ないように速く漕ぐようにと説明した．測定開始時には「全力で漕いで，それを15秒間保つように」と教示し，測定中は目標ステップ数が維持できるように「そのまま維持するように」と声掛けを行った．測定回数はそれぞれ1回とし，施行間は3分以上の休憩を挟み，口頭にて疲労感がないことを確認した．60 step，90 stepの施行順はコイントスにてランダムに設定した．駆動時のパワー（仕事率；W）は，解析ソフト（SpErgo2，酒井医療株式会社，日本）を用い，駆動開始からサンプリング周波数1Hzにて測定した．目標ステップ数に達した後の最大値をピークパワーとした．

駆動時の筋活動は，表面筋電図測定装置（Noraxon MyoTrace400，酒井医療株式会社，日本）を用い，サンプリング周波数を1000Hzとし，パワーの測定開始と筋電図測定を手動にて同期させて測定を行った．筋電位の信号をA/D変換し，パーソナルコンピュータに取り込んだ後，専用ソフト（Noraxon MyoResearch XP，酒井医療株式会社，日本）を用い，データの抽出を行った．被検筋は右下肢の内側広筋（VM），半腱様筋（ST），前脛骨筋（TA），腓腹筋内側頭（MG）の4筋とした．皮膚前処置剤およびアルコール綿にて処置を行った後，電極中心距離を2 cmとし，電極Blue sensor(ambu社，デンマーク）を筋線維の走行に沿って貼り付けた．電極貼り付け位置は，内側広筋は膝蓋骨上端から内側2～3横指の位置，半腱様筋は坐骨結節と脛骨内側顆を結ぶ線の遠位3分の1の位置，前脛骨筋は腓骨頭より内下側3～4横指の位置，腓腹筋内側は脛骨内側顆と踵骨を結ぶ線の近位3分の1の位置，アース電極は大腿骨外側上顆とした[19]．駆動時の筋収縮は，安静時の基線の平均＋2標準偏差を超えた時点を筋収縮とした．SpErgo2によるパワーおよびステップ数のグラフから，ピークパワーにおける時間を得た後，その時間を含む6駆動分の筋収縮を選択した．各々ピークパワーを発揮する時間は異なっており，ピークパワーから駆動終了までの間で，波形が安定している連続した駆動における筋の活動特性を比較するため，6駆動分を解析区間とした．すなわち60 step（1stepあたり1秒）の場合は6秒間，90 step（1stepあたり0.67秒）の場合は4秒間を解析区間とした．

6駆動分のデータは数値解析ソフトウェアScilab Ver.5.3.1（INRIA，フランス）を使用し，wavelet toolboxのプログラムを利用しmorlet関数を用いた連続ウェーブレット変換によるパワースペクトル解析を行った．解析周波数帯域は先行研究[20]に準拠し，11～200Hzとし，時間成分ごとのパワーを平均化した後，6駆動分のパワーの総和（Total power：以下TP）および45Hz以下の低周波帯域のパワーの合計（Low Frequency：LF），75Hz以上を高周波数帯域（High Frequency：HF）としたパワーの合計を算出した．そこからTPに対する低周波帯域の割合（LF/TP），高周波帯域の割合（HF/TP），および下記の式を用いて平均パワー周波数（Mean Power Frequency：MPF）を算出し，それぞれ分析対象とした．

$$MPF = \int_0^\infty fP(f)\,df \Big/ \int_0^\infty P(f)\,df \qquad P：\text{power値}，\ f：\text{周波数}$$

統計学的解析には，各変数に対しShapiro-Wilk検定を行い，正規性を確認できない変数が含まれていたため，ノンパラメトリック検定を使用した．各step数におけるピークパワーと各筋の活動特性との関係を調べるため，Spearmanの順位相関係数を算出した．また，60 stepと90 stepの駆動における筋の活動特性を比較するため，Wilcoxonの符号付順位和検定を行った．統計学的有意水準は5%とし，統計解析ソフト（IBM SPSS Statistics 19，日本IBM，日本）を用いた．

III. 結　果

60 step時のピークパワーの平均値は327.1 ± 42.8Wであり，90 step時のピークパワーの平均値は259.6 ± 84.0Wであった（表1）．60 step時のピークパワーと相関関係にあった変数は，前脛骨筋のMPF（$\rho = -.769$，$p < 0.01$），HF/TP（$\rho = .580$，$p < 0.05$）および前脛骨筋のLF/TP（$\rho = -.615$，$p < 0.05$）であった（表2）．一方で，90 step時のピークパワーは，有意な相関が認められなかった．MPFは，内側広筋，前脛骨筋ともに60 step時よりも90 step時の方が有意に高かった（それぞれ$Z = -2.510$，$p < 0.05$，$Z = -3.059$，$p < 0.01$）．LF/TPは，内側広筋，前脛骨筋ともに60 step時よりも90 step時の方が有意に低かった（それぞれ$Z = -2.353$，$p < 0.05$，$Z = -2.667$，$p < 0.01$）．HF/TPは，内側広筋，前脛骨筋ともに60 step

表2　ピークパワーと筋の活動特性との相関係数

	年齢	BMI	内側広筋			半腱様筋			前脛骨筋			腓腹筋（内側）		
			MPF	LF/TP	HF/TP	MPF	LF/TP	HF/TP	MPF	LF/TP	HF/TP	MPF	LF/TP	HF/TP
60 step時のピークパワー	.029	−.161	.070	−.098	.154	.035	−.336	.140	−.769**	.580*	−.615*	.007	.091	−.021
90 step時のピークパワー	−.298	−.378	.147	−.273	.364	−.336	.140	−.301	−.329	.371	−.462	.084	.140	−.098

