = 311)			*Age < 65yr* (n = 382)			*Age ⩾ 65yr* (n = 181)		
	Mean	*s.d.*	*Range*	*Mean*	*s.d.*	*Range*	*Mean*	*s.d.*	*Range*	*Mean*	*s.d.*	*Range*
Age (yr)	50.6	11.4	23.0–64.3	70.5	5.7	65.0–85.0	52.3	10.7	21.6–64.6	70.8	6.3	65.0–85.0
Height (cm)	169.9	6.1	154.0–187.5	164.9	6.1	146.0–183.0	157.7	5.7	140.3–174.3	152.7	5.5	136.9–166.1
Weight (kg)	71.7	11.3	39.6–131.6	63.2	8.2	44.5–93.0	58.1	11.1	32.9–107.2	51.8	8.7	33.1–86.2
BMI (kg/m^2)	24.8	3.4	15.7–41.2	23.2	2.7	16.2–35.0	23.4	4.3	13.2–41.5	22.2	3.3	16.5–34.9
Waist (cm)	88.9	11.0	61.9–164.5	84.0	8.2	63.3–104.3	87.0	12.0	66.0–163.5	82.5	8.7	62.0–117.1
VFA (cm^2)	115.2	52.6	6.5–355.1	101.4	44.1	17.7–242.5	71.2	39.2	11.1–257.8	75.1	39.0	13.3–221.6
SFA (cm^2)	149.7	69.0	20.5–630.8	121.5	48.8	28.5–311.5	198.9	95.5	48.2–759.7	167.2	68.0	40.1–307.9

Abbreviations: BMI, body mass index; SFA, subcutaneous fat area; VFA, visceral fat area.

($P < 0.05$) for over-65 males, 0.46 ($P < 0.05$) and 0.45 ($P < 0.05$) for under-65 females, and 0.37 ($P < 0.05$) and 0.22 ($P > 0.05$) for over-65 females.

As shown in Figure 1, several outlier values (four under-65 males and four under-65 females) were found (shown within the ellipse in Figure 1), with all lying outside the range of the mean SFA value ± 3 s.d. When correlations were calculated after exclusion of these outliers, the $r_{SFA-VFA}$ values changed from 0.41 ($P < 0.05$) to 0.26 ($P < 0.05$) for under-65 males and from 0.45 ($P < 0.05$) to 0.21 ($P > 0.05$) for under-65 females. When these outliers were excluded, the $r_{SFA-VFA}$ values were significantly higher for the NVO group than for the VO group except for over-65 females, and neither $r_{SFA-VFA}$ value in females was significant.

Statistical determination of a critical point

Figure 2 shows $r_{SFA-VFA}$ values for NVO and VO groups and ΣSEE values obtained for each cutoff point when changing the cutoff point for classifying VO from 50–150 cm^2 in 10-cm^2 increments. Irrespective of sex or age group, the difference in $r_{SFA-VFA}$ values between NVO and VO groups tended to widen with an increase in the cutoff point of VFA. For males, a significant difference in $r_{SFA-VFA}$ between NVO and VO groups was found at greater than 80 cm^2 of VFA in both age groups. The significance of $r_{SFA-VFA}$ for the VO group disappeared at 110 cm^2 for under-65 males and at 130 cm^2 for over-65 males. In contrast, in females, significant differences in $r_{SFA-VFA}$ were found from 90 to 120 cm^2 for the under-65 group and at 130 and 140 cm^2 for the over-65 group. The significance of $r_{SFA-VFA}$ for the VO group disappeared at greater than 100 cm^2 in both age groups.

In all sex and age groups, ΣSEE varied little among the cutoff points, and it was difficult to determine an optimal point using the ΣSEE values alone.

These results show that SFA tends to level-off as obesity increases, suggesting the presence of the storage capacity of subcutaneous fat, and we inferred that the optimal cutoff points of VFA that lead to the critical point for subcutaneous fat accumulation were 130 cm^2 for under-65 males, 110 cm^2 for over-65 males and 100 cm^2 for both age groups of females.

To statistically determine the critical point, we calculated the intersection of the two regression lines, when the optimal cutoff point of VFA was obtained. The *x* and *y* coordinates of the intersection, which correspond to the VFA and SFA values at the critical point, are shown in Table 2. VFA_{CP} values were higher for males and SFA_{CP} values were higher for females. For males, SFA_{CP} and VFA_{CP} values were higher for the under-65 than for the over-65 group. In females, SFA_{CP} was higher for the under-65 group, and VFA_{CP} was higher for the over-65 group.

