〈短　報〉

アルツハイマー型認知症の意欲の低下に対するコリンエステラーゼ阻害薬の効果

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要　約　**目的**：アルツハイマー型認知症の意欲の低下に，コリンエステラーゼ阻害薬が有効か検証する．**方法**：患者23名に対し塩酸ドネペジル5 mgを投与，前後にVitality Indexを測定し比較．**結果**：Vitality Indexは投与前7.87±0.25，投与後8.74±0.19と有意な改善がみられた．**結論**：アルツハイマー型認知症の生活の意欲の低下にコリンエステラーゼ阻害薬が有効である可能性が示唆された．

Key words：Vitality Index，donepezil hydrochloride

（日老医誌　2009；46：269–270）

認知症の診断基準には，「認知機能障害のため日常生活に支障がある」ことが含まれ，認知症の重症度判定にも，買物や排泄などの自立が含まれている．日常生活機能（ADL）は意欲の低下と密接な関連があり，意欲の向上はADL向上に先行する[1]．慢性疾患の療養環境において，意欲の低下は程度の差こそあれ例外なく認められるが，認知症において，意欲の低下は顕著である[2]．このような環境において，認知機能の低下と意欲の低下は相関する[1]．そこで今回，Vitality Indexを用い，軽症アルツハイマー型認知症に対し，Cholinesterase阻害薬である塩酸ドネペジルの効果を検討した．本文中では平均±SEMで表現した．

対象と方法：杏林大学医学部付属病院もの忘れセンター通院患者で，DSM IVによりアルツハイマー型認知症の診断基準を満たし，各種心理検査とMRI及び99mTc-ECDによる脳血流SPECTによる除外診断によってアルツハイマー型認知症とカンファランスで診断された患者23名（78.5±1.00歳）に対し，塩酸ドネペジル5 mgを投与し，前後でMini-mental State Examination；MMSE，Geriatric Depression Scale（15項目）：GDS15及びVitality Indexを測定し比較した．前後の期間は6カ月以上で平均17.4±2.6月であった．本研究は，寝たきりプロセス研究の一環として，もの忘れセンターにおける治療効果や経過などをデータを匿名化して研究に利用する同意書を得，杏林大学倫理委員会で承認されている．

結果：塩酸ドネペジル投与前後のMMSEは，19.3±0.95及び20.3±1.07で改善したものの有意差は認めなかった．投与前後のVitality Indexは7.87±0.25及び8.74±0.19で有意な（$p=0.0056$）上昇が認められた（図1）．投与前後のGDS15は5.13±0.54及び4.68±0.69と改善をみたが有意には至らなかった．

考察：アルツハイマー型認知症の意欲の低下に対する塩酸ドネペジルの効果は12週の短期観測では，意欲の向上が報告されているが[3]，6カ月以上の長期観察RCTでApathy Scaleで測定した成績では投与群が意欲が高かったものの有意差を見ていない[4]．今回，日常生活に対する意欲を客観的に測定するVitality Indexを用い，長期効果を検討したところ，有意な意欲の改善を認めた．一方，質問紙法であるGDSを用いた高齢者抑鬱尺度の検討では，自覚的抑鬱は有意な改善をみなかった．Apathy Scaleは，脳血管障害後の抑鬱，悲哀を質問紙法で自覚所見を測定するのに優れているが，アルツハイマー型認知症の場合初期の抑鬱を認めるケースと病識のない楽観的な場合があることは良く知られている．このようなケースにおいても自発的行動意欲が低下して，日常生活上の「促し」が必要になることがアルツハイマーの重症度にも記載されている．Vitality indexは認知症の客観的意欲の測定に優れているため，自発性の低下の感度に優れ，今回の結果を得たものと考える．脳内のアセチルコリン作動性ニューロンは，海馬，視床，帯状回後部

The effect of a cholinesterase inhibitor on the vitality in Alzheimer disease

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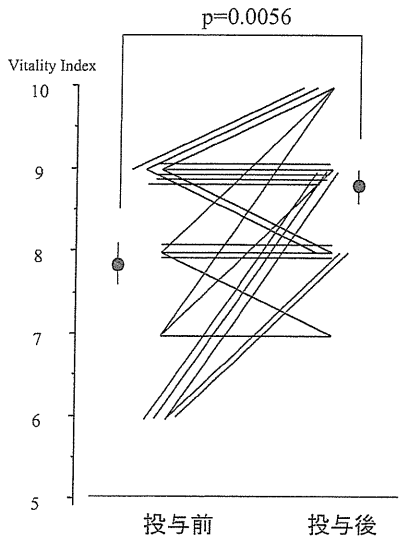

図1　ドネペジル投与前と投与後の意欲の指標の変化（n = 23）を個人ごと示す．観察期間は17.4±2.6月．Vitality Indexは，7.87±0.25から8.74±0.19へ有意に（p = 0.0056）上昇した．

などの記憶の経路だけでなく，前頭葉や頭頂葉に広がる．意欲の指標は，前頭葉眼窩面，尾状核などの血流と密接な関係が示されている[5]．今回の成績は，Cholinesterase阻害薬がアセチルコリン作動性ニューロンを介し，眼窩回を含む前頭葉症状である意欲の低下の改善が期待される結果を示したと考えられる．認知症に対する排尿誘導やリハビリテーションによってVitality Indexで測定した意欲が向上することが知られており[2]，今後Cholinesterase阻害薬の効果が発現している期間に，非薬物の併用によって，生活意欲の一層の向上をはかる試みが求められる．本研究は投与前後の比較であり，効果を判定するには限界がある．今後ランダム化した対照群をおいた研究が必要である．

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特集 転倒危険者の早期発見から予防まで —最新のエビデンスから—

総説

KEY WORD ●転倒 ●スクリーニング ●リスクファクター ●問診表 ●信頼性

1．簡単な転倒のスクリーニング手法の開発

大河内二郎

SUMMARY

本研究では，診察室などでも用いることが可能で，かつマススクリーニングにも用いることが可能な，簡便な転倒リスクのスクリーニング手法を紹介する．この手法は「過去1年に転んだことがありますか」「歩く速度が遅くなったと思いますか」「杖を使っていますか」「背中が丸くなってきましたか」「毎日お薬を5種類以上飲んでいますか」の5項目からなっている．このうち，過去1年間の転倒の既往に加え，もう1項目あれば，カットオフポイントを超えるため転倒ハイリスク者である．なお，敏感度は0.68，特異度は0.70であった．

はじめに

高齢者の転倒は，身体的な損傷を引き起こすと同時に，再転倒に対する恐怖心から活動の制限や歩行の不安定性を助長する原因となる．このため，転倒の発生や再発を予防することが重要である[1]．

転倒の発生を予防するためには，転倒を起こしやすい人をスクリーニングした上，適切な運動プログラムや環境の整備をすることが望まれる．

ところで，転倒のリスクファクターは多様である．国際生活機能分類(ICF)の考え方を借りれば，個人の機能・構造・活動と参加，そして環境，さらには個別の因子が相互に影響し合っていると考えられる[2]．

これまでの転倒ハイリスク者を発見するための研究では，対象者や目的によって，様々な因子が同定されてきた．例えばTinettiらは72歳以上の居宅高齢者における研究で，転倒の結果，外傷に至る因子として「認知機能の障害(オッズ比以下同2.2)」「2つ以上の慢性疾患を有する場合(2.0)」「歩行の障害(1.8)」「低BMI(1.8)」「女性(1.8)」を転倒と関連した因子とした[3]．

一方体力テストを用いた検討ではde Rekeneireらは，男性では，白人(1.4)，6メートル歩行速度の遅延(1.2)，椅子での起立動作の障害(1.7)，尿失禁(1.5)，下肢筋力の低下(1.5)が，女性では，ベンゾジアゼピン系薬剤の使用(1.6)，椅子からの起立動作の障害(1.4)が，それぞれ転倒のリスクと関連していると報告した[4]．このように，転倒のリスクファクターに関する論文は多数ある．わが国に適用できるように用いるために，このように転倒の多様なリスクファクターを，鳥羽らは，表1のようにまとめた[5]．この問診表の長所は，指摘された転倒リスクをほぼ網羅している点である．また，これら22項目の1カ月後の再テスト法による級内相関係数(inter-class correlation coefficient)は0.77(95%CI 0.46～0.89)と良好であり信頼性も高かった[5]．