※spearman's ρ，* : $p<0.05$，** : $p<0.01$

表3 60 stepと90 stepの駆動における筋の活動特性の差

	内側広筋			半腱様筋		前脛骨筋			腓腹筋(内側)	
	60 step	90 step		60 step	90 step	60 step	90 step		60 step	90 step
MPF (Hz)	84.5 ± 12.2	92.4 ± 13.5	*	104.3 ± 15.9	103.7 ± 13.4	84.7 ± 6.7	95.3 ± 10.5	**	107.6 ± 10.4	112.7 ± 13.4
LF/TP (%)	36.3 ± 9.0	31.3 ± 8.4	*	20.4 ± 9.1	19.2 ± 7.8	31.8 ± 5.0	26.4 ± 6.4	**	15.7 ± 5.5	13.7 ± 5.2
HF/TP (%)	49.1 ± 10.2	54.6 ± 9.5	*	65.2 ± 12.9	66.5 ± 10.6	49.4 ± 6.1	57.7 ± 8.6	**	70.2 ± 7.5	73.0 ± 9.3

※ * : $p<0.05$, ** : $p<0.01$

時よりも90 step時の方が有意に高かった（それぞれ$Z=-2.197$, $p<0.05$, $Z=-2.981$, $p<0.01$）(表3).

IV. 考 察

これまでステップエルゴメーター駆動は，サイクルエルゴメーターと比較し，大腿四頭筋の筋活動が高いことが知られている[21]ものの，ピークパワーまでの過程で，どの筋がどの程度活動しているかという部分は明らかにされていなかった．筋活動に参加している筋線維タイプとパワースペクトルの関係では，40Hz以下の低周波域はtype I線維，46～80Hzの中周波数帯域はtype IIa線維，81Hz以上の高周波数帯域ではtype IIb線維の活動に対応し[13]，低周波数帯域は遅筋系，高周波数帯は速筋系の活動を反映しているといわれている[22]．MPFは筋疲労の指標として用いられることが多く，疲労によりMPF低下が生じることが明らかにされている[20]．今回は，短時間の駆動での解析であり，筋疲労ではなく駆動条件による筋の活動特性の違いを検討するために，MPFを解析値として使用した．また，活動における低周波数成分と高周波数成分の相対的な割合を比較するために，LF/TPとHF/TPを解析値として使用した．

本研究の結果より，60 step時のピークパワーでは，前脛骨筋のMPF，およびHF/TPとの間にそれぞれ有意な負の相関が認められ，LF/TPとの間には有意な正の相関が認められた．60 step駆動時の前脛骨筋による低周波数帯域の筋活動の高さと，高周波数帯域の筋活動の低さ，すなわちMPFの低さとピークパワーの高さが関連していることから，強い力を発揮するよりも遅筋線維を中心とする駆動時の持続的な足関節固定のための筋活動が高まり，安定したステップ運動が可能になることにより高いパワーを発揮することに繋がったと推察された．また，多機能エルゴメーター（ストレングスエルゴ）の研究では，駆動速度が高まると屈曲相の前脛骨筋の活動が高まり，下肢引き上げの補助的作用や足関節背屈位による駆動を円滑にする作用が生じると述べられており[23]，ステップエルゴメーター駆動においても前脛骨筋に関しては多くの対象者で類似の作用が生じていた可能性があった．60 step，90 step時の内側広筋，半腱様筋，腓腹筋，90 step時の前脛骨筋ではピークパワーと筋の活動特性との間に有意な相関は認められなかった．このことは，ステップエルゴメーターを全力で駆動する戦略が個人により異なっていることが考えられた．測定前に十分な駆動練習を行っているものの，主要な移動手段である自転車（エルゴメーター）駆動に比較すると慣れない運動であり，アイソキネティック運動の強い抵抗を受け，それを下肢で押し出す（蹴り出す）動きの際に，体幹筋，股関節周囲筋，および膝関節周囲筋などの筋の活動戦略は個人間でばらつきが大きいことが考えられた．また，90 stepの前脛骨筋は，60 stepと同様に屈曲相の足の引き上げや足部の固定機能に関与すること予測されたものの，速度の増加に対応した前脛骨筋の活動が十分に発揮できなかった可能性が考えられた．本研究のデザインでは，駆動相ごとの分析は困難であるため，今後は駆動相ごとの筋活動の変化を検討していく必要があるといえる．

また，60 stepと90 stepにおける，筋の活動特性の比較では，内側広筋および前脛骨筋では60 stepよりも90 stepでMPF，HF/TPの有意な増加，LF/TPの有意な低下が認められた．この結果から，より速い速度での運動において，高周波数帯域の筋活動，つまり速筋線維の筋活動の増加やインパルスの発射頻度の増加が起こることが推察された．多機能エルゴメーター駆動において，半腱様筋や腓腹筋は速度の増加により，伸展相での筋活動が増加することが示されている[23]が，ステップエルゴメーター駆動においては速度変化に対しても速筋線維の活動やインパルスの発射頻度が変化しない可能性が考えられた．