Clinical implication of the critical point for subcutaneous fat accumulation

Table 2 shows WC_{CP} and BMI_{CP}, which are predicted values of these variables corresponding to the critical point. WC_{CP} and

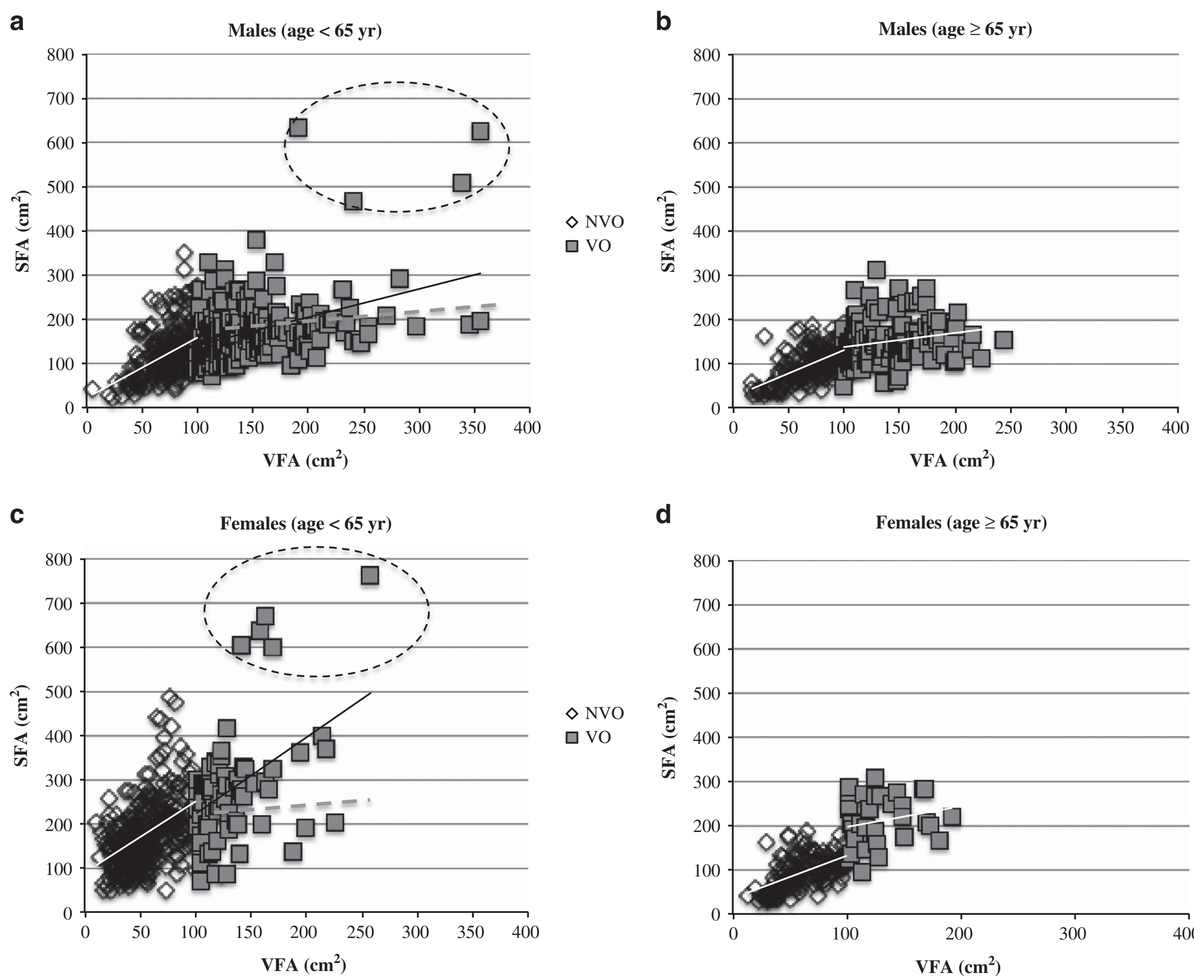

Figure 1. Scatter plot for the correlation between subcutaneous fat area and visceral fat area for each sex and age group. NVO: no-visceral fat obesity (VFA < 100 cm^2) group, VO: visceral fat obesity group. The dotted line in Figure 1 represents the regression line for the VO group after exclusion of these outliers (as shown within the ellipse). (**a**) Under-65 males, (**b**) over-65 males, (**c**) under-65 females, (**d**) over-65 females.