一方この問診表は，項目数が多いという点が難点である．高齢者が在宅，施設利用にかかわらず利用でき，かつ介護保険法の地域支援事業などでは，より多くの高齢者を簡便にスクリーニングすることが必要である．そこで筆者らは，在宅および施設で使用可能であり，かつ，より簡便なスクリーニング手法を開発したので紹介する[6]．

おおこうち じろう(介護老人保健施設竜間之郷)

表1　転倒ハイリスク者の発見のための問診表

1) 過去1年に転んだことがありますか	(はい，いいえ)
はい　の場合転倒回数(　　回/年)	
2) つまずくことがありますか	(はい，いいえ)
3) 手すりにつかまらず，階段の上り下りができますか	(はい，いいえ)
4) 歩く速度が遅くなってきましたか	(はい，いいえ)
5) 横断歩道を青のうちに渡り切れますか	(はい，いいえ)
6) 1キロメートルぐらい続けて歩けますか	(はい，いいえ)
7) 片足で5秒くらい立っていられますか	(はい，いいえ)
8) 杖を使っていますか	(はい，いいえ)
9) タオルを固く絞れますか	(はい，いいえ)
10) めまい，ふらつきがありますか	(はい，いいえ)
11) 背中が丸くなってきましたか	(はい，いいえ)
12) 膝が痛みますか	(はい，いいえ)
13) 目が見えにくいですか	(はい，いいえ)
14) 耳が聞こえにくいですか	(はい，いいえ)
15) もの忘れが気になりますか	(はい，いいえ)
16) 転ばないかと不安になりますか	(はい，いいえ)
17) 毎日お薬を5種類以上飲んでいますか	(はい，いいえ)
18) 家の中で歩くとき暗く感じますか	(はい，いいえ)
19) 廊下，居間，玄関によけて通るものが置いてありますか	(はい，いいえ)
20) 家の中に段差がありますか	(はい，いいえ)
21) 階段を使わなくてはなりませんか	(はい，いいえ)
22) 生活上，家の近くの急な坂道を歩きますか	(はい，いいえ)

(文献5より引用)

方法

転倒の定義はTrompらの「意図せず地面あるいは現在いる位置より低い位置に体が着くような体位の変化」とした[7]．社会福祉士，看護師，民生委員などが，調査開始後6カ月後に転倒の有無および転倒の回数を確認した．

スクリーニング法開発のための対象者は，日本の都市部および郊外の5カ所の地域に居住する65歳以上の高齢者(1,734名)であった．認知機能が低下している場合は，家族が代わりに回答した．6カ月後の調査を完了した対象者をランダムに2分し，半分をスクリーニング法開発用サンプルとし，残りの半分を妥当性確認用のサンプルとした．まず，開発用サンプルにおいて，22項目と転倒の有無との関係をχ^2検定により検討し，有意($p<0.05$)であった項目を選択した．その後，これらの項目をロジスティック回帰分析(前向きステップワイズ選択法 $p<0.05$)を用いて再検討した．その後妥当性確認用サンプルを用いて，選択された項目の予測力をReceiver-Operating Characteristic(ROC)の下の面積を用いて検討した．最後に適切なカットオフポイントを選び，敏感度と特異度を求めた．

結果

1,734名のうち1,378名(79.5%)が基礎調査および6カ月後の転倒の調査を完了した．平均年齢は75.8歳(SD 6.8)であった．このうち208名(15.1%)が6カ月間の間に転倒した．このうち，103名(49.5%)が複数回転倒した．この1,378名をスクリーニング法開発用サンプルと妥当性確認用に折半した結果，居住地，性別，質問の回答パターンには差を認めなかったが，平均年齢は，妥当性確認用のサンプル(75.3歳)よりスクリーニング法開発用サンプル(76.2歳)の方がやや高齢であった(t-test $p<0.01$)．

スクリーニング法開発用サンプルのうち108名(15.7%)に転倒が発生し，55名(8.0%)は複

表2　ロジスティック回帰分析で選択された質問項目

	オッズ比	95%信頼区間
Q1．過去1年に転んだことがありますか＝はい	5	(2.8～7.2)
Q4．歩く速度が遅くなったと思いますか＝はい	2	(1.0～3.6)
Q8．杖を使っていますか＝はい	2	(1.1～2.8)
Q11．背中が丸くなってきましたか=はい	2	(1.1～2.8)
Q17．毎日お薬を5種類以上飲んでいますか＝はい	2	(1.0～2.7)

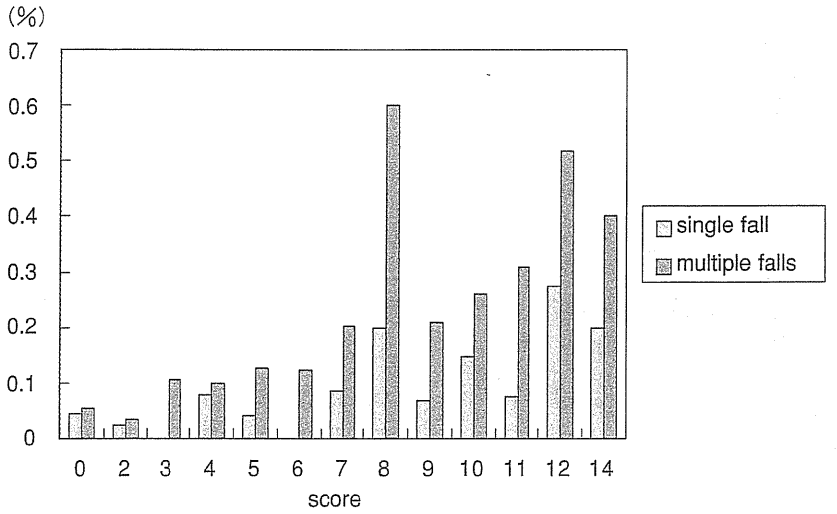

図1　転倒スコアの点数と転倒の頻度
single fall＝半年間に1回転倒
multiple falls 半年間に複数回転倒

数回転倒した．性別は転倒および複数回の転倒との関係を認めなかった．転倒発生者(平均年齢79.1歳)は，転倒発生しなかった方(平均年齢75.8歳)より高齢であった($p<0.01$)．

χ^2検定では，Q13，Q14，Q20～22以外の質問項目で転倒との関連を認めた．残りの17項目をロジスティック回帰分析で検討した結果，5項目が選択された(表2)．オッズ比を整数化し，重み付けをしたのち，それぞれの項目のスコアを算出した．この0～14点のスコアについて，妥当性確認用サンプルにおいてROC曲線の下の面積を求めたところ，74%(95%CI 69～79%)であった．これは，元の22項目のスコアの合計点数(0～22点)のROC曲線の下の面積と同程度であった(72%：95%CI 67～79%)．さらに6点をカットオフとすると敏感度0.68，特異度0.70であり，この簡易版は22項目全体を用いるよりも敏感度，特異度ともやや優れていた．

図1に点数ごとの転倒の割合を示す．6点のカットオフにおいて，陽性とされた高齢者のうち28%が6カ月以内に転倒するのに対し，6点未満の場合は7%(オッズ比3.9)であった．

まとめ

転倒のマススクリーニングに用いる目的で22項目の転倒スコアから，5項目の簡便なチェックリストを作成した．本方法は項目数が少ないが22項目による質問と同程度の検出力を伴っていた．

また，「過去1年に転んだことがありますか」「歩く速度が遅くなったと思いますか」「杖を使っていますか」「背中が丸くなってきましたか」

「毎日お薬を5種類以上飲んでいますか」の質問はいずれも診察室で容易に確認可能な情報である．これらの項目のうち，「過去1年に転んだことがありますか」に，残りの4つの項目の1項目があればカットオフ値を超えるため，転倒のリスクが高いと判断できる．

さらに興味深いことに，表1の問診表のうち，環境に関係している項目はいずれもロジスティック回帰分析では選択されなかった．これは環境に関する調査結果のバリエーションが大きく，かつ身体機能と相互作用を有しているため，頑強さに欠けたためと考えられた．

また，5項目程度であれば簡単に記憶できるので，その点も有用である．なお，転倒スコアなどによりハイリスクと判断された高齢者に対して有効である対処法は，医療機関などの受診・環境調整を含めた多職種によるケアマネジメントと，筋肉トレーニング・太極拳などが挙げられる．

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Plasma sex hormone levels and mortality in disabled older men and women

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Aim: To investigate the relationship between circulating sex hormone levels and subsequent mortality in disabled elderly.