本研究の結果では，ステップエルゴメーター駆動時のピークパワーと筋の活動特性との関連は60 step時の前脛骨筋以外に認められず，ピークパワーの評価のみで筋の活動特性の把握は困難であるといえた．近年では，加齢による筋量の減少だけでなく，α運動ニューロン活動の低下や，運動に動員される運動単位の減少など神経機構の変化を，ダイナペニア(dynapenia)と表している[24]．また，生理学的な研究では，筋小胞体からのCa^{2+}放出量の低下による興奮収縮連関における情報伝達効率の低下や，筋原線維の張力産生能力の低下などが加齢で生じることが明らかになりつつある[25]．そのため，高齢者に対し筋の収縮速度や筋パワーの評価が重要視されている．本研究の結果から，筋パワーの評価に加え，筋の活動特性

の評価を行い，継時的な変化を追うことは，加齢で変化しうる速筋線維の割合やインパルスの発射頻度，神経伝導速度などが複合した要因の変化を追うことができるため，ダイナペニアの評価に有益であると考えられる．また，60 stepよりも90 stepの方がより高周波数帯域の割合が高かったことから，臨床的に，ステップエルゴメーターを用いる場合は，より速い運動課題を与えることで，Type IIb線維のような速筋線維の活動が賦活できると考えられ，サルコペニアやダイナペニアの予防に有益であると考えられた．本研究は横断調査であり，因果関係までは述べられないことや，Biostep解析ソフトのサンプリング周波数の制限から，駆動における相ごとの解析が困難である点が限界点として挙げられた．

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サルコペニア診断のための筋量，筋力の評価法

The assessments of muscle mass and strength for diagnosis of sarcopenia

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抄録▶サルコペニアの中核症状は骨格筋量の減少と筋力低下で，その評価はサルコペニア診断にとって重要である．筋量と筋力の測定方法はいくつかあるが，いずれも一長一短がある．測定者は精度や簡便性，実用性といった点から適切な検査方法を選択する必要がある．近年では，サルコペニア判定のために筋量のみでなく筋力や歩行速度の評価を含めたアルゴリズムが提唱されているが，これらの判定基準は明確ではなく，サルコペニアを診断するための日本人を対象とした基準値の設定が必要である．

Key Words　生活機能障害，身体的虚弱，筋量，歩行機能，操作的定義

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サルコペニアの評価方法

高齢期における骨格筋の萎縮とそれに伴う筋力低下を表す造語であるサルコペニアは，概念としては古くから存在し，その判定は筋量の測定値から決定されてきた．筋量の測定は形態計測，生体電気インピーダンス法(bioelectrical impedance analysis: BIA)，二重エネルギーX線吸収法(dual energy X-ray absorptiometry: DXA)，magnetic resonance（MR）やcomputerized tomography（CT)画像の解析によってなされ，ある一定以上の筋量の減少をサルコペニアとしてきた．もっとも広く用いられている定義のひとつは，BaumgartnerらのNew Mexico Elder Health Surveyによる定義がある[1]．この定義は，DXAから得られた四肢の筋量の合計(appendicular skeletal muscle mass: ASM)を身長(m)の2乗で除したskeletal muscle mass index（SMI)を指標としたものである．サルコペニアの定義は，成人(18～40歳)におけるSMIの平均から2標準偏差以下に達した場合とされた．カットポイントは男性が7.26 kg/m^2，女性が5.45 kg/m^{2}と報告され，この操作的定義に基づくサルコペニアの有症率は，70歳以下において13～24%，80歳以上では50%以上とされた[1]．ただし，骨格が異なる日本人高齢者に対して同一の基準値を外挿することは適当ではない．

日本人を対象とした研究では，独立行政法人国立健康・栄養研究所による「生活習慣病一次予防に必要な身体活動量・体力基準値策定を目的とした大規模介入研究のベースラインデータ」を用いたサルコペニアの基準値と妥当性が，18～85歳の日本人1,894名のDXAから検討されている[2]．この研究において，Baumgartnerら[1]による成人SMIの2標準偏差以下をサルコペニアと定義したところ，日本人の参照値は男性SMIが6.87 kg/m^2，女性では5.46 kg/m^{2}であった．男性においては米国人のカットポイントを下回ったが，女性においてはほぼ同値を示した[1]．また，SMIのマイナス1標準偏差をサ

ルコペニア予備群の参照値とすると，男性ではSMIが7.7 kg/m^2，女性ではSMIが6.12 kg/m^{2}となった．この結果，70歳以上の高齢者では男性の57％，女性の33％，80歳以上では男性の76％，女性の41％がサルコペニアとその予備群に含まれた．このSMI値は以下の推定式により推定可能であり，推定誤差は男性で0.40 kg/m^2，女性で0.17 kg/m^{2}であり，推定式の妥当性の検討では，決定係数は男性0.73，女性0.61とされている[2]．

男性

SMI (kg/m^2) = 0.326 (BMI) − 0.047 (腹囲) − 0.011 (年齢) + 5.135 [R^2= 0.68] (2)

女性

SMI (kg/m^2) = 0.156 (BMI) + 0.044 (握力) − 0.010 (腹囲) + 2.747 [R^2= 0.57] (3)

DXAを直接測定することが難しい環境であっても，握力と腹囲の測定なら比較的容易に可能であり，この推定式を用いて筋量を推定することができる．筋量を把握してサルコペニアを有する高齢者を特定できれば，介入が必要とされる対象者に集中的なサルコペニアの予防対策を講じることが可能となる．

