変が存在しなくても起こりえる。これまで細胞生物学的に研究された発症機転を述べる。特に重要なのは2005年にJian-Su Shaoらによって報告された糖尿病マウスを用いた血管細胞間の情報伝達である[6]。Msx2強発現トランスゲニックマウスを作成，高脂肪食投与により冠動脈と大動脈の中膜にアルカリホスファターゼ（ALP）の発現と著明な石灰化を作ることができたが，このときMsx2の免疫原性は外膜のmyofibroblastに認められ，中膜に対するパラクライン刺激による骨誘導作用であることが証明された。一連の研究をまとめた仮説を述べると[7][8]，高血糖，過酸化物などによる酸化ストレスが血管外膜の脂肪細胞などに作用して低レベルの炎症（TNF〔tumor necrosis factor〕-α分泌）と血管新生を引き起こし，周皮細胞（pericyte），内皮細胞を刺激して骨化の最初のシグナルであるBMP-2/4を産生させる。これが外膜に予備として存在していたmyofibroblastなどのSca1$^+$ CD34$^+$ mesangial progenitor cellに作用して（転写因子）Msx2を発現，Wntタンパクを産生分泌し，Msx2-Wntシグナルが活性化され，異所性骨形成が行われる。このとき，mesangial progenitor cellが中膜に遊走するか，中膜平滑筋細胞が形質転換して骨形成を行うかは確定されていない。ここでMsx2-Wntシグナルは正常発生における骨形成時にも働いているものである（**図1**）。

さらに，中膜平滑筋細胞の骨への形質転換という面から骨化が起こるという立場の一連の研究がある。糖尿病患者で高血糖にさらされた組織でお

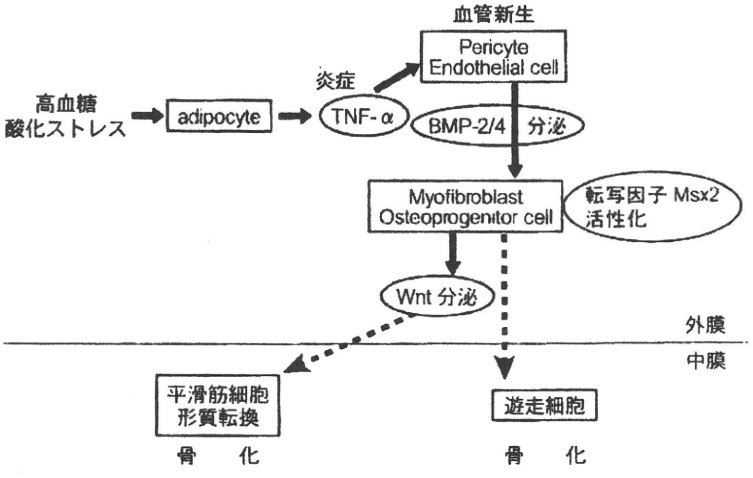

図1　糖尿病の血管における異所性石灰化のメカニズム

高血糖，過酸化物などによる酸化ストレスが，血管外膜の脂肪細胞を刺激してTNF-αを分泌させ，周皮細胞と内皮細胞を刺激してBMP-2/4を産生分泌させる。これは外膜myofibroblastに作用して転写因子Msx2を発現，Wntタンパクを産生分泌し，Msx2-Wntシグナルが活性化され，異所性骨形成が行われる。このとき，myofibroblastが中膜に遊走するか，中膜平滑筋細胞が形質転換して骨形成を行うかは確定されていない。

（文献7，8より）

ALP：アルカリホスファターゼ，TNF：tumor necrosis factor

こるメイラード反応の最終産物である最終糖化反応生成物（**AGEs**）が培養ヒト血管平滑筋細胞にRAGE/P38 MAP kinase系を介してALP活性を増加，osteocalcinを分泌，骨への分化転換をおこした[9]。

ところで，生体は血管石灰化抑制因子と抑制機序を複数有しており，ほとんどすべての血管石灰化の病態には，石灰化促進情報の亢進とともに抑制因子の低下も同時に共存していることが明らかになってきた[7]。糖尿病において関係する可能性のあるものを述べる。まず，内因性のピロリン酸（**PPi**）がある。これは血管平滑筋が産生し間質に蓄積している陰イオンで，血管平滑筋の正常分化状態を維持する働きをもつ。次にmatrix G1aタンパクは血管平滑筋が産生するマトリックスタンパクで**BMP-2**（bone morphogenetic protein 2）の発現を抑制する。Fetuin-Aは肝臓で産生され血中に放出されてマトリックスにも沈着する糖タンパクでシスタチオン・スーパーファミリーに属し，異所性石灰化機構を抑制する働きがある。実際，これらの物質をそれぞれノックアウトマウスなどで抑制すると，広範囲な異常石灰化が起こった。透析腎不全患者では，特にこれが減少することが報告されているが，糖尿病では透析とは無関係にこれが減少する可能性が示唆された[10]。

さらに糖尿病における冠動脈石灰化には，その初期過程の免疫-炎症反応で重要なトリガーとなるCD40-CD40L反応における*CD*遺伝子のもつSNPsが有意に関与することが報告され注目されている[11]。

血管stiffnessと石灰化病変

糖尿病では動脈脈波伝導速度（pulse wave velocity：**PWV**）や超音波法による検討から，血管のstiffnessが増加していることがわかった。臨床的にはX線写真による動脈の石灰化所見，さらには病理学的な動脈の中膜硬化所見などが高頻度に認められる。実際に，Oxlundらは9例のインスリン依存型糖尿病群と年齢，性をマッチさせた18例の対照群から採取した胸部大動脈標本で生体工学的検討を行った結果，糖尿病群では壁の肥厚と伸展性の低下がみられ，硬化度は上昇し，さらに胸部大動脈の伸展性は，糖尿病罹患期間が長いほど低下することを報告している[12]。2型糖尿病で冠動脈疾患を合併しても無症候である場合が多い。このとき冠動脈病変を有する可能性を末梢動脈硬化の有無から予想することができる可能性が探られてきた。すなわち，末梢動脈のPWVとresistance indexがCTによる冠動脈石灰化スコアと逆相関した[13]。また，一般に動脈stiffness増加の原因は，動脈硬化性病変とそれに伴う内膜石灰化よりも中膜石灰化を反映する可能性が高いと報告されている[14]。

治療

1．血糖コントロール

疫学研究ならびに細胞生物学研究から，高血糖が中膜石灰化を起こすリスクになることはほぼ間違いない。では，血糖コントロールのみにより石灰化を抑制することができるかどうか興味のあるところである。1型糖尿病に対する疫学研究が冠動脈と末梢動脈の石灰化がきびしい血糖コントロールによるHbA1c低下により抑制されることを明らかにした[15]。同時に心血管病の発症も抑制しえた[16]。