Methods: This prospective observational study was comprised of 214 elderly subjects aged 70–96 years (117 men and 97 women; mean ± standard deviation age, 83 ± 7 years), receiving services at long-term care facilities in Nagano, Japan. All-cause mortality by baseline plasma sex hormone levels was measured.

Results: After excluding deaths during the first 6 months, 27 deaths in men and 28 deaths in women occurred during a mean follow up of 32 months and 45 months (up to 52 months), respectively. Mortality rates differed significantly between high and low testosterone tertiles in men, but did not differ significantly between middle and low tertiles. Compared with subjects in the middle and high tertiles, men with testosterone levels in the low tertile (<300 ng/dL) were more likely to die, independent of age, nutritional status, functional status and chronic disease (hazard ratio [HR] = 3.27, 95% confidence interval [CI] = 1.24–12.91). In contrast, the low dehydroepiandrosterone sulfate (DHEA-S) tertile was associated with higher mortality risk in women (multivariate adjusted HR = 4.42, 95% CI = 1.51–12.90). Exclusion of deaths during the first year and cancer deaths had minimal effects on these results. DHEA-S level in men and testosterone and estradiol levels in women were not related to mortality.

Conclusion: Low testosterone in men and low DHEA-S in women receiving care at facilities are associated with increased mortality risk, independent of other risk factors and pre-existing health conditions. **Geriatr Gerontol Int 2011; 11: 196–203.**

Keywords: dehydroepiandrosterone, disabled elderly, mortality risk, testosterone.

Introduction

Japan has the longest life expectancy at birth in the world for both men and women, although women live 8 years longer than men on average.[1,2] One explanation for this phenomenon is that estradiol production during the premenopausal years partially protects women from cardiovascular disease (CVD). In contrast, there has been a suspicion that testosterone itself is harmful; however, recent studies support the hypothesis that testosterone may be beneficial to survival in aging men.[3–8]

It is well established that endogenous androgens decline with advancing age in men.[9] Because testosterone has important physiological effects on muscle, bone, brain, erythropoietin and the vascular system, decreased testosterone levels could contribute to age-associated symptoms and diseases in older men, such as decreased muscle mass and strength,[10] impaired physical performance,[11,12] osteoporosis[13] and fractures,[12,14]

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depressed mood,[15] cognitive impairment,[16,17] anemia[18,19]and frailty.[20] In our previous study in which older persons receiving day-care services or admitted to a facility were investigated, higher plasma testosterone levels were associated with better activities of daily living (ADL), cognitive function and vitality in men.[21] On the other hand, several epidemiological studies have demonstrated that a decline in testosterone level was associated with mortality risk in community-dwelling middle-aged or older men.[3–8] In cause-specific analyses, some studies have shown that a low testosterone level was associated with an increased risk of death due to CVD.[4,5] However, the above-mentioned studies were performed in community samples of Caucasian men, and this issue remains to be clarified in frail or disabled older men.

The majority of dehydroepiandrosterone (DHEA), an endogenous steroid precursor to testosterone and estrogen, exists as the sulfated form (DHEA-S) in the circulation, and DHEA and DHEA-S are the most abundant adrenal sex steroid hormones, with concentrations reported to be more than 100-fold higher than those of testosterone and estradiol,[22] suggesting an important physiological role of DHEA(-S). Their circulating levels also peak in young adults and decline with age in both men and women. Although the role of androgens in older women's health is not fully understood, postmenopausal women with intact ovaries continue to produce androgens, DHEA and testosterone, while their production of estradiol is minimal.[23] In our previous study,[21] in older women, higher DHEA and DHEA-S levels were related to better ADL, while estradiol and testosterone levels showed no relations. Other reports have shown a correlation between DHEA level and cognitive function,[24] depression,[25] osteoporosis[26] and frailty in older women.[27] Several studies that examined the association between DHEA-S and mortality in women have shown mixed results,[28–32] and mostly found no relation; however, both low and high levels of DHEA-S at baseline[28] and some trajectory patterns such as a steep decline or extreme variability[32] have been reported to correlate with increased mortality.

These lines of evidence suggest that endogenous androgens, including testosterone and DHEA(-S), may play a role in physical and mental function as well as longevity in older individuals. We hypothesized that low plasma androgen levels could be a mortality risk factor even in elderly with disability who are receiving facility services.

Methods

Study population

In this longitudinal observational study, 218 consecutive persons aged 70 years or older (121 men aged 70–96 years and 97 women aged 70–95 years; mean ± standard deviation [SD] age, 83 ± 6 and 83 ± 5 years, respectively) who attended health service facilities for the elderly (facilities that provide nursing care and rehabilitation services to elderly people with disability, *Mahoroba-no-Sato*) located in Nagano Prefecture, Japan were enrolled. The participants were in a chronic stable condition and receiving services under Long-term Care Insurance, which is provided by the Japanese Government, either under admission or as day care. The principal exclusion criteria were malnutrition (serum albumin <3.5 mg/dL or body mass index [BMI] <16 kg/m^2), extremely low ADL status (Barthel Index[33] <50), malignancy, acute inflammation (fever, white blood cell count >10 000/μL, or other signs of infection within 4 weeks before enrollment), severe anemia (blood hemoglobin <10.0 g/dL) and overt endocrine disease because these conditions may affect both plasma sex hormone levels and mortality. Deaths that occurred during the first 6 months of follow up (four men and no women) were also excluded to minimize the influence of comorbidity on both sex hormone levels and mortality; therefore, the remaining 214 persons were analyzed in this study. The institutional review board of *Mahoroba-no-Sato* approved the study protocol, and all participants and/or their family members gave written informed consent.

Hormone measurements

Blood samples were obtained from the participants in the morning after an overnight fast, and plasma hormone levels in addition to blood cell counts and blood chemical parameters were determined by a commercial laboratory (Health Sciences Research Institute, Yokohama, Japan). Testosterone and estradiol were assayed using chemiluminescence immunoassays with minimum detection limits of 7 ng/dL (0.2 nmol/L) and 4 pg/mL (14.7 pmol/L), respectively. DHEA-S was assayed using a sensitive radioimmunoassay with a minimum detection limit of 2.0 μg/dL (0.05 μmol/L). The intra-assay coefficients of variation for these measurements were less than 5%.

Functional and anthropometric measurements

Trained nurses and physical therapists visited the participants at the health facilities and performed comprehensive geriatric assessments. Basic ADL was assessed by Barthel Index,[33] cognitive function by Hasegawa Dementia Scale – Revised (HDS-R, 30-point scale),[34] mood by the Geriatric Depression Scale (GDS, 15 items),[35] and ADL-related vitality by Vitality Index (10-point scale).[36] BMI was calculated

as weight in kilograms divided by the square of height in meters.

Comorbidity

Diseases were ascertained by experienced physicians according to pre-established criteria that combine information from self-reported physician diagnoses, medical records, current medication, clinical examinations and blood tests. Diseases included in the current analysis were hypertension, heart disease (including any of angina pectoris, myocardial infarction, congestive heart failure and arrhythmia), stroke, diabetes mellitus, osteoarthropathy (arthritis, rheumatism, osteoporosis and history of fractures), lung disease (including bronchial asthma and chronic obstructive pulmonary disease) and other chronic diseases (chronic kidney disease, gastrointestinal disease, Parkinson's disease and psychological disorders). We also obtained data on anti-androgenic treatment and intake of glucocorticoids, opiates and hormone supplements that could affect plasma hormone levels, but no subject was taking any of these.