他方では，サルコペニアの国際的な合意形成を目的としてthe European Geriatric Medicine Society，the European Society for Clinical Nutrition and Metabolism，the International Association of Gerontology and Geriatrics，European Region and the International Association of Nutrition and Agingの4組織が参加したthe European Working Group on Sarcopenia in Older People（EWGSOP）によるサルコペニアの操作的定義が発表された[3]．この定義は従来の骨格筋量のみによりサルコペニアを判定するのではなく，筋力と歩行速度をサルコペニアの構成要素として含め，サルコペニアと生活機能障害との関係が密接となるように改訂がなされた．このように，サルコペニアの操作的定義はいまだ確定されていないものの，その中核症状は高齢期における骨格筋量の減少と筋力低下であり，サルコペニア診断にとって筋量と筋力の評価は極めて重要であるといえる．ここでは高齢者における筋量と筋力の評価方法について概観し，サルコペニア診断の課題や問題点を整理する．

筋量の加齢変化

身体組成は加齢とともに変化するが，高齢期に特徴的な組成変化のひとつが骨格筋量の減少で，50歳以降その減少率は毎年1～2％程度になる．高齢期の筋量減少は性差に関係なく認められ，特に上肢筋より下肢筋において著しい．このような筋量減少は，運動あるいは身体活動量の低下によっても生じるため，いわゆる廃用性の筋委縮と混同されやすいが，十分な運動習慣がある高齢者でも同様の筋量変化が認められることから，高齢期に特有の組成変化と考えるのが適切であろう．一般的には，筋断面積の減少や筋細胞数の減少に加え，サテライト細胞の活性化が低下したことによる筋の再生と分解の不均衡が原因と考えられている．

筋量測定における留意点

筋量に関してこれまでさまざまな測定方法が考案されたが，それぞれの方法には一長一短がある．例えば，MRやCT画像から筋量を推定する方法は，測定精度が高い反面，検査費用が高額で限られた施設にしか機器が設置されていないため，大多数を対象とした測定には不向きである．また，DXA法は機器の操作に放射線技師が必要である．一方，BIA法は非侵襲性かつ安価で可搬性にも優れており，大規模集団を対象とした調査に適している．測定時間が短く対象者への負担も少ないことから，近年最も普及している測定方法のひとつといえるだろう．ただし，BIA法で推定しているのは体水分量であり，

発汗量や水分摂取量によって測定結果が左右される．心不全や脱水症状を呈する対象者の場合も，正確な測定結果が得られにくい．しかも，筋量の推定に用いられる回帰式には集団特異性があるため，人種や年齢，性別が異なる対象者間で測定結果を比較する際には注意が必要である．測定者は各検査方法の特性を理解し，測定精度，簡便性，実用性といった観点から測定目的に照らし合わせて最も適切な方法を選択しなければならない．

筋力の加齢変化とサルコペニアの基準

筋力は通常20～30歳代にピークを迎え，その後は徐々に低下を示す．620名の高齢者を対象として4年間の縦断調査を行った研究では，握力の変化は男性で12%，女性は19%とされ，高齢期には年間3～5%程度の筋力の低下が認められ[4]，筋量の低下率よりも著しい．また，この筋力の低下は上肢より下肢に強く現れる．筋力の低下とともに，筋力を素早く発揮する筋パワーも加齢に伴い低下する．これは，加齢に伴い筋萎縮が生じるのみでなく，タイプⅡ線維の減少による高速度のミオシン重鎖タンパクの減少によるものである．筋パワーの低下は，歩行や階段昇降などの日常生活動作能力と関連し，転倒回避能力の低下にもつながることから，高齢期において保持すべき筋機能であると考えられる．

筋力におけるサルコペニアのカットポイントについてはいまだ明白ではなく，サルコペニア診断の統一した見解は得られていない．参考値として，サルコペニア判定の握力のカットポイントは男性で30 kg，女性で20 kg未満という報告[5]や，虚弱の定義に用いられている握力基準が示されている[6]ものの，日本人におけるサルコペニア判定の筋力の基準値は明らかとされていない．今後，日本人におけるサルコペニアのカットポイントを筋力の側面から決定していく必要がある．

筋力測定における留意点

筋の収縮様式には，関節運動を伴わない等尺性収縮と，筋が短縮しながら収縮する求心性収縮と，伸長しながら収縮する遠心性収縮とに分けられる．また，日常生活では生じ得ないが，角速度が一定の関節運動を等速性収縮と呼んでいる．筋力測定では，これらの収縮様式に応じて発揮できる最大筋力を測定することが望ましいが，関節運動を伴う筋力の測定には大掛かりな測定機器を用意する必要があり，実施困難であることが多い．また，高齢者では筋力測定に慣れるまでに時間がかかり，最大筋力を発揮しにくい特徴を持つ．信頼性のある値を取得するために，若年成人と比較して，高齢者では2倍の練習が必要であるとした報告もあり[7]，筋力測定値を解釈するときに注意が必要である．ここでは，代表的な測定方法として握力および下肢筋力検査を紹介する．

1．握力検査

筋力測定の実現可能性を高めるためには，小型で安価な測定機器を用いて，簡便に測定可能な方法を採用する必要がある．代表的な筋力測定は握力検査であり，安価な握力計を用意すればよく，検査時間は教示の時間を含めても5分以内で測定可能である．また，握力検査は高齢者の上肢の筋力のみならず他の筋群の筋力も反映する指標として用いることができ[8]，高齢者の日常生活機能低下の予測因子として重要な役割を有しているため[9]，スクリーニング検査として最適な検査方法であろう．