2．骨粗鬆症治療薬

異所性石灰化である血管石灰化の治療として，

AGE：最終糖化反応生成物，BMP-2：bone morphogenetic protein 2，BP：ビスホスホネート，DCCT：Diabetes Control and Complications Trial，PPi：ピロリン酸，PWV：pulse wave velocity

異所性石灰化を伴っている骨粗鬆症に対する治療薬は注目されている。ビスホスホネート（BP）は破骨細胞の骨吸収作用を抑制することで骨粗鬆症に有効である。このなかで，エチドロネート（etidronate）は血管石灰化抑制因子であるピロリン酸を安定化させた薬物であり，確かに腎不全で透析を施行している患者に生じる血管石灰化を抑制するという数多くの報告がある[17]。この透析による血管石灰化と糖尿病による血管石灰化には，ある程度共通の機序があると考えられている。さらに最近，糖尿病の頸動脈硬化と大動脈石灰化に対して退縮効果を有したという報告がなされた[18]。現在のところ，まだ糖尿病の純粋な中膜石灰化に有効かどうかは報告されていないが，期待されるところである。

おわりに

糖尿病への挑戦は，BantingとBestの発見したインスリンが治療の表舞台に登場した1921年，さらに合併症（腎症や網膜症）克服のためのDiabetes Control and Complications Trial（DCCT）勧告のあった1993年を経て，今や心血管疾患予防の時代ともいえよう。糖尿病の血管石灰化にかかわる調節タンパクについての新しい知見を利用した治療法開発が待たれる。

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Quadriceps sarcopenia and visceral obesity are risk factors for postural instability in the middle-aged to elderly population

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Aim: Aging shifts body composition to comprising more fat and less muscle. Sarcopenia, particularly in the knee extensors, and obesity, particularly visceral obesity, either alone or in combination, may exacerbate age-related physical disability. We investigated the association between age-related quadriceps (Qc) sarcopenia and visceral obesity, as measured by cross-sectional area (CSA), on postural instability.

Methods: Mid-thigh muscle CSA and abdominal visceral and subcutaneous fat area at the level of the umbilicus were assessed from computed tomography (CT) images in 410 apparently healthy independent middle-aged to elderly subjects attending the medical check-up program in Ehime University Hospital. Static postural instability using a posturograph and one-leg standing time with eyes open were assessed.

Results: Both abdominal visceral fat area and Qc muscle CSA corrected by body weight (BW) were associated with static postural instability, in addition to age and sex, while BW-corrected Qc muscle CSA predicted a short one-leg standing time. The combination of Qc sarcopenia, defined as greater than 1 standard deviation below the mean of a young group (age <60 years), and visceral obesity, defined as a visceral fat area of more than 100 cm^2, were associated with static postural instability, while Qc sarcopenia was related to a higher prevalence of one-leg standing time of less than 30 s, irrespective of visceral obesity.

Conclusion: Thigh Qc sarcopenia and visceral obesity are associated with postural instability in middle-aged to elderly subjects. These findings suggest that age-related, site-specific fat and muscle mass alterations are associated with functional impairment. **Geriatr Gerontol Int 2010; 10: 233–243.**

Keywords: balance, quadriceps, sarcopenia, visceral obesity.

Introduction

Among the dramatic changes in body composition which occur with aging, sarcopenia, the age-related loss of skeletal muscle mass, has been associated with a range of physiological, metabolic and functional impairments.[1–3] Sarcopenia of the lower extremities is

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particularly important as it may lead to various physical dysfunctions,[4] of which postural instability stands out owing to its role as a risk factor for falls and fracture.[5] Despite the widespread research for risk of falls,[6–8] the role of sarcopenia of the quadriceps (Qc) on postural instability has not been fully elucidated.

A second concern in the aging of society is the increasing prevalence of obesity, which is a risk factor for disease and physical dysfunction. Several studies have reported that obesity is an independent factor for postural instability.[9–13] Although aging is associated with a progressive increase in fat mass, it is also associated with changes in bodyfat distribution,[14,15] namely, an increase in visceral abdominal fat and decrease in subcutaneous abdominal fat.[14,15] Although the accumulation of visceral fat carries an established risk of metabolic disorders, atherosclerosis and immobility, we are unaware of any investigation into the possible influence of visceral obesity on postural instability.

Together, these age-related changes in body composition, a combination of excess weight and reduced muscle mass or strength (or both), have been recently defined as sarcopenic obesity.[16–18] It is postulated that, on co-occurrence, their individual effects on physical disability, morbidity and mortality might be synergistically potentiated and maximized.[16–18]

Two recent studies of the influence of sarcopenia and obesity in combination on subjective and objective physical functions in the elderly[12,13] found that obesity was related to physical dysfunction both in the presence and absence of sarcopenia, whereas sarcopenia in the absence of obesity was not. Although both studies defined obesity and sarcopenia using dual X-ray absorption (DEXA), a gross measurement of total lean mass, age-related physical dysfunction may be more strongly associated with thigh muscle mass. In particular, given their dominant role in standing, the muscles of knee extension, the Qc muscles, may be more closely related to postural instability.

Here, we investigated the association between age-related sarcopenia and obesity, defined as thigh muscle mass and abdominal obesity quantified by CT, respectively, on postural instability. Thigh muscle mass was further divided into Qc and non-Qc muscle mass, and abdominal obesity into subcutaneous and visceral fat.

Methods

Study subjects

Subjects were apparently healthy middle-aged to elderly persons recruited from among consecutive visitors to the Anti-Aging Center at Ehime University Hospital from March 2006 to September 2007. They attended the voluntary medical check-up program "Anti-Aging Doc", a program provided to general residents of Ehime Prefecture, Japan, which is specifically designed to evaluate aging-related disorders, including atherosclerosis, cardiovascular disease, physical function and mild cognitive impairment. Among 450 consecutive participants, a total of 410 subjects who agreed with the study aims and protocols, gave written consent to all procedures, and were free of any history of symptomatic cerebrovascular events including TIA, coronary heart disease and congestive heart failure, were analyzed. All participants were physically independent in daily living. The series of studies to which the present study belongs was approved by the Ethics Committee of Ehime University Graduate School of Medicine.