Follow up

The subjects were followed up in 2002–2009, for a period of up to 52 months (mean ± SD, 32 ± 13 [34] months in men and 45 ± 11 [49] months in women). Time and causes of death of deceased persons were ascertained using medical records and death certificates. All deaths were registered with International Classification of Diseases, 10th version (ICD-10) codes,[37] based on the information from death certificates. We categorized deaths into the following four specific causes: (i) diseases of the circulatory system (I00–I99) including heart disease and cerebrovascular disease; (ii) diseases of the respiratory system (J00-J99); (iii) neoplasms (C00-D48); and (iv) other causes. Subjects who were alive were confirmed by checking appointment records of the facilities. Survival of 16 subjects whose records were not available was ascertained by the phone interview of each subject. Causes of death were determined for all the subjects without any missing cases.

Statistical analysis

Differences between testosterone tertiles in men and between DHEA-S tertiles in women were analyzed using ANOVA for continuous variables and χ^2-test for categorical variables. Survival was analyzed using Kaplan–Meier plots and log-rank tests. Hazard ratios (HR) for mortality were analyzed using Cox proportional hazards regression. Significance tests were two-sided, with an α-level of 0.05. Data were analyzed using SPSS statistical software.

Results

Characteristics of study subjects

Over the follow-up period, 27 men and 28 women died, yielding a mortality rate of 86.5/1000 person-years at risk in men; and 69.9/1000 person-years at risk in women. Of those, 13 deaths were due to diseases of the circulatory system (eight to ischemic and other heart disease and five to cerebrovascular disease), 10 to diseases of the respiratory system and four to cancer in men; while 14 deaths were due to diseases of the circulatory system (nine to ischemic and other forms of heart disease and four to cerebrovascular disease), eight to diseases of the respiratory system, five to cancer and two to other causes in women. Men who died were significantly older, had lower serum albumin and cholesterol, lower ADL and cognitive status, higher prevalence of heart disease, and lower testosterone level than survivors; whereas in women, subjects who died were older, had lower hemoglobin, higher prevalence of heart disease and lower plasma DHEA-S level than survivors (data not shown).

Table 1 shows the baseline characteristics of the male subjects by tertile of plasma testosterone. A significant difference was observed in serum albumin and hemoglobin levels, ADL and cognitive status among tertiles of testosterone in men. Table 2 shows the baseline characteristics of the female subjects by tertile of plasma DHEA-S. A significant difference was found in age and ADL status among DHEA-S tertiles in women, while other variables did not differ between the tertile groups.

Mortality and plasma sex hormone levels in men

As shown in Figure 1(a), Kaplan–Meier survival analysis by tertile of plasma testosterone level revealed that testosterone level was associated with mortality in men. After adjusting for age, Cox proportional hazards models showed that there was an inverse relation between testosterone level and mortality. Mortality rate differed significantly between the high and low testosterone tertiles, but not significantly between the middle and low tertiles: tertile 3 (high), reference; tertile 2 (middle), HR = 2.51 (95% confidence interval [CI] = 0.66–9.50); and tertile 1 (low), HR = 6.63 (95% CI = 1.92–23.21). Accordingly, we investigated the increased mortality in tertile 1 versus tertiles 2–3 (Table 3). Compared with subjects within tertiles 2–3,

Table 1 Association between potential confounding variables and testosterone tertiles in men

Characteristic	Testosterone tertiles T1 <10.4 nmol/L (<300 ng/dL), $n = 39$	T2 10.4–16.3 nmol/L (300–470 ng/dL), $n = 40$	T3 >16.3 nmol/L (>470 ng/dL), $n = 38$	*P*-value
Age, years	83 ± 7	83 ± 6	81 ± 6	0.11
Nutritional parameters				
Body mass index, kg/m^2	21.3 ± 3.4	22.8 ± 3.8	21.7 ± 3.0	0.21
Hemoglobin, g/dL	12.7 ± 1.9	13.8 ± 1.3	14.0 ± 1.7	<0.01
Albumin, g/dL	4.0 ± 0.3	4.1 ± 0.2	4.2 ± 0.3	<0.01
Total cholesterol, mg/dL	173 ± 38	195 ± 36	176 ± 28	0.05
Prevalent diseases, *n* (%)				
Hypertension	17 (44)	16 (40)	12 (32)	0.53
Heart disease	10 (26)	5 (13)	7 (18)	0.32
Stroke	12 (31)	15 (38)	8 (21)	0.34
Diabetes mellitus	8 (21)	5 (13)	8 (21)	0.31
Osteoarthropathy	8 (21)	9 (23)	7 (18)	0.94
Lung disease	2 (5)	3 (8)	3 (8)	0.52
Other chronic diseases	17 (44)	19 (48)	18 (47)	0.95
Functional parameters				
Barthel Index	79 ± 12	82 ± 11	87 ± 13	0.04
HDS-R	18 ± 7	19 ± 6	22 ± 5	0.02
Vitality Index	9.2 ± 1.1	9.3 ± 0.9	9.5 ± 0.9	0.46
GDS	5.0 ± 3.1	5.6 ± 3.7	5.6 ± 2.9	0.66
Sex hormone levels				
Testosterone, nmol/L	7.6 ± 2.5	13.3 ± 1.6	20.9 ± 3.9	<0.01
(ng/dL)	(219 ± 73)	(382 ± 43)	(602 ± 112)	
DHEA-S, μmol/L	1.7 ± 1.1	1.8 ± 1.6	1.7 ± 1.2	0.94
(μg/dL)	(64 ± 42)	(69 ± 57)	(63 ± 45)	

Values are shown as mean (standard deviation). Differences between the groups were analyzed using ANOVA for continuous variables and χ^2-test for categorical variables. DHEA-S, dehydroepiandrosterone sulfate; GDS, Geriatric Depression Scale; HDS-R, Hasegawa Dementia Scale – Revised.

a testosterone level within tertile 1 was associated with approximately fourfold higher mortality risk. Adjustment for age, nutritional parameters (BMI, albumin, hemoglobin, total cholesterol) and functional parameters (Barthel Index, HDS-R, Vitality Index, GDS), and prevalent diseases showed no major influence on the result. In order to examine how follow-up time and cancer impacted on the results, assuming that the subjects may have had subclinical cancer or a fatal illness at baseline, we performed further analyses excluding deaths that occurred in the first 12 months ($n = 9$) and deaths from cancer ($n = 4$). However, the significant associations remained after these exclusions (Table 3). On the other hand, DHEA-S level was not associated with mortality when DHEA-S was entered as tertiles (data not shown).

Although the statistical power was not strong enough, we studied the risk for cause-specific mortality by tertiles of testosterone level in men. Neither deaths from diseases of the circulatory system nor those from non-circulatory causes showed a significant association with testosterone tertiles (tertile 1 vs tertile 2–3, HR = 3.18, 95% CI = 1.87–11.6, $P = 0.17$; HR = 3.46, 95% CI = 0.29–7.29, $P = 0.64$, respectively).

Mortality and plasma sex hormone levels in women

As shown in Figure 1(b), a low DHEA-S level was associated with higher mortality by Kaplan–Meier survival analysis. Age-adjusted Cox proportional hazards models revealed that the association was not significant when each tertile of DHEA-S was entered as a continuous variable; however, a significant association was observed when tertile 1 was compared with tertiles 2–3 (Table 3). The association remained significant after excluding deaths that occurred in the first 12 months ($n = 2$) and deaths from cancer ($n = 5$). Moreover, further adjustment had no major influence on the result. In women, testosterone and estradiol levels were not associated with mortality when they were entered as tertiles (data not shown).