高齢者に筋力検査などの運動機能検査を適用する場合には，検査実施時の安全性や実行可能性を考慮する必要がある．握力検査は，現在まで広く行われてきた検査であり，高齢者にとってもなじみがあり，検査に対する不安が少ない利点を持つ．さらに，握力検査は他の運動機能

表1　高齢者における握力と膝伸展筋力の基準値

		レベル1	レベル2	レベル3	レベル4	レベル5
握力(kg)	男性	25未満	25～28	29～32	33～36	37以上
	女性	15未満	15～17	18～20	21～23	24以上
膝伸展筋力(N)	男性	135未満	135～208	209～261	262～322	323以上
	女性	81未満	81～140	141～176	177～215	216以上
歩行速度(m/s)	男性	1.00以下	1.01～1.14	1.15～1.25	1.26～1.39	1.40以上
	女性	0.89以下	0.90～1.04	1.05～1.19	1.20～1.32	1.33以上

鈴木隆雄，大渕修一監修．指導者のための介護予防完全マニュアル：包括的なプラン作成のために．財団法人東京都高齢者研究・福祉振興財団，2004．より作表した．

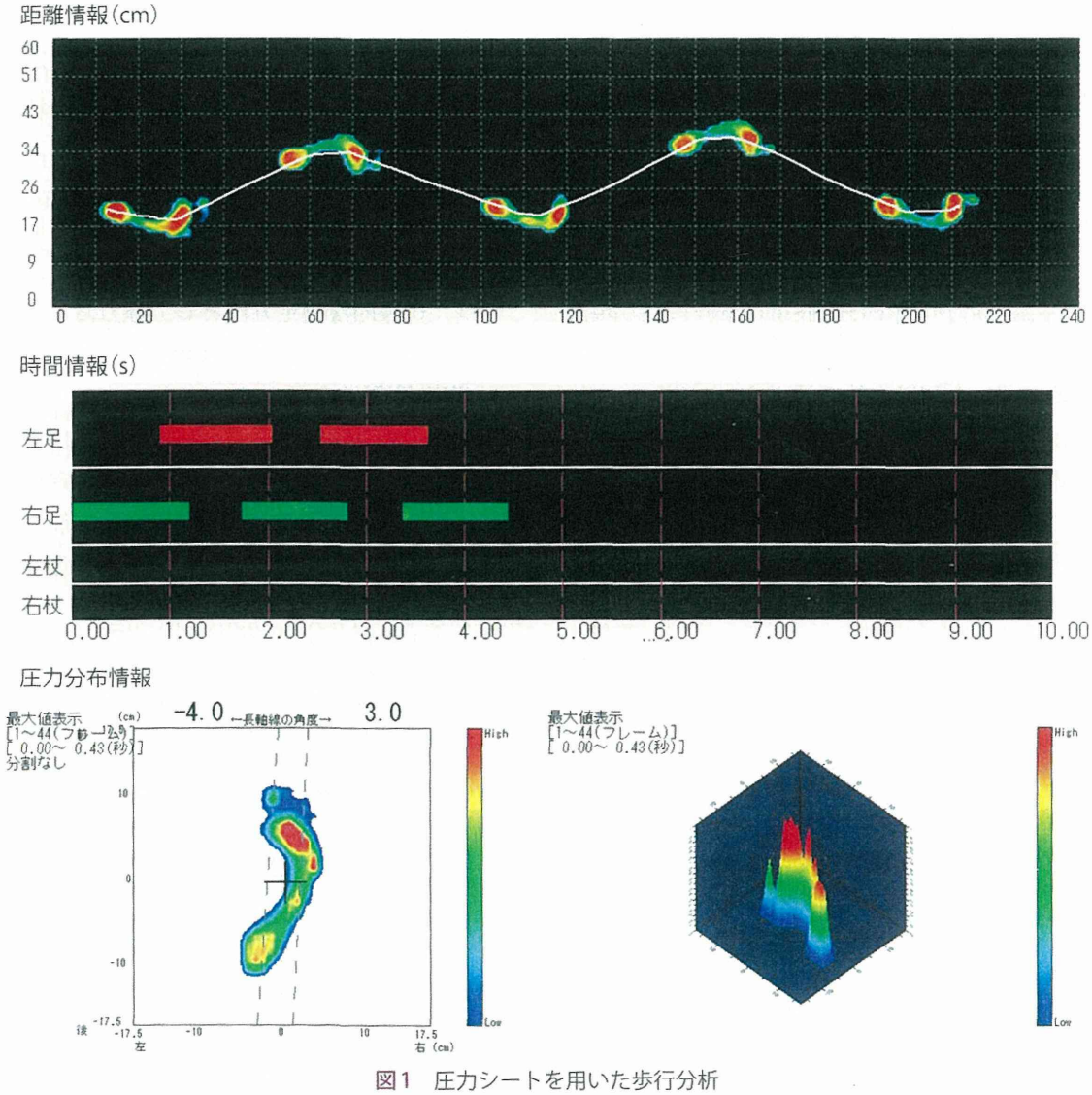

図1　圧力シートを用いた歩行分析

検査と比較して，機能障害を有する要介護高齢者においても90％以上の対象者に実施可能である[10]．表1に高齢者における握力の基準値を示した[11]．

2. 下肢筋力検査

握力検査は簡便性において高い優位性を持つが，日常生活機能の低下に直接影響する下肢筋力と握力検査値が乖離する例も少なくなく，下肢筋力検査を並行して行うことが望ましい．握力計と比較し，下肢筋力測定器は簡易なものでも高価であるが，定量的な測定をするために用意したい物品のひとつである．高齢者における膝伸展筋力の基準値を表1に示した．