Measurement of femoral muscle cross-sectional area

Femoral muscle cross-sectional area (CSA) was measured from a CT image (LightSpeed VCT; GE Healthcare, Tokyo, Japan) at the mid-thigh, measured as the midpoint from the inguinal crease to the proximal pole of the patella.[19] CT images were obtained with a minimal slice width of 5 mm and analyzed using OsiriX software.[20] Connected voxels within the CT attenuation range of 0–100 Hounsfield units were identified as muscle and CSA of the muscle was calculated. Femoral CSA was further divided into Qc and the rest of the musculature (non-Qc) at the level of the intermuscular incisura (Fig. 1). All images were analyzed blindly by a single investigator (O. M.). CSA was corrected by bodyweight (BW) and sarcopenia was defined as Qc muscle CSA/BW less than mean minus 1 standard deviation (SD) value of the CSA distribution in a young reference group aged less than 60 years independently for men and women.[21]

Measurement of abdominal fat area

Visceral fat area (cm^2) was measured from a CT image (LightSpeed VCT, GE Healthcare) at the level of the umbilicus (Fig. 1). CT images were obtained with a minimal slice width of 5 mm and analyzed using OsiriX software.[20] Connected voxels with the CT attenuation range of −150 to −50 Hounsfield units were identified as fat and calculated. Total abdominal fat area were further divided into subcutaneous fat area and visceral fat areas (Fig. 1). Visceral obesity was defined as a visceral fat area of more than 100 cm^2 in both men and women.[22]

Assessment of postural instability

Two functional parameters were measured for each participant, static postural instability and one-leg standing (OLS) time. Static postural instability was measured using a posturograph (Gravicorder G-5500; Anima, Tokyo, Japan) consisting of an equilateral triangular footplate with three built-in vertical force transducers to

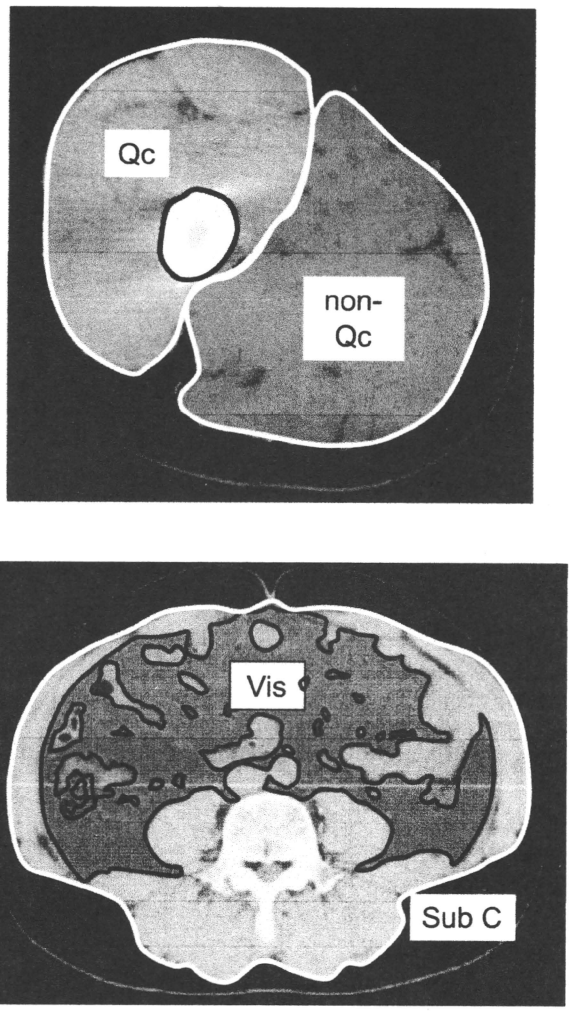

Figure 1 Mid-thigh computed tomography (CT) (top). Quadriceps (Qc) muscle cross-sectional area (CSA) and non-Qc muscle CSA obtained are shown. Abdominal CT at the level of the umbilicus (bottom). Visceral fat area (Vis) and abdominal subcutaneous (Sub C) fat area obtained are shown.

determine instantaneous fluctuations in the center of gravity (COG).[23,24] Signals were processed with a DC amplifier and low-pass filters (cut-off frequency 10 Hz) and stored in a computer after analog–digital conversion at a sampling rate of 20 Hz. Subjects were instructed to maintain a static upright posture on the footplate with their feet together and watch a circular achromatic target placed 200 cm directly ahead of them at eye level for 1 min. Measurements were performed barefoot with the arms held at the side of the body. Path length and circumferential area of the COG were used as indices of postural instability.

One-leg standing time with eyes open was measured as a second index of postural stability.[6,24] The leg used was at the subject's discretion. Time interval until the raised leg was returned to the floor was measured twice, with a maximum time of 60 s, and the longer measurement was used for statistical analysis.

Statistical analysis

Values are expressed as the mean ± SD unless otherwise specified. Differences in numeric variables among groups were assessed by ANOVA followed by Tukey's multiple comparison, while differences in frequency were assessed using the χ^2-test. Factors independently associated with postural instability were assessed using multiple regression analysis. All analyses were conducted using commercially available statistical software (SPSS ver. 17.0), with a probability value of <0.05 considered statistically significant.

Results

Age-related changes in thigh muscle CSA and abdominal fat area

Clinical characteristics of the study subjects are summarized in Table 1. Figure 2 summarizes the relationship between age and thigh muscle CSA and abdominal fat area. Thigh muscle CSA showed a significantly negative association with age in both men and women. Further analysis showed that Qc muscle CSA was more closely associated with age than non-Qc muscle CSA.

Because thigh muscle CSA showed a strong association with BW (Fig. 2), BW-corrected muscle CSA were analyzed as sarcopenic indices. Figure 2 also shows the relationship between age and BW-corrected thigh muscle CSA, with Qc muscle CSA/BW showing a closer association with age than non-Qc muscle CSA/BW in both men and women.

There was a weak positive correlation between age and visceral fat area in women but not in men. There were no associations between age and total abdominal fat area as well as subcutaneous fat area in both men and women.

Thigh muscle CSA and postural instability

Simple correlation coefficient analysis showed a significant negative association between path-length COG and both Qc muscle CSA/BW ($r = -0.35$, $P < 0.0001$) and non-Qc muscle CSA/BW ($r = -0.21$, $P = 0.0066$) in men, but only with Qc muscle CSA/BW ($r = -0.24$, $P = 0.0001$) in women.

Similar findings were observed in circumferential area of the COG: a significant negative association was seen between COG area and both Qc muscle CSA/BW and non-Qc muscle CSA/BW in men ($r = -0.28$, $P = 0.0003$; and $r = -0.26$, $P = 0.0008$, respectively), but only with Qc muscle CSA/BW in women ($r = -0.22$, $P = 0.0005$).