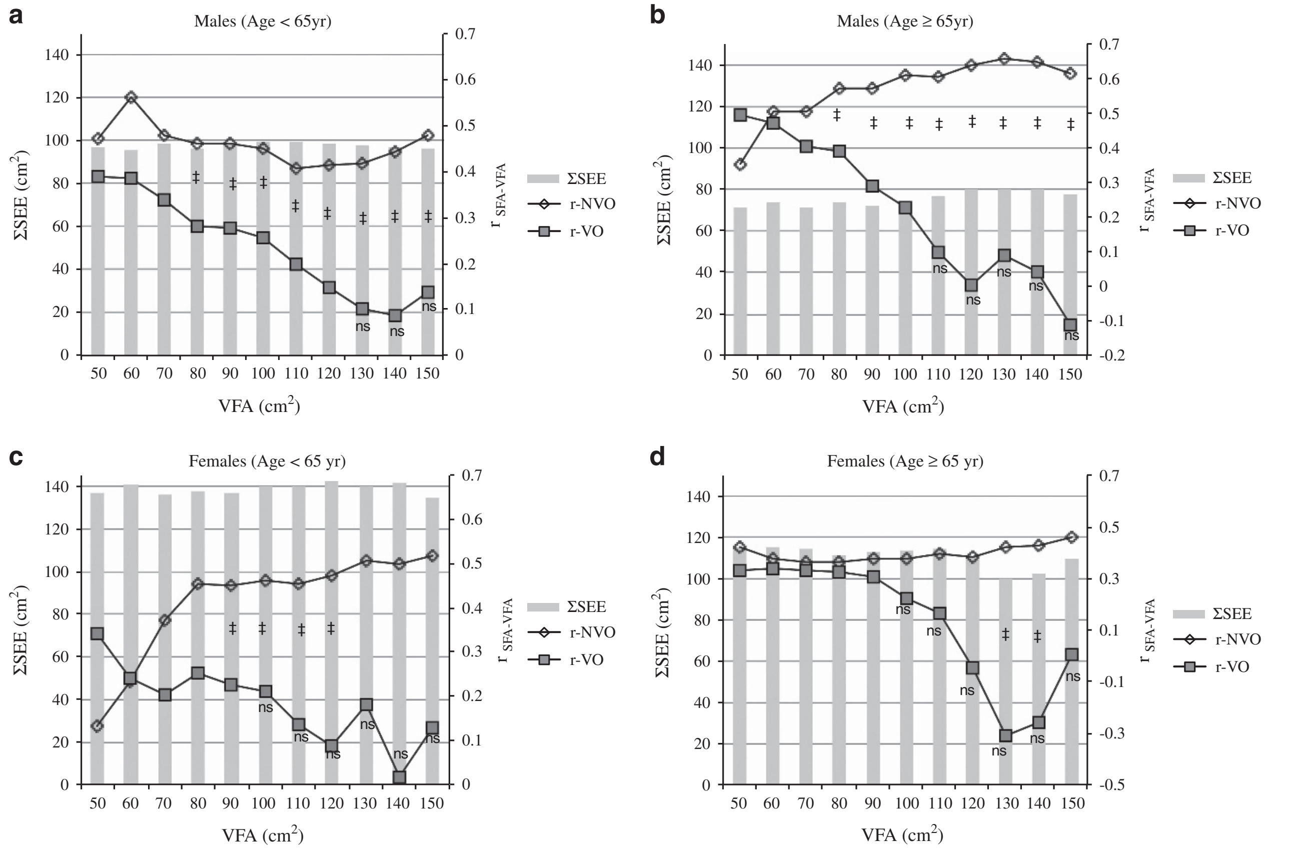

Figure 2. Determination of critical point when the cutoff point for visceral fat obesity was changed. NVO: no-visceral obesity group, VO: visceral fat obesity group. $r_{SFA-VFA}$: the correlation between subcutaneous fat area and visceral fat area. Summing the standard error of estimation values: the goodness of fit for the two regression lines was assessed by summing the standard error of estimation values for the two regression lines. ns: the correlation between subcutaneous fat area and visceral fat area was not significant. ‡: There was significant difference in correlations between no-visceral obesity and visceral fat obesity groups. (**a**) Under-65 males, (**b**) over-65 males, (**c**) under-65 females, (**d**) over-65 females.