等尺性膝伸展筋力の測定は，代表的な下肢筋力検査方法であるが，その測定に際しては下肢の関節角度の設定とその位置での固定に注意する必要がある．関節角度が変化すると発揮される筋張力が変化するため，検者は測定中の肢の固定性を注意深く観察しなければならない．

3. 歩行速度の測定

EWGSOPが発表したサルコペニア診断のアルゴリズムには，骨格筋量や筋力(握力)のみでなく，歩行速度の測定が推奨されている[3]．高齢者の運動機能のなかでも歩行速度は，運動機能バッテリーテスト全体から定義される“運動能力”を最も代表する[12]ので，多数の種目が実施できない場合には，少なくとも歩行検査だけでも実施することが推奨される[13]．代表的に実施される歩行検査としては，一定距離あたりの所要時間を計測して歩行速度を算出する方法がよく用いられる．歩行距離は5～10 m程度の短距離で計測される場合が多く，歩行開始と終了時の加速と減速の影響を排除するために，歩行路の両端に2～3 mの予備路を設ける場合が多い．計測はストップウォッチを用いて行えばよいが，短距離の歩行路では測定誤差が大きくなりやすいので，検査に熟練が必要となる．その他の計測法としては，圧力シート上を歩行することで歩行速度や歩幅の計測が可能な機器や動作解析装置を用いた測定があげられる．圧力シートを用いた計測は，比較的測定が容易であり，足圧分布の表示が可能で歩行状態をフィードバックしやすい利点を持ち，病院や地域保健活動に導入しやすい(図1)．

サルコペニアの判定に用いられている歩行速度の基準値は0.8 m/s以下とされているが，この程度に歩行速度が低下した高齢者は中等度以上の機能低下を有する者であり，サルコペニアの予防という観点から考えると，基準値を厳しくして早い段階から予防的対処を検討する必要があるかもしれない．

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Geriatr Gerontol Int 2012; **12 (Suppl. 1):** *7–17*

ORIGINAL ARTICLE

Long-term multiple risk factor interventions in Japanese elderly diabetic patients: The Japanese Elderly Diabetes Intervention Trial – study design, baseline characteristics and effects of intervention

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Aim: To evaluate long-term, multiple risk factor intervention on physical, psychological and mental prognosis, and development of complications and cardiovascular disease in elderly type 2 diabetes patients.

Methods: Our randomized, controlled, multicenter, prospective intervention trial included 1173 elderly type 2 diabetes patients who were enrolled from 39 Japanese institutions and randomized to an intensive or conservative treatment group. Glycemic control, dyslipidemia, hypertension, obesity, diabetic complications and atherosclerotic disease were measured annually. Instrumental activity of daily living, cognitive impairment, depressive symptoms and diabetes burden were assessed at baseline and 3 years.

Accepted for publication 26 September 2011.

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doi: 10.1111/j.1447-0594.2011.00808.x

Results: There was no significant difference in clinical or cognitive parameters at baseline between the two groups. The prevalence of low activities of daily living, depressive symptoms and cognitive impairment was 13%, 28% and 4%, respectively, and was similar in the two groups. A small, but significant difference in HbA1c between the two groups was observed at 1 year after the start of intervention (7.9% *vs* 8.1%, $P < 0.05$), although this significant difference was not observed after the second year. With the exception of coronary revascularization, there was no significant difference in fatal or non-fatal events between the two groups. Composite events were also similar in the two groups.

Conclusions: This study showed no significant differences in fatal or non-fatal events between intensive and conventional treatment. The present study might clarify whether treatment of risk factors influences function and quality of life in elderly diabetic patients.
Geriatr Gerontol Int 2012; 12 (Suppl. 1): 7–17.

Keywords: diabetes mellitus, elderly, geriatric assessment, intervention, vascular complications.

Introduction

The prevalence of diabetes increases with age, with approximately 15% of elderly people in Japan having the disorder.[1] These patients often suffer from diabetic microvascular and macrovascular complications.[2] Treatment goals in this elderly diabetic population are to maintain functional abilities and quality of life, and to prevent diabetic complications. Physical functional activities[3,4] and cognitive function[5,6] are more impaired in elderly diabetic patients, with depression and low well-being being major concerns.[7,8] It is therefore important to evaluate the effects of clinical interventions on physical, psychological and mental functions, as well as on disease-related variables, such as diabetic complications, atherosclerotic disease and mortality.

The impact of intensive blood glucose, blood pressure or multiple risk factor intervention on diabetic complications in type 2 diabetes has been evaluated in the United Kingdom Prospective Diabetes Study (UKPDS),[9,10] Kumamoto Study[11] and Steno-2 Study.[12] As only a few elderly people were included in these studies, little is known on the effects of multiple risk factor intervention on diabetic complications and functional prognosis.