Table 1 Clinical characteristics of the study population

	Men ($n = 162$)	Women ($n = 248$)
Age, years	69.1 ± 7.5	66.4 ± 7.8
Body height, cm	164.6 ± 5.6	152.1 ± 5.3
Bodyweight, kg	63.9 ± 8.5	52.2 ± 7.6
Body mass index, kg/m^2	23.6 ± 2.8	22.6 ± 3.1
Mean thigh muscle CSA, cm^2	126.8 ± 16.9	90.7 ± 13.6
Mean quadriceps muscle CSA, cm^2	56.7 ± 8.3	40.8 ± 6.5
Mean non-quadriceps muscle CSA, cm^2	70.1 ± 10.3	49.8 ± 8.4
Abdominal visceral fat area, cm^2	130.8 ± 67.5	84.3 ± 53.3
Abdominal subcutaneous fat area, cm^2	121.6 ± 52.4	169.9 ± 71.0
One-leg standing time, s	45.8 ± 19.1	49.8 ± 17.8
Path-length of COG, cm	101.7 ± 36.8	80.8 ± 25.3
Circumferential area of COG, cm^2	3.7 ± 1.9	3.0 ± 1.6
Antihypertensive drug use, *n*	53	58
Hypnotics/ anti-depressants use, *n*	4/0	15/2
Bisphosphonates/vitamin D3 use, *n*	0/0	5/6
Premenopause, *n*	–	11

Mean ± standard deviation. COG; center of gravity; CSA, cross-sectional area.

Figure 3 depicts the path-length COG by tertile of BW-corrected thigh muscle CSA. In men, the lowest tertile of Qc and non-Qc muscle CSA/BW showed a significantly higher path-length COG than other groups, while in women, path-length COG was significantly higher in the lowest tertile of Qc muscle CSA/BW.

Figure 4 shows thigh muscle CSA/BW in three groups by OLS time. In men, both Qc and non-Qc muscle CSA/BW were significantly different among OLS-time groups. In women, in contrast, only Qc muscle CSA/BW was significantly different among the three OLS-time groups.

Abdominal fat area and postural instability

Simple correlation coefficient analysis showed that abdominal visceral fat area was significantly and positively associated with path-length COG in both men ($r = 0.34$, $P < 0.0001$) and women ($r = 0.28$, $P = 0.0001$). In contrast, abdominal subcutaneous fat area was significantly associated with path-length COG in men ($r = 0.23$, $P = 0.0027$) but not in women ($r = 0.12$, $P = 0.06$), while body mass index (BMI) showed no association with path-length COG in either men or women.

Figure 5 illustrates path-length COG by tertile of BMI, and abdominal subcutaneous and visceral fat area. In both men and women, subjects in the highest tertile of abdominal visceral fat showed a significantly higher path-length COG, while the highest tertile of abdominal subcutaneous fat showed a significantly higher path-length COG in men. In contrast, path-length COG did not differ among BMI tertiles.

Body mass index, abdominal subcutaneous and visceral fat area in the three OLS-time groups are shown in Figure 6. Visceral fat area significantly differed among the three groups. In separate analyses by sex, visceral fat area ($F = 3.5$, $P = 0.031$) significantly differed among the three OLS-time groups in women, while neither BMI nor visceral fat area significantly differed in men. On the contrary, abdominal fat area significantly differed among the three OLS-time groups in men but not in women.

Sex difference in postural instability

Men had higher path-length COG ($P < 0.0001$) and circumferential area of COG ($P < 0.0001$) than women (Table 1). The prevalence of subjects with OLS time of less than 30 s was marginally higher in men than women (43/119 versus 47/201, $P = 0.07$). However after correction with age, visceral fat area, Qc CSA/BW and body height, there was no difference in path-length COG (92.3 ± 45.4 vs 87.0 ± 40.0 cm, $P = 0.33$) and circumferential area of COG (3.23 ± 2.72 vs 3.36 ± 2.40 cm^2, $P = 0.71$). Similarly after correction of age, there was no difference in the prevalence of subjects with OLS time of less than 30 s ($\chi^2 = 0.09$, $P = 0.76$)

Multiple regression analysis for postural instability

To investigate whether thigh muscle CSA and obese parameters are independently related to postural instability, multiple regression analyses were performed for path-length COG (Table 2). In addition to age and sex, visceral fat area and Qc muscle CSA/BW were independently associated with path-length COG. Multiple logistic regression analysis showed that, in addition to age and sex, Qc muscle CSA/BW also had a negative impact on OLS time of less than 30 s (Table 3).

Sarcopenia and visceral obesity for metabolic postural instability

To further investigate whether thigh Qc sarcopenia and visceral obesity are related to postural instability,