In cause-specific mortality analysis, compared with tertiles 2–3, the low tertile of DHEA-S level was associated with higher risk of death from diseases of the

Table 2 Association between potential confounding variables and DHEA-S tertiles in women

Characteristic	DHEA-S tertiles T1 <1.17 μmol/L (<43 μg/dL), *n* = 33	T2 1.17–1.49 μmol/L (43–55 μg/dL), *n* = 32	T3 >1.49 μnmol/L (>55 μg/dL), *n* = 32	*P*-value
Age, years	83 ± 6	82 ± 6	80 ± 6	0.08
Nutritional parameters				
Body mass index, kg/m^2	22.3 ± 2.7	22.5 ± 3.2	23.7 ± 2.7	0.31
Hemoglobin, g/dL	12.6 ± 1.4	12.6 ± 1.2	13.1 ± 1.1	0.16
Albumin, g/dL	4.1 ± 0.3	4.2 ± 0.3	4.3 ± 0.2	0.18
Total cholesterol, mg/dL	205 ± 30	204 ± 35	205 ± 35	0.99
Prevalent diseases, *n* (%)				
Hypertension	10 (30)	14 (44)	15 (47)	0.47
Heart disease	4 (12)	7 (22)	8 (25)	0.46
Stroke	5 (15)	4 (13)	6 (19)	0.79
Diabetes mellitus	5 (15)	4 (13)	5 (16)	0.90
Osteoarthropathy	8 (24)	11 (34)	13 (40)	0.47
Lung disease	3 (9)	2 (6)	2 (6)	0.56
Other chronic diseases	17 (52)	19 (59)	18 (56)	0.90
Functional parameters				
Barthel Index	90 ± 7	93 ± 8	95 ± 8	0.04
HDS-R	23 ± 6	22 ± 7	25 ± 5	0.39
Vitality Index	9.2 ± 1.4	9.1 ± 2.2	8.8 ± 2.9	0.35
GDS	6.8 ± 2.6	5.9 ± 3.4	6.9 ± 3.3	0.16
Sex hormone levels				
DHEA-S, μmol/L	0.8 ± 0.2	1.3 ± 0.1	2.0 ± 0.3	<0.01
(μg/dL)	30 ± 7	49 ± 4	73 ± 12	
Testosterone, nmol/L	1.2 ± 0.6	1.2 ± 0.6	1.3 ± 0.5	0.81
(ng/dL)	35 ± 17	36 ± 17	37 ± 13	
Estradiol, pmol/L	56 ± 32	57 ± 37	67 ± 46	0.41
(pg/mL)	15.3 ± 8.6	15.5 ± 10.2	18.3 ± 12.5	

Values are shown as mean (standard deviation). Differences between the groups were analyzed using ANOVA for continuous variables and χ^2-test for categorical variables. DHEA-S, dehydroepiandrosterone sulfate; GDS, Geriatric Depression Scale; HDS-R, Hasegawa Dementia Scale – Revised.

circulatory system (HR = 13.1, 95% CI = 2.39–72.3, $P < 0.01$), while there was no association with deaths from non-circulatory causes (HR = 0.93, 95% CI = 0.86–1.02, $P = 0.14$).

Discussion

In this small prospective study of Japanese elderly who were receiving care in facilities, a low testosterone level was associated with mortality in men independent of multiple risk factors and pre-existing health conditions. In addition, a low DHEA-S level in older women was related to increased mortality. In contrast, DHEA-S level in men and testosterone and estradiol levels in women were not related to mortality.

Recent prospective cohort studies in Western countries have yielded inconsistent findings about the use of a low total testosterone level as a predictor of all-cause and cardiovascular mortality in middle-aged to older men.[4,5,38,39] In the two studies that found no significant prediction of mortality,[38,39] the populations were younger (mean or median ages were in the early 50s), testosterone levels were higher and mortality rates were lower (11.6 and 15.4/1000 person-years, respectively) compared to those in studies that found positive results. In the present study, although the sample size was small, the subjects were frail and older than those in any previously reported studies, with a relatively small age range and higher mortality rate. Therefore, the relation between testosterone level and mortality might have been easier to detect in our study than in other studies with healthy middle-aged and older men.

There could be several mechanisms by which endogenous testosterone affects mortality in men. Although the number of subjects was too small to perform cause-specific analysis in the present study, other studies have reported that a low testosterone level predicted increased risk of death due to CVD.[4,5] Further, in addition to the relation to muscle strength, physical performance and ADL,[10–12,21] some but not all reports have

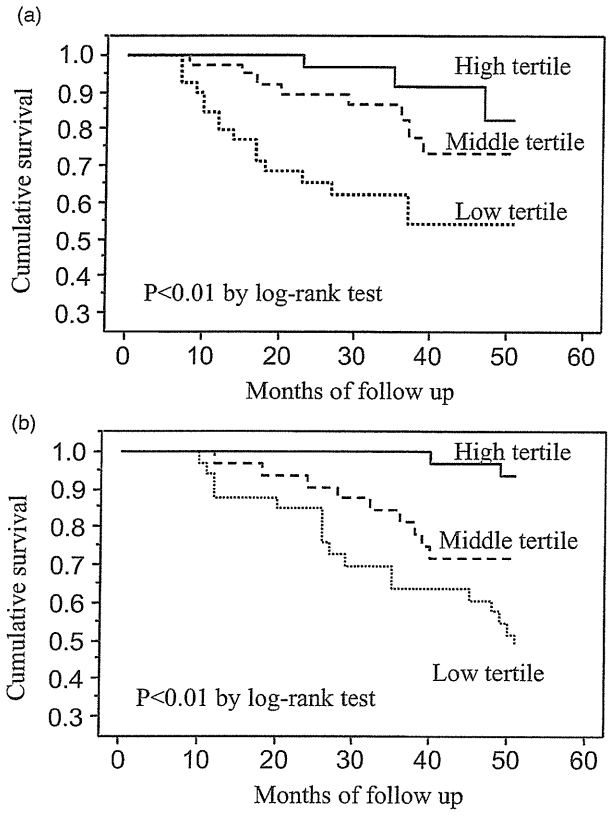

Figure 1 (a) Survival curves by tertile group of plasma testosterone level in men. (b) Survival curves by tertile group of plasma dehydroepiandrosterone sulfate level in women.

demonstrated an association between low testosterone level in older men and risk of a fall or fracture and frailty.[12–14,20] It is noteworthy that in the 10 men who died of respiratory infection, four had a history of a fall and fracture, which resulted in worse disability. Accordingly, a low testosterone level may contribute to frailty, which influences men's susceptibility to illness and falls and the capability to recover from disease or fractures, and thereby affects mortality.

Other than aging, systemic illness can result in decreased testosterone levels; therefore, low testosterone levels in older men could be attributable to acute and chronic diseases,[40] and the possible reverse causality should be considered. To evaluate this possibility, we excluded the first 12 months of observation and still found that in 12–52 months of observation, men in the low testosterone tertile had a greater risk of mortality from all causes than those in higher tertiles. We carefully excluded subjects with critical diseases and conditions at baseline, although our subjects were old with multiple chronic diseases, and it is difficult to exclude the possibility that men with subclinical critical conditions might have been included. Moreover, at baseline, there was a significant difference in functional status (ADL and cognition) and nutritional parameters (serum albumin and hemoglobin levels) between testosterone tertiles, as reported previously;[21] thus, our results need to be confirmed in a cohort with no difference in these factors between testosterone groups to exclude the influence of these biases on mortality. Also, it needs to be explored whether low testosterone in older men plays a pathogenic role, such as affecting the immune system, developing physical frailty and depression, or simply serves as a marker for biological vulnerability and poor prognosis. Long-term studies also need to test whether testosterone treatment should yield clinically significant improvements in mortality in appropriately selected older men, with consistent symptoms and signs and unequivocally low serum testosterone levels.

Low DHEA-S has been associated with increased all-cause and cardiovascular mortality in older men;[26,27,41] however, no association was found in the present study. Because DHEA(-S) is an inactive prohormone and we and others have found an association between testosterone and mortality,[3–8] it is suggested that testosterone could be a stronger predictor of mortality in older men.

On the other hand, a low DHEA-S level in older women was associated with a poor prognosis after adjusting for multiple factors related to mortality. Other previous reports showed an inconsistent relationship between DHEA-S level and mortality in older women,[29–31] possibly due to differences in the cohorts including age, DHEA-S level, heterogeneity of health status and mortality rate, and the method of statistical analysis used to demonstrate the relationship, regression models with linear/non-linear assumption.