We therefore carried out a randomized clinical trial to evaluate the efficacy of multiple risk factor intervention on functional prognosis, and development and/or progression of diabetic complications and cardiovascular disease in elderly people with type 2 diabetes. The present study presents baseline demographic and biomedical characteristics, and describes the major outcome variables measured at baseline.

Methods

Participants

The participants recruited for the Japan Elderly Diabetes Intervention Trial (J-EDIT) were diabetic outpatients at 39 representative hospitals in Japan between March 2001 and February 2002. Written informed consent was obtained from all participants before screening, consistent with the Helsinki Declaration and the guidelines of each center's institutional ethical committee.

Initial screening tests included glycated hemoglobin A1c (HbA1c), body mass index (BMI), blood pressure, serum total cholesterol, triglycerides and high-density lipoprotein cholesterol (HDL-C). Inclusion criteria included age 65–85 years, HbA1c ≥ 7.9% or HbA1c ≥ 7.4% with at least one of following criteria: BMI ≥ 25 kg/m^2, blood pressure ≥ 130/85 mmHg, serum total cholesterol ≥ 200 mg/dL (or low-density lipoprotein cholesterol [LDL-C] ≥ 120 mg/dL in participants without coronary heart disease [CHD]) or ≥180 mg/dL (or LDL-C ≥100 mg/dL in participants with CHD), triglycerides ≥ 150 mg/dL and HDL-C < 40 mg/dL. Exclusion criteria included a recent (<6 months) myocardial infarction (MI) or stroke, acute or serious illness, aphasia and severe dementia.

Randomization and intervention

A total of 1173 diabetic outpatients were enrolled and randomly allocated to either the intensive or conventional treatment group. The randomized factors were age, sex, diabetes treatment, HbA1c, total cholesterol, triglycerides, HDL-C, blood pressure, diabetic

Table 1 Treatment goals of multiple risk factor intervention studies in patients with type 2 diabetes

	J-EDIT	UKPDS	Steno-2 Study
Mean age (years)	72	52	55
Range	(65–84)	(25–65)	(40–65)
Treatment goals			
Glucose control			
FPG (mmol/L)		<6.0	
HbA1c (%)	<6.9		<6.5
Blood pressure control (mmHg)	<130/85	<150/85	<140/85 (1993–1999) <130/80 (2000–2001)
Cholesterol (mg/dL)	<200 (<180) if one has CHD	none	<190 (1993–1999) <175 (2000–2001)
Triglycerides (mg/dL)	<150	none	<150
HDL-C (mg/dL)	>40	none	>40
Other interventions	BMI <25		Smoking cession Aspirin use

CHD, coronary heart disease; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol, J-EDIT, Japan Elderly Diabetes Intervention Trial; UKPDS, United Kingdom Prospective Diabetes Study.

microangiopathy, atherosclerotic disease, hypertension, hyperlipidemia and institutions.

The treatment goal in the intensive treatment group was HbA1c < 6.9%, BMI < 25 kg/m^2, systolic blood pressure (SBP) < 130 mmHg, diastolic blood pressure (DBP) < 85 mmHg, HDL-C > 40 mg/dL, serum triglycerides < 150 mg/dL and serum total cholesterol < 180 mg/dL (or LDL-C < 100 mg/dL if patients had CHD) or <200 mg/dL (or LDL-C < 120 mg/dL if patients did not have CHD; Table 1). If HbA1c levels did not reduce to <6.9%, oral hypoglycemic drugs (sulphonylurea, biguanides, α-glucosidase inhibitors and pioglitazone) or insulin therapy was introduced by the physician. If total cholesterol or LDL-C levels did not reach the treatment goal, the physicians were advised to use atorvastatin. Patients with a history of cerebral infarction also had antiplatelet therapy where possible.

The conventional treatment group continued their baseline treatment for diabetes, hypertension or dyslipidemia without a specific treatment goal.

Each participant had a standardized medical history and physical examination at baseline, and then annually. Baseline information included age, sex, medical history, family members with whom they lived, education, employment, height, bodyweight, waist-to-hip ratio, maximum body weight, diabetes duration, family history of diabetes and diabetes treatment. Standardized questionnaires were used to obtain self-reported data on smoking, alcohol, hypoglycemia frequency, nutritional status, dietary habits and adherence, self-efficacy, activities of daily living (ADL), physical activities, comprehensive cognitive function, and psychological status including diabetes burden and depressive symptoms.

Basic ADL was assessed by the Barthel index,[13] whereas functional disabilities were examined by the Tokyo Metropolitan Institute of Gerontology (TMIG) Index of Competence.[14] This index includes 13 items and three subscales: instrumental ADL, intellectual activity and social role. The index is well validated and is widely used to measure functional abilities in community-dwelling or institutionalized elderly subjects.[15]

Physical activities were assessed using the Baecke questionnaire.[16] The Folstein Mini-Mental State Examination (MMSE) was carried out to assess comprehensive cognitive function including orientation, memory recall and calculations.[17]

Depressive symptoms were evaluated using a short form of the Geriatric Depression Scale (15 items, GDS-15),[18] whereas diabetes-specific burden and concerns were examined using the elderly diabetes burden scale (EDBS).[19] EDBS is a short revised version of the elderly diabetes impact scale reported previously,[4] and consists of six subscales: symptom burden (4 items), social burden (5 items), diet restrictions (4 items), concern (4 items), treatment satisfaction (3 items) and burden by tablets or insulin (3 items). Each of the 23 EDBS items was rated on a four-point multiple-choice scale. The elderly diabetes burden score was calculated by reversing the scores of the treatment satisfaction subscale and summing the scores of the six subscales. EDBS has good test–retest reliability, construct validity, convergent validity and satisfactory internal consistency.