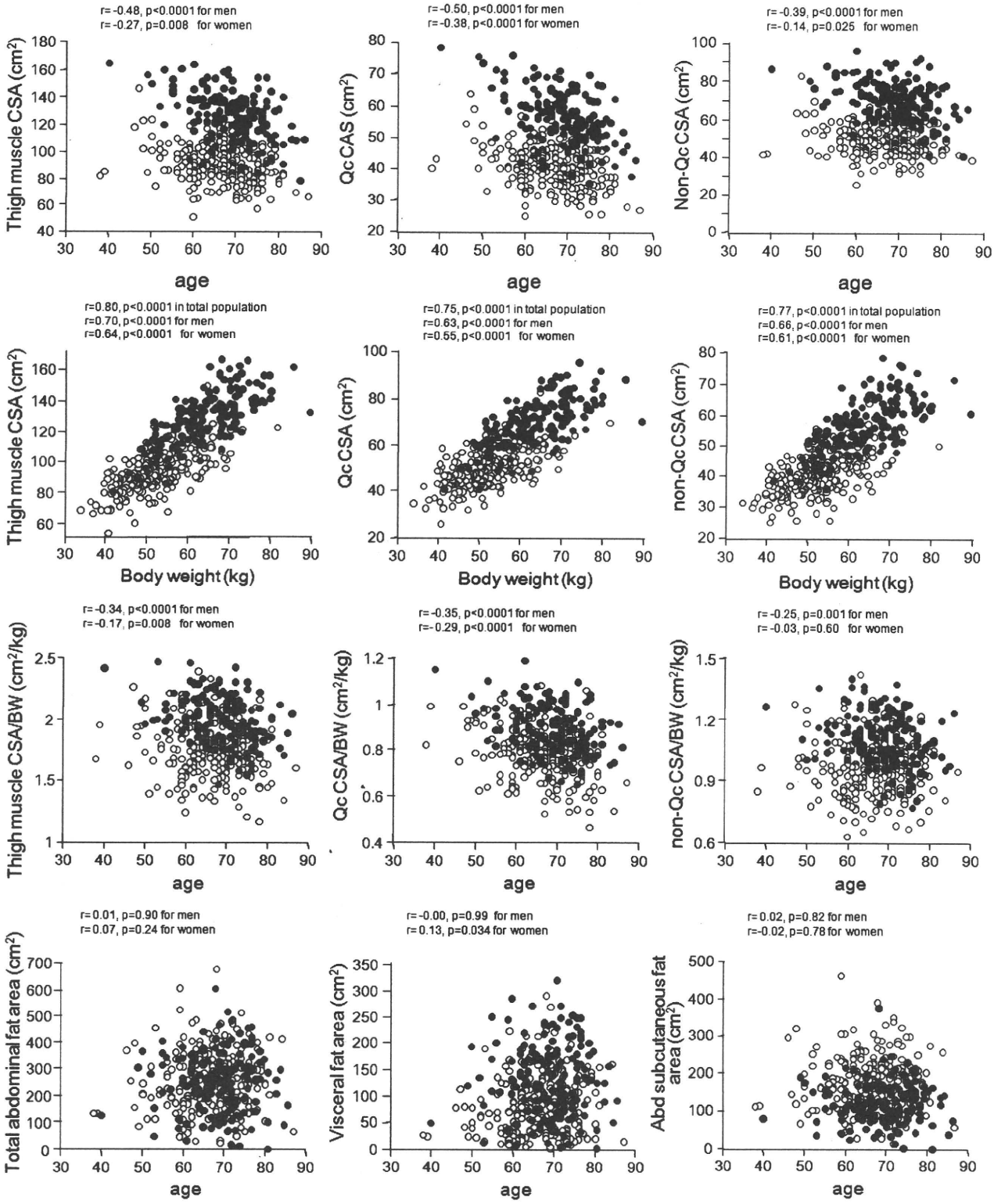

Figure 2 The relationship between thigh muscle cross-sectional areas (CSA) and age (top), bodyweight (BW, second top), the relationship between BW corrected thigh muscles CSA and age (third top), and the relationship between age and abdominal fat are (bottom). Total thigh muscle CSA (left), thigh quadriceps (Qc) muscle CSA (middle), and non-Qc (right) muscle CSA were analyzed. Total abdominal fat area (left), visceral fat area (middle), and abdominal (Abd) subcutaneous fat area (right) were analyzed (bottom). Closed circles indicate men, and open circles are women.

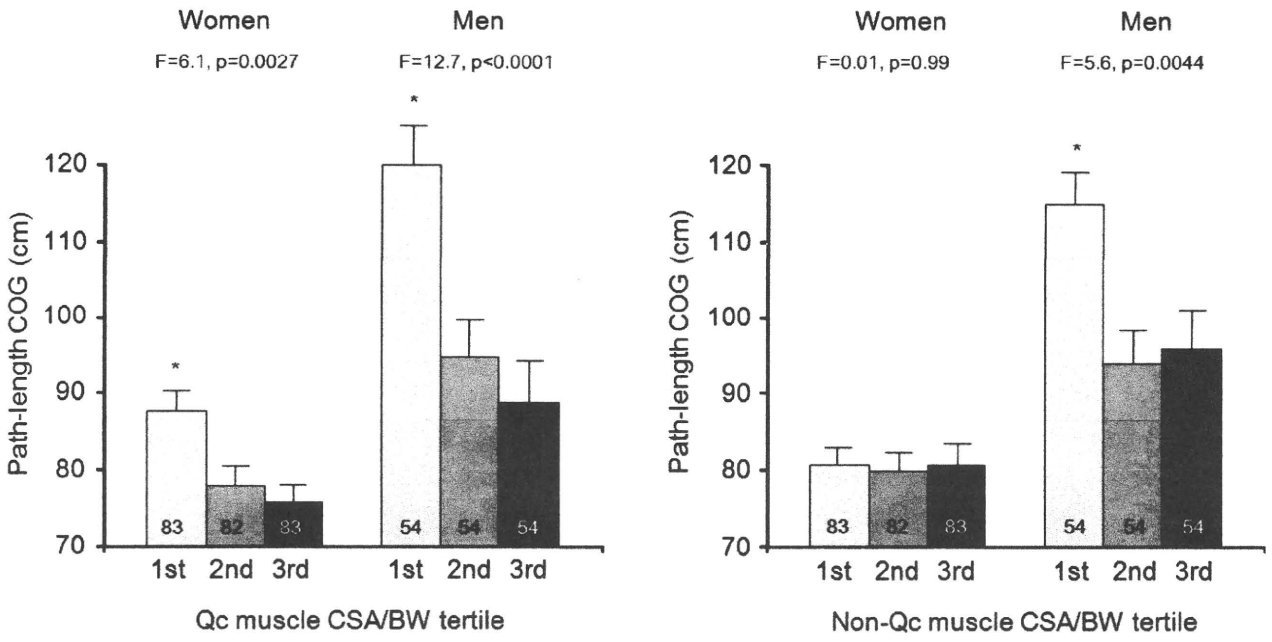

Figure 3 Path-length of the center of gravity (COG) by tertile of bodyweight (BW) corrected quadriceps (Qc) muscle cross-sectional area (CSA) (left) and BW corrected non-Qc muscle CSA (right). Men and women were separately analyzed. *F*-values for ANOVA are shown. Values are mean ± standard error. $*P < 0.01$ versus third tertile. Number in the column indicates the number of subjects.