BMI_{CP} values were higher for males than for females in both age groups and were higher for the under-65 group than for the over-65 group for both sex groups.

Table 2. SFA, VFA and anthropometric measurements correspondint to the critical point

	Critical point		*Predicted anthromopetric measures*	
	SFA_{CP}	*VFA_{CP}*	*WC_{CP}*	*BMI_{CP}*
Male				
Age < 65	174.7	133.1	92.0	25.8
Age ⩾ 65	152.3	125.8	88.1	24.5
Female				
Age < 65	229.6	87.2	90.5	24.5
Age ⩾ 65	194.9	96.1	85.7	23.3

Abbreviations: BMI, body mass index; SFA; subcutaneous fat area; VFA; visceral fat area; WC, waist circumference. SFA_{CP} and VFA_{CP}: *y* and *x* cordinate of the intersection of the two regression lines, which using SFA as a dependent variable and using VFA as an independent variable, respectively. WC_{CP} and BMI_{CP}: waist circumference and BMI values corresponding to the critical point, which are calculated from the regression analysis using waist circumference or BMI as dependent variable and using SFA as an independent variable.

DISCUSSION

Proliferation of fat mass is due to increased adipocyte size and an increased number of fat cells, with the former having a predominant role.[2,19] Previous studies have shown that hypercellularity of adi pose tissue is most likely to occur very early within the first few years and again from 9 to 13 years,[20] that hypertrophic obesity is associated with metabolic abnormalities,[12,14,21] and that sex and site differences exist in the relationship between adipocyte size and metabolic abnormalities.[12,14,20] Moreover, subcutaneous abdominal adipocyte size is positively associated with unfavourable metabolic health,[15] and adipocyte size is associated with the regulation of adipocyte function. Impaired capacity of fat storage in the subcutaneous adipose tissue leads to compensatory storage of excess fat in visceral and ectopic depots.[12] These studies support our hypothesis for the presence of that some storage capacity of subcutaneous fat. Our focus on the storage capacity of subcutaneous fat is meaningful because a defect in adipogenesis in subcutaneous adipose tissue leads to deposition of visceral and ectopic fat.

In this study, leveling-off of SFA was found irrespective of sex or age group, but it is suggested that there are sex and age differences in the VFA level that leads to the critical point. Given that there are sex and age differences in subcutaneous fat distribution and amounts of subcutaneous fat,[16] sex- and age-specific assessments are indicated.

The correlation between SFA and VFA for the NVO group was significant but remained at the level of a moderate relationship. Considering that obesity-related disease has been assessed not

only by BMI and percent body fat but also by visceral fat accumulation, there is a certain independence between SFA and VFA accumulation, although they have a significant correlation. In contrast, in our previous study,[11] strong relationships have been found between VFA and %RFM in the trunk among Japanese male adults. This finding suggests a limitation of this study with respect to the method of measurement by which subcutaneous and viscera fat are obtained from a single cross-sectional scan. A stronger relationship may be obtained by use of total visceral and subcutaneous fat volume.

In contrast, there are individuals who can accumulate a certain amount of subcutaneous fat, as shown in the ellipse in Figure 1. If there is a group of individuals who can bridge the gap between these outliers, our hypothesis of the existence of a critical point for subcutaneous fat accumulation is rejected. However, considering that our study sample comprised ~1200 adults with widely varying age and obesity levels, it is unreasonable to explain this phenomenon by sample deficiencies alone.

We speculate that these outlier individuals can be considered elites who can freely accumulate large amounts of subcutaneous fat. These outliers ('elites') were not found in the over-65 groups of either sex. It cannot be determined from our results alone whether this finding is associated with age-specific changes in metabolic mechanism or with a Japanese elderly specific characteristic such as long-term consumption of the Japanese diet. Further investigations including members of different races and second-generation Japanese elderly who had adopted Western-style dietary habits are desirable.

In Japan, a VFA cutoff point of 100 cm^2 is used as the threshold for the risk of obesity-related diseases.[18] In addition, waist circumference (males, 85 cm; females, 90 cm, corresponding to VFA of 100 cm^2) and BMI (25 kg/m^2 in both males and females) are used screening criteria for metabolic syndrome. These criteria are based on the evidence that the mean number of obesity-related diseases increases in proportion to an increase in VFA, and that the average is greater than 1.0 at 100 cm^2 of VFA.[18] If the critical point has any clinical implication as mentioned above, we expect that this point and the cutoff point for obesity-related diseases occur at similar VFA levels.