Previous studies support a potential physiological role of DHEA-S, which could contribute to reduced mortality, an anti-inflammatory action and immune regulatory activity.[42] However, there are still many unanswered questions regarding DHEA's role in aging, and there is insufficient evidence to support DHEA replacement for increasing longevity in older women. It also needs to be explored whether the DHEA-S level contributes to mortality or is merely a biomarker of the underlying health condition of older women.

Our study has some limitations. First, the sample size was too small to reach a clear conclusion with strong statistical power, thus limiting the precision of the estimates, which is reflected in the broad range of HR for mortality. Second, the results are based on single measurements of sex hormones, which do not allow assessment of changes in levels over time; therefore, they may overestimate or underestimate the association between hormone levels and mortality. Third, we did not measure estradiol levels in men, although it would have been helpful to see whether the effects of testosterone on mortality are mediated by testosterone itself or by aromatization to estradiol in older men. Finally, active forms of testosterone such as bioavailable and

Table 3 Hazard ratios for low tertile 1 vs tertiles 2–3 of plasma sex hormone levels for all-cause mortality in men and women

	Unadjusted	Model 1	Model 2
Men (n = 117)			
HR of low testosterone for mortality	3.83 (1.74–8.40)**	3.71 (1.54–8.04)**	3.27 (1.24–12.91)*
Excluding first-year deaths (n = 108)	3.81 (1.53–6.93)**	3.49 (1.14–7.39)**	3.08 (1.11–13.62)*
Excluding deaths from cancer (n = 113)	4.18 (1.77–9.86)**	4.03 (1.70–9.58)**	5.02 (1.51–15.41)*
Women (N = 97)			
HR of low DHEA-S for mortality	3.77 (1.77–8.07)**	3.86 (1.79–8.32)**	4.42 (1.51–12.90)*
Excluding first-year deaths (n = 95)	3.38 (1.55–7.37)**	3.43 (1.56–9.54)**	3.58 (1.12–11.46)*
Excluding deaths from cancer (n = 92)	3.82 (1.69–8.60)**	3.55 (1.54–8.19)**	3.92 (1.28–11.98)*

*P < 0.05; **P < 0.01 vs reference group (tertile 2–3). Values are expressed as HR (95% CI). Model 1, adjusted for age; Model 2, adjusted for age, nutritional parameters, functional parameters and prevalent disease. DHEA-S, dehydroepiandrosterone sulfate; HR, hazards ratio.

calculated free testosterone were not measured, because a direct assay of bioavailable testosterone or an assay of sex hormone binding globulin, which is necessary for free testosterone calculation, is not available in Japan. However, because most of the above-mentioned previous reports have shown an association of total testosterone with mortality, the fundamental findings might not have differed if active forms of testosterone had been analyzed.

In conclusion, a low testosterone level in men and a low DHEA-S level in women are associated with increased mortality risk, independent of multiple risk factors and several pre-existing health conditions in disabled elderly. To our knowledge, the present study is the first that showed testosterone as a predictor of mortality in Asian men. Also, this is the first study that investigated frail or disabled older persons receiving care at facilities. Our results imply the clinical importance of measuring plasma androgen levels even in disabled elderly to estimate their prognosis.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Association of plasma sex hormone levels with functional decline in elderly men and women

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Aim: We aimed to determine whether plasma sex hormone levels are associated with activities of daily living (ADL), cognition, depression and vitality in elderly individuals with functional decline.

Methods: Two hundred and eight consecutive persons 70 years or older (108 men and 100 women; mean ± standard deviation, 81 ± 7 years) with a chronic stable condition, receiving long-term care at a long-term care facilities located in Nagano Prefecture, Japan, were enrolled. Plasma total testosterone, free testosterone (only in men), dehydroepiandrosterone (DHEA), DHEA sulfate (DHEA-S) and estradiol levels were determined in the morning after an overnight fast. Comprehensive geriatric assessment was performed including basic ADL by Barthel Index, instrumental ADL, cognitive function by Hasegawa Dementia Scale – Revised, mood by Geriatric Depression Scale and ADL-related vitality by Vitality Index.

Results: Simple regression analysis showed that, in men, plasma total and free testosterone levels were associated with basic ADL ($R = 0.292$ and $R = 0.282$), instrumental ADL ($R = 0.261$ and $R = 0.408$), cognitive function ($R = 0.393$ and $R = 0.553$) and vitality ($R = 0.246$ and $R = 0.396$), while DHEA(-S) was associated with cognitive function, and estradiol with cognitive function as well as vitality. In women, the only significant correlation was between DHEA(-S) and basic ADL. Adjustment for age and nutritional markers did not influence the associations of plasma sex hormone levels with functional scores except for that of free testosterone with Barthel Index.

Conclusion: These results suggest that sex hormones have sex-specific associations with physical and neuropsychiatric functions in elderly individuals, and that endogenous testosterone is related to global function in elderly men.

Keywords: activities of daily living (ADL), comprehensive geriatric assessment, dehydroepiandrosterone sulfate, estradiol, testosterone.

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Introduction

In addition to the abrupt reduction in estrogen production in women during the menopause, both men and women experience an age-associated decrease in the levels of androgens.[1–3] Physical and neuropsychiatric

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function also declines with age; however, the association of sex hormones with functional decline is not fully understood. One nursing home study found that a higher total testosterone (T) level was associated with better activities of daily living (ADL) performance such as transferring and eating among frail elderly men, while estrone and dehydroepiandrosterone (DHEA) levels were inversely related to ADL in women.[4] Although several observational studies examining the relationship between endogenous androgen and cognitive function in elderly men have also been published,[5–8] most surveys have investigated only a few aspects of functions rather than the whole spectrum and have been carried out based on community samples of white people in Western countries. In addition, many studies are restricted to one sex and few have focused on frail or disabled elderly individuals.

Thus, additional data are needed to elucidate the relationship between plasma hormone levels and functional status in elderly individuals with functional decline to better understand the application of hormone replacement therapy to bring about the most beneficial effects. In our preliminary study in a small sample of frail elderly men, a higher plasma T level was associated with higher functional scores.[9] To extend this pilot study, we included a larger sample of elderly men and women with functional decline, and evaluated whether sex hormone levels, including DHEA sulfate (DHEA-S) and estradiol, are associated with functioning on the basis of comprehensive geriatric assessment.

Methods

Study design and participants

In this cross-sectional observational study, 208 consecutive persons aged 70 years or older (108 men aged 70–95 years and 100 women aged 70–93 years; mean ± standard deviation, 82 ± 7 and 81 ± 6 years, respectively) who attended health service facilities for the elderly (facilities that provide nursing care and rehabilitation services to elderly people with disability, "Mahoroba-no-Sato") located in Nagano Prefecture, Japan, were enrolled. The participants were in a chronic stable condition and receiving Long-term Care Insurance either for facility admission or day-care service. The principal exclusion criteria were malnutrition (serum albumin, <3.5 mg/dL), extremely low ADL status (Barthel Index,[10] <50), malignancy, acute inflammation (fever, white blood cell count of >10 000/mL, or other signs of infection within 4 weeks before enrollment), severe anemia (blood hemoglobin, <10.0 g/dL) and overt endocrine diseases because these diseases may affect both plasma sex hormone levels and functions. The following information was collected from medical history charts or by interviewer-administered questionnaire; past medical history, present diagnosis of any disease, medication and nutritional intake. Comorbid conditions included in the current analysis were hypertension, chronic heart disease (angina, myocardial infarction, congestive heart failure, arrhythmia), stroke, osteoarthropathy (arthritis, rheumatism, osteoporosis, history of fractures) and diabetes mellitus. We also obtained data on anti-androgenic treatment or intake of glucocorticoids, opiates or hormone supplements which could affect plasma hormone levels, but no subject was taking any of these. The institutional review board of Kikyogahara Hospital approved the study protocol, and all participants or their families gave written informed consent.