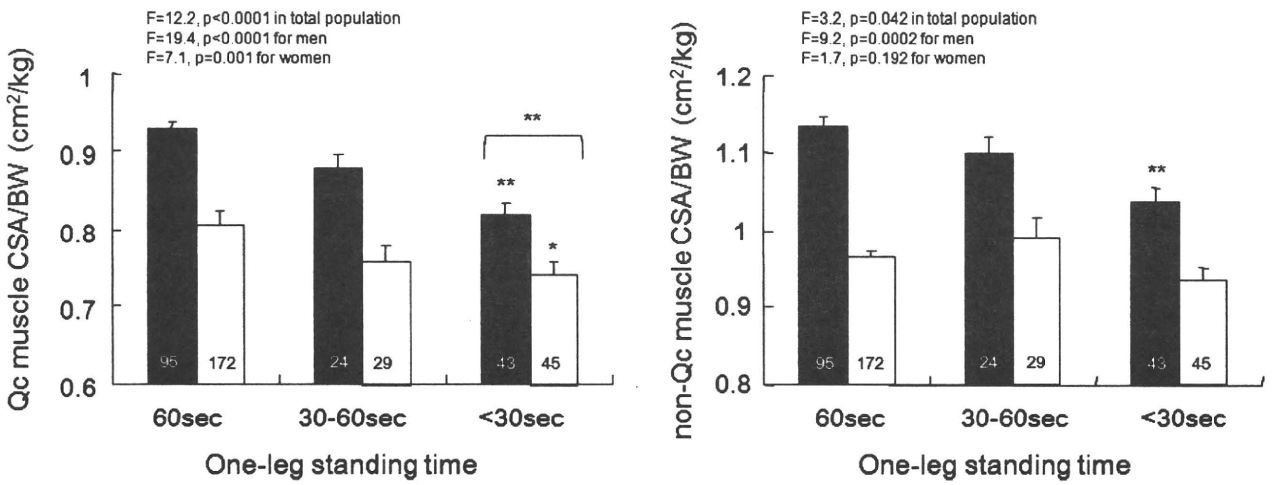

Figure 4 Quadriceps (Qc) muscle cross-sectional area (CSA) (left) and non-Qc muscle CSA (right) in three groups divided by the one-leg standing time. Men, women and total subjects were analyzed. The black column indicates men and the white column indicates women. *F*-values for ANOVA are shown. Square brackets in the figure indicate the combination of men and women. Values are mean ± standard error. $*P < 0.05$, $**P < 0.01$ versus subjects with a one-leg standing time of 60 s. Number in the column indicates the number of subjects.

path-length COG and prevalence of subjects with OLS time of less than 30 s were analyzed in four groups divided by the presence or absence of visceral obesity and Qc sarcopenia (Fig. 7). After correction for age and sex, path-length COG was significantly higher in the sarcopenic obesity group. In contrast, both the sarcopenic non-obesity group and sarcopenic obesity group had a significantly higher prevalence of OLS time of less than 30 s compared with the non-sarcopenic non-obesity group.

Blood chemical profiles of four groups are summarized in Table 4. Although obesity had lower high-density lipoprotein cholesterol and higher triglycerides and fasting glucose than normal groups, there was no

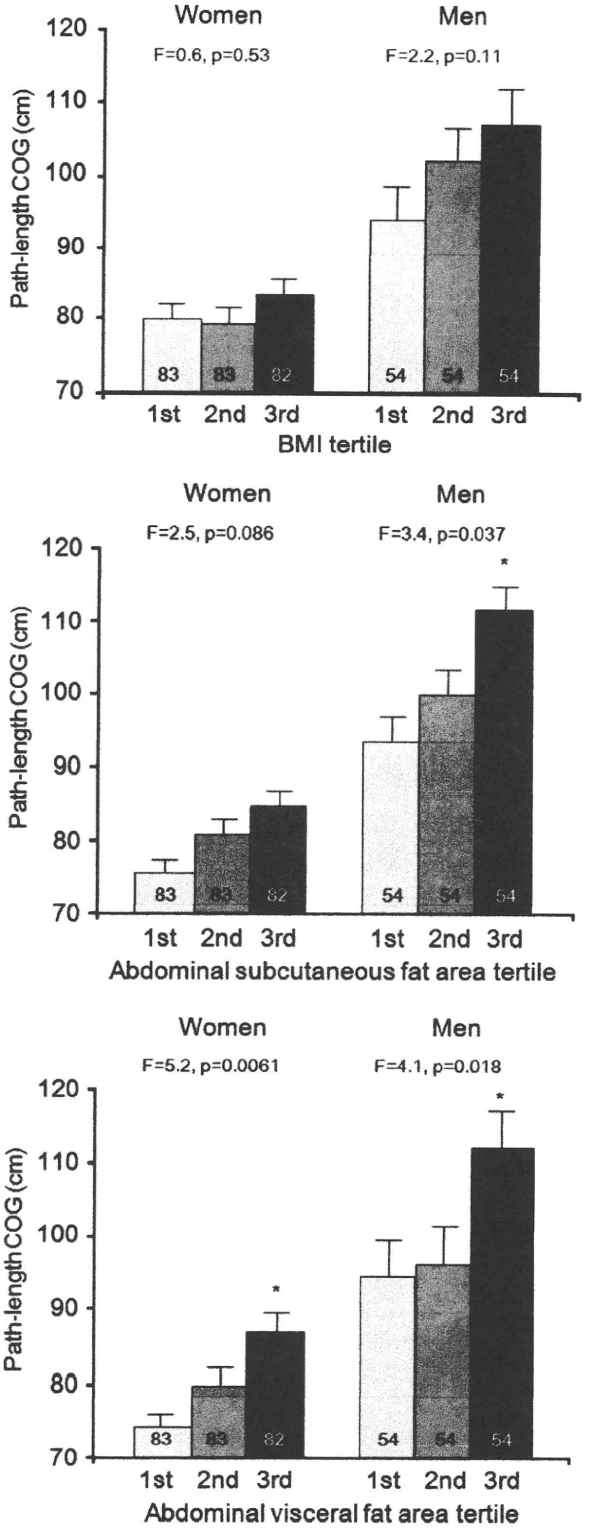

Figure 5 Path-length of the center of gravity (COG) by tertile of body mass index (BMI) (top), abdominal subcutaneous fat area (middle) and visceral fat area (bottom). Men and women were separately analyzed. *F*-values for ANOVA are shown. Values are mean ± standard error. **P* < 0.05 versus first tertile. Number in the column indicates the number of subjects.

difference in metabolic profiles between obesity and sarcopenic obesity.

Discussion

In this study, we found that Qc CSA but not non-Qc CSA at the mid-thigh level was significantly related to postural instability. We also observed that abdominal visceral fat area was more closely related to postural instability than abdominal subcutaneous fat area or BMI. The combination of visceral fat obesity and Qc sarcopenia was found to be a risk factor for both static postural instability and short OLS time.

The association of visceral fat mass and postural instability has been investigated. The age-related increase in fat mass is associated with the redistribution of fat,[14,15] and visceral fat increases with age. Of note, these changes can occur without significant changes in BMI. Obese subjects have been shown to have postural instability,[9] and BMI is related to postural instability.[10] In the present study, we extended these findings to show that visceral fat area, but not BMI or abdominal subcutaneous fat, were associated with static postural instability as evaluated by posturography. Our findings may indicate that age-related accumulation of visceral fat is more relevant to postural instability than obesity as defined by BMI.

Although we did not directly address the mechanisms linking visceral fat accumulation and postural instability in the present study, it is conceivable that accumulation raises the position of the body center, which could cause postural instability in the same way as would a large head on a balancing toy. The finding that the inclusion of waist circumference into the model did not change the results of multiple regression analyses, however, suggests that instability may not be due to abdominal size (data not shown). Further, the relationship between abdominal fat and OLS time is different from that for static postural instability. In women, shorter OLS time was associated with higher visceral fat area, while in men, OLS time of less than 30 s was associated with higher subcutaneous fat area. However, after correction with Qc muscle CSA /BW, subcutaneous fat area was not significantly different among OLS time (data not shown).