However, both the predicted optimal cutoff point and the critical point of VFA in males were greater than the standard of VFA for calculating the risk of obesity-related disease in Japan, and these values tended to be greater for males than for females. Further, there was little difference in these values between age groups. These results suggest that instead of a uniform standard, sex- and age-specific standards of VFA are needed to screen for obesity-related diseases, and that the existing standard of VFA (100 cm^2) underestimates the risk of obesity-related diseases for Japanese males. Similarly, the predicted waist circumference corresponding to the critical point were greater for under-65 and smaller for over-65 groups, compared with the standard waist circumference to screen for metabolic syndrome in Japanese. In particular, this trend was pronounced for under-65 males (92.0 cm) and for over-65 females (85.7 cm). In addition, with respect to the standard of waist circumference for metabolic syndrome in Japanese, the magnitude of the relationship between sexes in these predicted waist circumference values was reversed. Thus, the predicted waist circumference was greater for males than for females of both age groups. These results obtained in this study suggest the necessity of a re-examination of the standard waist circumference to screen for metabolic syndrome in Japanese.

This study proposed predicted SFA values corresponding to the critical point, as targets to screen for obesity-related diseases. If, as this study assumes, a critical point for the subcutaneous fat accumulation exists, it may be a sign of enhanced visceral fat accumulation and provide a parameter for assessing the risk of obesity-related diseases. These SFA values may provide an indication of the storage capacity of subcutaneous fat among Japanese adults. Thus, these SFA values may be available as risk-assessment criteria for fat deposition other than subcutaneous fat (ectopic and visceral fat). If sex-, race- and age-specific standard SFA vales can be proposed, useful information for assessment of obesity-related diseases is a distinct possibility. In addition, we have attempted to define anthropometric variables corresponding to the storage capacity of subcutaneous fat accumulation (WC_{CP}, BMI_{CP}). These variables offer the possibility of a simplified screening procedure for the storage capacity of subcutaneous fat. In any case, our approach, different from existing approaches focusing only on accumulation of visceral fat, may suggest a new possibility to screen for obesity-related diseases.

However, there are several limitations in generalisation of these results obtained in this study. Data consistently show the Japanese to be a race that cannot metabolise glucose as well as Caucasians when overnourished, thus being susceptible to developing glucose intolerance and complications with just a mild excess of adiposity.[16,22–24] Furthermore, many obese Japanese individuals exhibit a mild degree of adiposity compared with their Western counterparts.[18] Similarly, Sindreman *et al.* (2007)[13] also indicated that the superficial subcutaneous adipose tissue compartment is larger for Caucasians than for South Asians and that South Asians tend to exhaust the storage capacity of their superficial subcutaneous adipose tissue compartment before Caucasians do. Thus, there is race-specific difference in metabolic mechanisms, but these results are limited to Japanese adults to date. In addition, our female study sample, in particular visceral obesity over-65 females, was limited. Further investigations accounting for race-, sex- and age-specific effects are essential for generalising the storage capacity of subcutaneous fat and its parameters to screen for obesity-related diseases.

In summary, increase in SFA tended to level-off with increasing obesity in Japanese adults. This finding indicates the presence of some storage capacity of subcutaneous fat and the possibility of refining risk assessment for obesity-related diseases using the critical point for subcutaneous fat accumulation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This research was supported by JSPS KAKENHI Grant Number 23700847 and by Warani Medical Corporation, Hoju Memorial Hospital (Midorigaoka, Nomi, Ishikawa, Japan, URL http://www.houju.or.jp). The authors would like to thank Enago (www.enago.jp) for the English language review.

REFERENCES

1 Huffman DM, Barzilai N. Contribution of adipose tissue to health span and longevity. *Interdiscip Top Gerontol* 2010; **37**: 1–19.
2 McLaughlin TM, Liu T, Yee G, Abbasi F, Lamendola C, Reaven GM *et al.* Pioglitazone increases the proportion of small cells in human abdominal subcutaneous adipose tissue. *Obesity* 2010; **18**: 926–931.
3 McLaughlin T, Sherman A, Tsao P, Gonzalez O, Yee G, Lamendola C *et al.* Enhanced proportion of small adipose cells in insulin-resistant vs insulin-sensitive obese individuals implicates impaired adipogenesis. *Diabetologia* 2007; **50**: 1707–1715.
4 Danforth E Jr. Failure of adipocyte differentiation causes type II diabetes mellitus? *Nat Genet* 2000; **26**: 13.
5 Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW *et al.* Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N Engl J Med* 2004; **350**: 2549–2557.
6 Mohammed BS, Cohen S, Reeds D, Young VL, Klein S. Long-term effects of large-volume liposuction on metabolic risk factors for coronary heart disease. *Obesity* 2008; **16**: 2648–2651.
7 Ybarra J, Blanco-Vaca F, Fernández S, Castellví A, Bonet R, Palomer X *et al.* The effects of liposuction removal of subcutaneous abdominal fat on lipid metabolism are independent of insulin sensitivity in normal-overweight individuals. *Obes Surg* 2008; **18**: 408–414.