Hormone measurements

Blood samples were obtained from the participants in the morning after an overnight fast, and plasma hormone levels, in addition to blood cell counts and blood chemical parameters, were determined by a commercial laboratory (Health Sciences Research Institute, Yokohama, Japan). Free-T, DHEA-S and DHEA were assayed using sensitive radioimmunoassays. Total-T and estradiol were assayed using chemiluminescence immunoassays with minimum detection limits of 7 ng/dL (0.2 nmol/L) and 4 pg/mL (14.7 pmol/L), respectively. The intra-assay coefficients of variation for these measurements were less than 5%.

Functional and anthropometric measurements

Trained nurses and physical therapists visited the participants at the health service facilities and performed comprehensive geriatric assessments. Basic ADL was assessed by Barthel Index,[10] instrumental ADL (IADL) by Lawton and Brody's IADL,[11] cognitive function by Hasegawa Dementia Scale – Revised (HDS-R, 30-point scale),[12] mood by Geriatric Depression Scale (GDS, 15 items)[13] and ADL-related vitality by Vitality Index (10-point scale).[14] In the current study, three items (food preparation, household tasks and laundering) were removed from the original version of Lawton and Brody's IADL scale to assess men; thus, IADL scale ranged 0–5 points in men and 0–8 in women. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Statistical analysis

Data were analyzed using SPSS statistical software (version 11.0). Data were compared between men and women using the Student's *t*-test for continuous variables and χ^2-tests for categorical variables. Pearson's simple correlation coefficients were determined by plasma sex hormone levels, age and functional

measures. Standardized regression coefficients from multivariate linear regression analysis of functional measurements in relation to age, nutritional markers and plasma hormone levels were determined. An unpaired Student's *t*-test was used for the differences in hormone levels and functional status according to associated diseases. $P < 0.05$ was considered statistically significant.

Results

The characteristics of the study subjects are presented in Table 1. Sex differences were found in the levels of hemoglobin and total cholesterol, and also in the percentage of subjects with heart disease and stroke. On average, subjects showed mild-to-moderate functional decline, and scores of Barthel Index, HDS-R and Vitality Index were higher in women than in men. Plasma level of total-T in male cohorts was lower than that reported in healthy elderly men,[15] but comparable to those in frail elderly men.[4] All plasma hormone levels were significantly higher in men than in women.

In simple regression analysis, age was negatively correlated with most of the functional scores except for instrumental ADL and GDS in men and GDS in women (data not shown). Because an age-associated decline of plasma sex hormone levels[1–3] and an influence of nutritional status on hormone levels[16,17] have been reported, we analyzed the correlations between hormone levels, age and BMI (Table 2). However, only free-T in men was significantly associated with age, and only total-T in women was correlated with BMI. Because DHEA, testosterone and estradiol have precursor-metabolite relationships in the steroid-hormone biosynthesis cascade, we evaluated the correlations between each of the plasma hormone levels (Table 2). Some, but not all, plasma sex hormone levels showed significant correlations in both sexes.

Table 1 Distribution of variables in study subjects

	Men	Women
No. of subjects	108	100
Age, years	82 ± 7 (70–95)	81 ± 6 (70–93)
Nutritional parameters		
Body mass index, kg/m^2	21.8 ± 3.3 (15.1–29.0)	22.9 ± 3.8 (16.0–33.6)
Hemoglobin, g/dL	13.7 ± 1.7 (10.4–18.7)	12.8 ± 1.3 (10.0–15.6)**
Albumin, g/dL	4.2 ± 0.3 (3.5–4.9)	4.2 ± 0.3 (3.5–4.9)
Total cholesterol, mg/dL	181 ± 32 (119–273)	205 ± 33 (126–288)**
Chronic diseases		
Hypertension, *n* (%)	31 (28.7)	36 (36.0)
Heart disease, *n* (%)	9 (8.3)	19 (19.0)*
Stroke, No. (%)	35 (32.4)	19 (19.0)*
Osteoarthropathy, *n* (%)	23 (21.3)	31 (31.0)
Diabetes mellitus, *n* (%)	10 (9.3)	14 (14.0)
Functional parameters		
Barthel Index	84 ± 17 (50–100)	93 ± 9 (60–100)**
Instrumental ADL†	2.6 ± 2.0 (0–5)	5.9 ± 2.3 (0–8)
HDS-R	19 ± 7 (2–30)	23 ± 6 (5–30)**
Vitality Index	9.2 ± 1.1 (5–10)	9.7 ± 0.6 (6–10)**
GDS	5.6 ± 3.2 (0–13)	5.4 ± 3.0 (0–13)
Hormones		
Total testosterone, nmol/L	14.8 ± 5.8 (2.5–30.5)	1.3 ± 0.6 (0.2–2.9)**
Free testosterone, pmol/L	22.2 ± 8.7 (3.1–43.4)	
DHEA-S, μmol/L	1.75 ± 1.18 (0.26–5.47)	1.34 ± 0.54 (0.38–2.70)**
DHEA, nmol/L	7.63 ± 3.82 (2.43–25.7)	4.86 ± 2.08 (1.04–11.1)**
Estradiol, pmol/L	109.4 ± 48.1 (14.7–228.0)	59.5 ± 38.9 (14.7–206.7)**

Probability values of chronic diseases were compared between men and women by χ^2-test; *$P < 0.05$. Age, nutritional parameters, functional parameters (except for instrumental ADL) and hormone measurements were compared between men and women by Student's *t*-test; **$P < 0.001$. Values except those for chronic diseases are shown as mean ± standard deviation (range). †Lawton and Brody's instrumental ADL scale ranges 0–5 points in men and 0–8 in women, respectively. ADL, activities of daily living; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; GDS, Geriatric Depression Scale; HDS-R, Hasegawa Dementia Scale – Revised.

Table 2 Correlation between plasma sex hormone levels, age and body mass index

	Age	BMI	Total-T	Free-T	DHEA-S	DHEA	Estradiol
Men							
Age	–	0.035	−0.121	−0310**	−0.254	−0.111	−0.047
BMI		–	0.006	0.026	−0.177	−0.151	−0.055
Total-T			–	0.672***	0.043	0.075	0.476***
Free-T				–	0.468***	0.392**	0.414***
DHEA-S					–	0.382**	0.342*
DHEA						–	0.084
Estradiol							–
Women							
Age	–	−0.187	0.079		−0.062	0.017	−0.028
BMI		–	0.320*		0.121	−0.070	0.040
Total-T			–		0.202*	0.355**	0.162
DHEA-S					–	0.561***	0.131
DHEA						–	0.097
Estradiol							–

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. All data are presented as Pearson correlation coefficients. BMI, body mass index; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; Free-T, free testosterone; Total-T, total testosterone.

We also assessed whether plasma hormone levels were different between individuals with or without chronic diseases including hypertension, heart disease, cerebrovascular disease, osteoarthropathy and diabetes mellitus, using a Student's *t*-test, but there were no significant differences in hormone levels according to these conditions (data not shown). On the other hand, a significant difference was observed in Barthel Index scores between subjects with and without cerebrovascular disease in men (77 ± 16 vs 86 ± 16, $P < 0.01$).

The associations between plasma hormone levels and functional scores were evaluated. As shown in Table 3, in men, plasma total-T and free-T levels were positively correlated with functional scores except for GDS. DHEA(-S) and estradiol were positively correlated with cognitive function, and DHEA and estradiol were associated with Vitality Index as well. In contrast, in women, a significant correlation was observed only between DHEA(-S) and Barthel Index.

Multiple regression analysis revealed that the associations between sex hormones and functions were independent of age and BMI except that the associations between free-T and Barthel Index in addition to DHEA and vitality were not significant after adjustment. The statistical results were similar when serum albumin or total cholesterol was entered into the regression model instead of BMI (data not shown).

Because all measured sex hormones were associated with HDS-R in men, we entered free-T, DHEA-S and estradiol into the regression model as covariates in addition to age and BMI (Table 4). Free-T remained a significant determinant of HDS-R, while DHEA-S and estradiol did not hold a significant association with HDS-R. When a stepwise model (forward selection) was used to test for the determinants for HDS-R with the same five covariates, the *P*-value for the regression was minimized when only free-T was chosen as a variable ($R^2 = 0.227$, overall *P*-value for the regression <0.05).