Sex difference in postural instabilities is inconclusive. Several studies reported no difference[24–27] and others reported higher instability in women.[28,29] In the present study, static postural instability and OLS time were not significantly different between men and women after correction with other confounding parameters. These findings may indicate that sex difference in postural instability may reflect the difference of anthropometric parameters including visceral fat and thigh muscle CSA which have not been evaluated in the past studies.

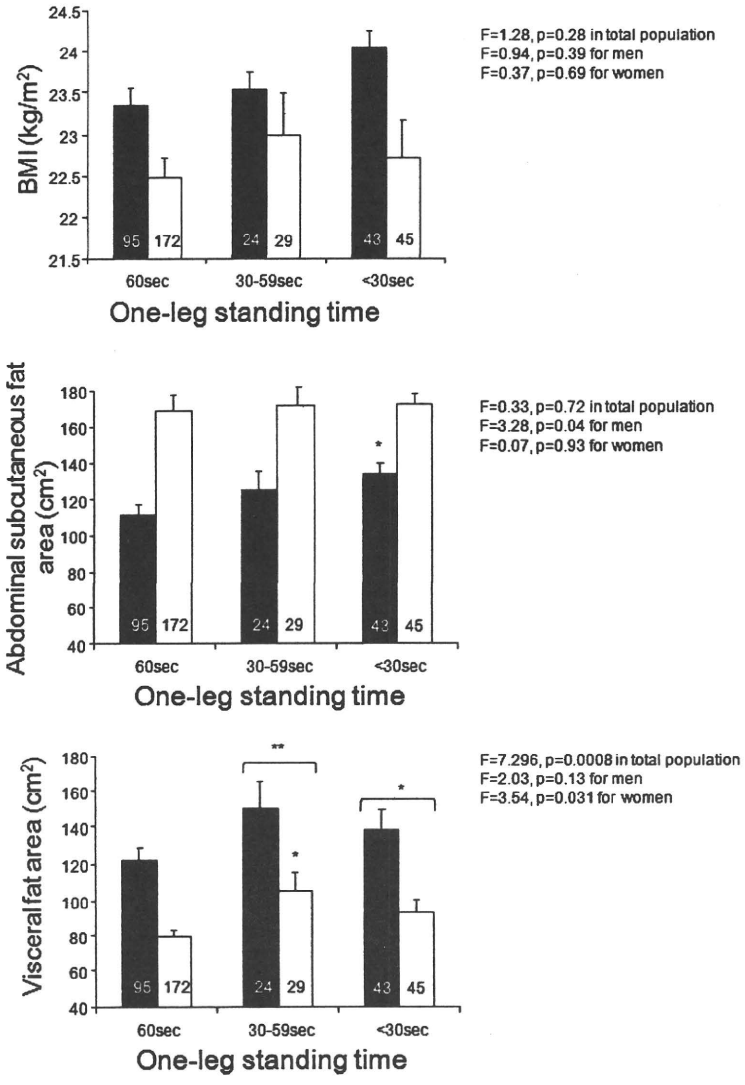

Figure 6 Body mass index (BMI) (top), abdominal subcutaneous fat area (middle) and visceral fat area (bottom) in three groups divided by the one-leg standing time. Men, women and total subjects were analyzed. The black column indicates men, and white column indicates women. *F*-values for ANOVA are shown. Square brackets in the figure indicate the combination of men and women. Values are mean ± standard error. $*P < 0.05$, $**P < 0.01$ versus subjects with a one-leg standing time of 60 s. Numbers in the column indicate the number of subjects.

Table 2 Multiple regression analysis for the path-length of the center of the gravity

Factor	β	*P*
Age, years	0.29	<0.0001
Sex, female	−0.27	<0.0001
Body mass index, kg/m^2	−0.17	0.052
Abdominal visceral fat area, cm^2	0.26	0.0001
Abdominal subcutaneous fat area, cm^2	0.10	0.24
Quadriceps muscle CSA, cm^2/kg	−0.17	0.0037
Non-quadriceps muscle CSA, cm^2/kg	0.08	0.19
Antihypertensive drugs use	−0.05	0.30
Hypnotics/anti-depressant use	−0.00	0.90
Bisphosphonates/vitamin D3 use	0.02	0.73

CSA, cross-sectional area.

Lower limb muscle strength, especially that of the knee extensors, has been shown to be associated with balance.[30,31] Extensors play a more dominant role in standing than flexor muscles. In the present study, we also observed that Qc muscle CSA/BW was more closely associated than non-Qc muscle CSA/BW with path-length and circumferential area of the COG, and OLS time. These findings may be clinically important in the elderly population, because Qc muscle CSA/BW showed a closer association with age than non-Qc muscle CSA/BW in our cross-sectional population. The present findings may also suggest that the prevention of age-related sarcopenia in the Qc may promote postural stability in the elderly. It has been shown that resistance training is functionally beneficial in the elderly.[32] Further an intervention aimed at the Qc has been proved effective in reducing the risk of fall as well as improving activities of daily living.[33]

Table 3 Logistic regression analysis for the presence of a one-leg standing time <30 s

Factor	Odds ratio	95% CI	*P*
Age, years	1.17	1.12–1.24	<0.0001
Sex, male	2.54	1.07–6.25	0.035
Body mass index, kg/m^2	0.98	0.80–1.19	0.83
Abdominal visceral fat area, cm^2	1.00	0.99–1.01	0.72
Abdominal subcutaneous fat area, cm^2	1.00	0.99–1.01	0.79
Quadriceps muscle CSA, 100 cm^2/kg	0.67	0.48–0.92	0.013
Non-quadriceps muscle CSA, 100 cm^2/kg	0.83	0.64–1.06	0.114
Antihypertensive drugs use	1.62	0.90–2.92	0.11
Hypnotics/anti-depressant use	2.26	0.67–7.21	0.18
Bisphosphonates/vitamin D3 use	1.11	0.18–6.05	1.90

CI, confidence interval; CSA, cross-sectional area.