8 Busetto L, Bassetto F, Zocchi M, Zuliani F, Nolli ML, Pigozzo S *et al.* The effects of the surgical removal of subcutaneous adipose tissue on energy expenditure and adipocytokine concentrations in obese women. *Nutr Metab Cardiovasc Dis* 2008; **18**: 112–120.
9 Kim JY, van de Wall E, Laplante M, Azzara A, Trujillo ME, Hofmann SM *et al.* Obesity-associated improvements in metabolic profile through expansion of adipose tissue. *J Clin Invest* 2007; **117**: 2621–2637.
10 Huffman DM, Barzilai N. Role of visceral adipose tissue in aging. *Biochim Biophys Acta* 2009; **1790**: 1117–1123.
11 Demura S, Sato S. Nonlinear relationships between visceral fat area and percent regional fat mass in the trunk and the lower limbs in Japanese adults. *Eur J Clin Nutr* 2008; **62**: 1395–1404.
12 Tchoukalova YD, Koutsari C, Karpyak MV, Votruba SB, Wendland E, Jensen MD. Subcutaneous adipocyte size and body fat distribution. *Am J Clin Nutr* 2008; **87**: 56–63.
13 Sniderman AD, Bhopal R, Prabhakaran D, Sarrafzadegan N, Tchernof A. Why might South Asians be so susceptible to central obesity and its atherogenic consequences? The adipose tissue overflow hypothesis. *Int J Epidemiol* 2007; **36**: 220–225.
14 Björntorp P, Sjöström L. Number and size of adipose tissue fat cells in relation to metabolism in human obesity. *Metabolism* 1971; **20**: 703–713.
15 Imbeault P, Lemieux S, Prud'homme D, Tremblay A, Nadeau A, Després JP *et al.* Relationship of visceral adipose tissue to metabolic risk factors for coronary heart disease: is there a contribution of subcutaneous fat cell hypertrophy? *Metabolism* 1999; **48**: 355–362.
16 Tchernof A, Belanger C, Morisset AS, Richard C, Mailloux J, Laberge P *et al.* Regional differences in adipose tissue metabolism in women. *Diabetes* 2006; **55**: 1353–1360.
17 Yoshizumi T, Nakamura T, Yamane M, Islam AH, Menju M, Yamasaki K *et al.* Abdominal fat: standardized technique for measurement at CT. *Radiology* 1999; **211**: 283–286.
18 Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. *Circ J* 2002; **66**: 987–992.
19 Björntorp P, Gustafson A, Persson B. Adipose tissue fat cell size and number in relation to metabolism in endogenous hypertriglyceridemia. *Acta Med Scand* 1971; **190**: 363–367.
20 Salans LB, Cushman SW, Weismann RE. Studies of human adipose tissue. *J Clin Invest* 1973; **52**: 929–941.
21 Rolfe Ede L, Loos RJ, Druet C, Stolk RP, Ekelund U, Griffin SJ *et al.* Association between birth weight and visceral fat in adults. *Am J Clin Nutr* 2010; **92**: 347–352.
22 Fujimoto WY, Bergstrom RW, Boyko EJ, Leonetti DL, Newell-Morris LL, Wahl PW. Susceptibility to development of central adiposity among populations. *Obes Res* 1995; **3**: 179S–186S.
23 Yano K, MacLean CJ, Reed DM, Shimizu Y, Sasaki H, Kodama K *et al.* A comparison of the 12-year mortality and predictive factors of coronary heart disease among Japanese men in Japan and Hawaii. *Am J Epidemiol* 1988; **127**: 476–487.
24 Egusa G, Murakami F, Ito C, Matsumoto Y, Kado S, Okamura M *et al.* Westernized food habits and concentrations of serum lipids in the Japanese. *Atherosclerosis* 1993; **100**: 249–255.