Discussion

The present study demonstrated that men with higher plasma T levels had better ADL, cognitive function and vitality. Also, a higher estradiol level was related to better cognitive function as well as vitality, and a higher DHEA(-S) level was related to better cognitive function. In women, DHEA(-S) level was related to higher basic ADL, but T and estradiol levels showed no correlation with functional scores. The positive associations between sex hormones and functional scores were independent of age and nutritional status, suggesting that plasma sex hormone levels, especially that of testosterone in men, are independently related to functional status in elderly individuals.

Concerning cognitive function, our findings are consistent with the results of the previous observational studies examining the relationship between endogenous androgen and cognitive function in elderly men.[5,7,8] Several interventional studies have shown an improvement in spatial cognition and working memory after treatment with T, suggesting that T might have a beneficial effect on cognitive function.[18–21] Also, DHEA(-S), the most abundant circulating steroid in both sexes and the biosynthetic precursor of T, has been shown to have neurotrophic and neuronal remodeling activity.[22,23]

Table 3 Linear regression model of hormone levels on functional scores unadjusted and adjusted for age, and age and body mass index

	Total-T	Free-T	DHEA-S	DHEA	Estradiol
Men					
Unadjusted					
Barthel Index	0.292**	0.282**	0.094	−0.058	0.110
Instrumental ADL	0.261*	0.408**	0.239	0.140	0.129
HDS-R	0.393***	0.553***	0.390*	0.393**	0.266*
Vitality Index	0.246*	0.396***	0.210	0.297*	0.291*
GDS	−0.103	−0.097	−0.181	−0.027	−0.060
Adjusted for age					
Barthel Index	0.250**	0.183	0.044	−0.077	0.107
Instrumental ADL	0.255*	0.402***	0.216	0.137	0.124
HDS-R	0.366***	0.488***	0.317*	0.361**	0.243*
Vitality Index	0.218*	0.348***	0.160	0.176	0.288*
GDS	−0.068	−0.065	−0.146	−0.024	−0.005
Adjusted for age and BMI					
Barthel Index	0.281**	0.112	0.101	0.109	0.114
Instrumental ADL	0.229*	0.414**	0.314*	0.400*	0.053
HDS-R	0.340**	0.443**	0.329*	0.480**	0.236*
Vitality Index	0.285*	0.321*	0.140	0.227	0.292*
GDS	−0.067	−0.015	−0.013	0.002	0.079
Women					
Unadjusted					
Barthel Index	0.085		0.280*	0.293*	−0.068
Instrumental ADL	−0.050		0.071	0.171	0.071
HDS-R	−0.051		0.080	−0.034	0.121
Vitality Index	−0.076		0.167	0.091	0.043
GDS	0.004		−0.087	−0.014	0.052
Adjusted for age					
Barthel Index	0.120		0.225*	0.288*	−0.068
Instrumental ADL	−0.003		0.041	0.166	0.052
HDS-R	−0.028		0.038	−0.037	0.120
Vitality Index	−0.060		0.140	0.089	0.043
GDS	−0.008		−0.066	−0.012	0.052
Adjusted for age and BMI					
Barthel Index	0.142		0.269*	0.221*	0.035
Instrumental ADL	−0.067		0.092	0.178	0.046
HDS-R	−0.110		0.045	−0.051	0.106
Vitality Index	−0.103		0.137	0.043	0.104
GDS	0.063		−0.020	0.038	0.056

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Data are presented as standardized regression coefficients. ADL, activities of daily living; BMI, body mass index; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; Free-T, free testosterone; GDS, Geriatric Depression Scale – 15 items; HDS-R, Hasegawa Dementia Scale-Revised; Total-T, total testosterone.

In addition, our recent study showed that a low plasma T level is related to endothelial dysfunction in middle-aged men,[24] suggesting a mechanistic link between T and cerebrovascular function.

With respect to mood, although some large scale epidemiological studies[25,26] failed to show a clear correlation between T and depression in middle-aged men, another study has shown that low T levels are associated with depression in healthy elderly men.[27] The reason is unknown but it might be due simply to the cohort difference between community-dwelling healthy men and frail elderly men, or to the low reliability of GDS in demented people.[14] In the current study, in men, estradiol was also associated with cognitive function and vitality. However, multiple regression analysis with both free-T and estradiol as covariates suggested that estradiol is merely a marker as a metabolite of androgens and does not exert a direct action on neuropsychiatric

Table 4 Multiple regression analysis on cognitive function with free-T, DHEA-S and estradiol as covariates in addition to age and BMI in men

	HDS-R	
	β	*P*
Age	−0.346	0.087
BMI	0.091	0.649
Free-T	0.466	0.030
DHEA-S	0.011	0.964
Estradiol	−0.213	0.321

β, standardized regression coefficient; BMI, body mass index; DHEA-S, dehydroepiandrosterone sulfate; Free-T, free testosterone; HDS-R, Hasegawa Dementia Scale – Revised.

function in men consistent with the results of cross-sectional studies.[5,7,8]

Because T has anabolic effects on muscle and may improve cognition, our findings on the association of T with ADL are not surprising. While several observational studies have demonstrated the correlation of endogenous testosterone with muscle mass and strength[28–31] and physical performance[4,32] in older men, interventional surveys have provided mixed findings[33–38] and the studies using healthy men have found only increased muscle mass and strength but not improved physical function.[35–38] In addition, results of studies investigated the correlation between endogenous testosterone and fall risks are inconsistent.[30,32] Future interventional studies enrolling frail and/or disabled elderly men might clarify the causal relationship between testosterone and frailty. Although the correlation between sex hormones and physical function or ADL in women is contradictory across studies,[39–43] our findings are consistent with one report showing that the plasma level of DHEA(-S) is related to basic ADL in middle-aged to elderly women.[39]

The explanations for the sex difference in the correlation between hormones and function could be due to sex differences in hormone secretion and metabolism.[41,44,45] In fact, plasma estradiol level in women was approximately half of that in men, and distributed in a narrow range (52% cases fell into a range of 14.7–53.1 pmol/L), providing a possible explanation for no association of estrogen levels with functioning in women. Measurement of active forms of estrogens such as free or bioavailable estradiol, although the assays are not available in Japan, might show some significant correlations with functional levels; however, most of the previous studies investigating the relationship between endogenous estrogen levels and physical performance or cognitive function in postmenopausal women, including one study that measured bioavailable estradiol levels, found negative results.[46–50] Accordingly, in the ranges of circulating endogenous hormone levels, estradiol may not be related to functional levels in older women. On the other hand, information on the sex-specific distribution of steroid hormone receptors is limited. Recently, Bezdickova *et al.* reported that nuclear androgen receptor staining was observed in the mammillary body, precentral gyrus and hippocampus in the human male brain but not in the female brain.[51] The sex difference in the correlation between hormones and functions should be further determined based on the ligand–receptor relationship.

The limitations of our study should be acknowledged. First, we cannot exclude an influence of the associated diseases or the comorbid condition on our results, although no significant differences were observed in hormone levels or functional status in subjects with or without chronic diseases, except that the Barthel Index was significantly lower in male subjects with cerebrovascular disease. Second, only free-T was measured as the active form of T by radioimmunoassays instead of bioavailable or calculated free-T, because sex hormone-binding globulin and direct assays of bioavailable T were not available. Finally, it should be recognized that our results were obtained from a cross-sectional study and do not provide direct evidence of a causal relationship; therefore, it is possible that high sex hormone levels were the result of enhanced physical or mental health.

In summary, our cross-sectional survey revealed that sex hormones have sex-specific relationships with physical and neuropsychiatric function in elderly individuals. In men, endogenous androgen is independently associated with ADL, cognitive function and vitality. Although it has been reported that testosterone or DHEA supplementation in healthy elderly men did not affect physical or cognitive function,[37,38] our findings suggest that elderly men with functional decline could be a better target for androgen replacement to improve physical and cognitive function.

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