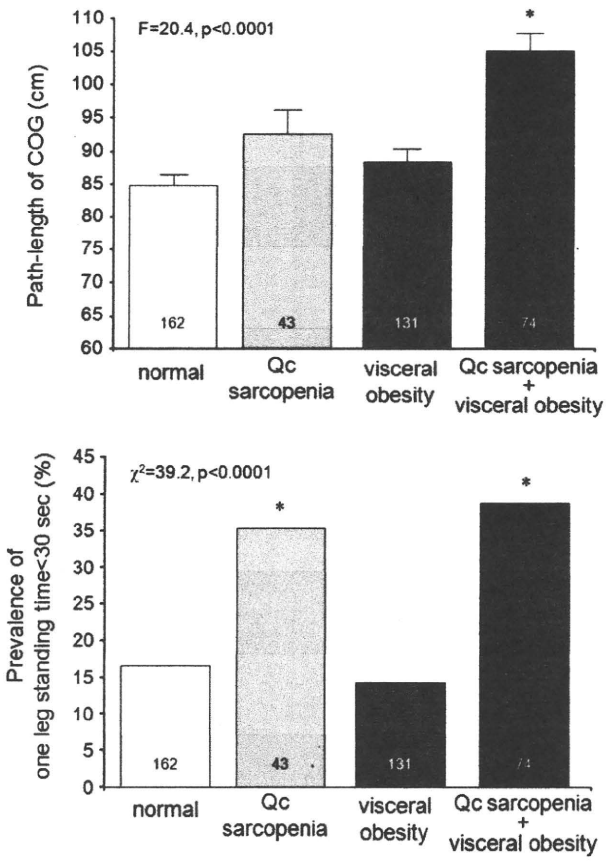

Figure 7 Path-length of the center of gravity (COG) (top) and the prevalence of subjects with a one-leg standing time less than 30 s (bottom) in four groups divided by the presence and absence of quadriceps (Qc) sarcopenia and visceral obesity. *F*-value for ANOVA and χ^2-test value after correction with age and sex are shown. Values of path-length COG are mean ± standard error. *$P < 0.01$ versus normal subjects free from both sarcopenia and visceral obesity. Numbers in the column indicate the number of subjects.

Recently, sarcopenic obesity has been postulated to represent a novel body composition abnormality, associated with not only metabolic alterations but also with physical functional disability in elderly subjects.[16–18] Two previous studies observed that obesity, but not sarcopenia itself, was associated with physical disability, including a shorter duration of OLS time.[12,13] In the present study, we confirmed that the combination of visceral obesity and Qc sarcopenia was associated with static postural instability. However, we also observed that Qc sarcopenia but not visceral obesity alone was associated with a short OLS time.

A major difference between the present and previous studies is that we evaluated abdominal visceral fat as a sign of obesity and Qc mass as a sarcopenic parameter. In contrast, previous studies used whole bodyfat and muscle as evaluated by DEXA. Because Qc muscle strength has been found to correlate with balance[34] and a risk of fall,[35] regional-specific evaluation of sarcopenia may provide a more direct association with related disability.

Sarcopenic obesity was first described by Baumgartner *et al.*[36] as a muscle mass index more than 2 SD below the sex-specific reference for a young, healthy population. In the present study, we defined Qc sarcopenia as Qc muscle CSA/BW more than 1 SD below the mean of a young reference group.[21] The Japanese criteria define visceral obesity as a visceral fat area of more than 100 cm^2.[22] With these definitions, 10.5% (men 12%, women 10%) of our population were classified as sarcopenic, 32% (men 38%, women 28%) as having visceral obesity and 18% (men 28%, women 11%) as having sarcopenic obesity. Due to our less stringent criteria for both visceral obesity and Qc sarcopenia, the prevalence of sarcopenic obesity in the present study is higher than in previous reports.[16–18,37] Further, high prevalence of visceral obesity, especially in men, in the

Table 4 Blood chemical data in four groups divided by the presence and absence of quadriceps sarcopenia and visceral obesity

	Normal ($n = 162$)	Sarcopenic ($n = 43$)	Visceral obesity ($n = 131$)	Sarcopenic ($n = 74$)	F	P
Total cholesterol (mg/dL)	216.9 ± 32.9	210.4 ± 33.8	219.3 ± 32.8	206.4 ± 32.3	2.8	0.04
HDL cholesterol (mg/dL)	76.1 ± 19.1	72.4 ± 18.5	61.2 ± 16.1*	56.9 ± 14.1*	29.7	<0.0001
Triglyceride (mg/dL)	82.5 ± 38.6	84.9 ± 38.9	122.8 ± 70.5*	118.4 ± 53.4*	17.6	<0.0001
Fasting glucose (mg/dL)	98.2 ± 11.0	101.3 ± 12.5	108.3 ± 28.1*	113.0 ± 24.4*	11.0	<0.0001

*$P < 0.05$ versus normal. There were no difference between visceral obesity and sarcopenic visceral obesity in any parameters examined. Mean ± standard deviation. F-values for ANOVA. HDL, high-density lipoprotein.

studied population may also explain the absence of age-related increase in visceral fat area. However, our Qc sarcopenic visceral obesity group showed impaired postural instability, indicating that the present definition using Qc CSA/BW and visceral fat area may represent a useful index in the extraction of risk subjects.

In the present study, the ratio of sarcopenic obesity to obesity (74 : 131) was significantly higher than that of sarcopenia to non-obesity (43 : 162) ($P = 0.001$). This finding may support the hypothesis that sarcopenia and obesity are pathophysiologically connected, which in turn makes them more likely to be associated than expected by chance alone.[16–18] Several causality mechanisms have been postulated to link the two conditions, including physical activity, inflammation, oxidative stress, insulin resistance, lower levels of growth hormone and testosterone, and a low protein diet. Our findings may favor some of these hypotheses, because we directly evaluated visceral fat. Although an intervention aimed at these factors has been shown to be effective,[38] a practical strategy for the prevention of this category of obesity is required.

Menopause has potential impact on body component.[39] In the present study, Qc muscle CSA/BW, visceral fat area and postural instability indices in 11 premenopausal women were not significantly different from those in postmenopausal women after correction with age (data not shown). However, it would be necessary to investigate whether menopause-related alteration of body composition has any effect on postural instability in a larger population.

Several limitations of the present study warrant mention. First, the study was a cross-sectional investigation, and was thus unable to assess causality between body composition and postural instability. Second, study participants were recruited from among anti-aging check-up examinees, and accordingly do not necessarily represent the general population. Hypnotics[40] and vitamin D[41] have been reported to show influence on postural instability. Although the use of these medications had no effects on either static postural stability and OLS time in the present study, this may be due to the finding that only a small proportion of the study subjects used these medications.

In summary, we found that Qc CSA/BW and visceral fat area were related to postural instability independently of age and sex. Subjects with sarcopenic obesity as defined by visceral fat and Qc muscle CSA/BW had a significantly higher path-length COG and higher prevalence of inability to stand for less than 30 s on one leg. Further, these findings suggest that age-related site-specific fat and muscle mass alterations are associated with functional impairment.

Acknowledgments

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