The frequency of mild or severe hypoglycemia was assessed using questionnaires (number of hypoglycemic episodes and number of comas or emergency hospital visits or admissions as a result of hypoglycemia in a year, month or week). Mild hypoglycemia episodes included the appearance of or recovery from hypoglycemic symptoms. Severe hypoglycemia episodes were defined as

coma, convulsion or incapacity of the patient sufficient to require the assistance of another person.

Nutritional intake was assessed for 1 week using the Yoshimura food frequency questionnaire[20] that estimated food and total energy intake, carbohydrate-, protein- and fat-to-energy ratios, and intake of cholesterol, salt, iron, calcium, vitamins and dietary fiber from portion sizes (relative to the standard amount) and frequency (intake number for 1 week) of 29 food groups.

Measurements

Venous blood was drawn for determination of blood glucose, HbA1c and serum concentrations of total cholesterol, HDL-C and triglycerides at baseline, and then at least twice a year. Plasma glucose was measured by the glucokinase method, and HbA1c by ion-exchange high-performance liquid chromatography. The Japan Diabetes Society (JDS) has standardized several HbA1c assays with the international standard value adjusted by the equation of HbA1c (JDS) (%) plus 0.4%. Serum insulin was measured by an enzyme immunoassay, and total cholesterol, triglycerides, HDL-C, white blood cells, red blood cells, hematocrit (Ht), blood urea nitrogen (BUN), serum creatinine, uric acid, total protein and albumin by established methods.

Blood pressure was measured with a mercury sphygmomanometer using a cuff of appropriate size. Diastolic blood pressure was determined as Korotkoff phase V. Body mass index was calculated as weight in kilograms / (height in meters)^2.

Microangiopathy (retinopathy, nephropathy and neuropathy), macroangiopathy (ischemic heart disease [IHD]), stroke and peripheral vascular disease [PVD]) were assessed at baseline, and then annually. Funduscopic examinations were carried out on dilated pupils by experienced ophthalmologists using direct ophthalmoscopy. Retinopathy status was assessed by the Japanese Diabetes Complication Study method and classified into five stages: stage 0: no retinopathy; stage 1: dot hemorrhages, hemorrhages or hard exudates; stage 2: soft exudates; stage 3: IRMA or venous deformities; stage 4: neovascularization, preretinal proliferative tissues, vitreous hemorrhages or retinal detachment. Diabetic maculopathy was assessed according to findings of hemorrhages, local edema, hard exudates and diffuse edema at macular areas. Uncorrected and corrected visual acuities, the occurrence of cataract, corneal opacity, glaucoma, age-related macular degeneration, laser photocoagulation, cataract operations and vitrectomy were assessed. Urinary albumin was measured by immunological assay. Mean urinary albumin-to-creatinine ratio (ACR; μg/mg creatinine) in two or three successive urinalyses was used to classify diabetic nephropathy as no nephropathy (ACR < 30), microalbuminuria (30 ≤ ACR < 300) or persistent proteinuria (ACR ≥ 300 or urinary protein ≥30 mg/dL). Diabetic neuropathy was defined as loss of Achilles tendon reflexes and diminished vibration sensation, and/or neuropathic symptoms including paresthesia.

Follow up

The annual examinations included bodyweight, BMI, waist-to-hip ratio, treatment of diabetes, fasting plasma glucose, serum insulin, total cholesterol, triglycerides, HDL-C, lipoprotein(a), white blood cells, red blood cells, Ht, platelet, BUN, serum creatinine, uric acid, total protein, albumin, blood pressure, visual acuity, microalbuminuria, deep tendon reflexes, neuropathic symptoms, resting electrocardiogram (ECG), chest X-ray, and the occurrence of retinopathy, nephropathy, neuropathy, IHD, stroke and PVD. HbA1c and ACR were measured biannually. Basic ADL, functional abilities, cognitive function, depressive symptoms and nutrition were assessed every other year. Use of medications, including insulin and hypoglycemic, antihypertensive, antihyperlipidemic, antiplatelet and anticoagulant drugs, was checked annually.

Data management and analyses

The main database was stored at the data management and statistical analysis center. A data sheet of each patient was mailed from the study institutions to the data management and statistical analysis center each year. The data was validated by range, combinatorial and historical checks of compatibility with previous data. A visual check of the list of abnormalities and information in the data sheets was carried out by trained staff. The study institutions were notified of unexplained abnormalities in the data that were completed or corrected before entry into the main database.

Data are presented as means ± SD or as proportions, unless otherwise specified. Data for analysis was extracted from the main database, and statistical analysis was carried out using the SAS computer programs. For univariate analysis, we used unpaired *t*-test and χ^2-test to compare baseline clinical characteristics in the two treatment groups. $P < 0.05$ was considered statistically significant.

Data security was maintained by exclusion of patient identities, password access and secure output within the data management and statistical analysis center.

End-points

Fatal and non-fatal events during follow up were certified by at least two members of the expert committee, masked to the participants' diagnosis and risk factor status. Death as a result of diabetes was defined as sudden death or death from atherosclerotic CHD (MI or heart failure as a result of ischemia) or stroke, death as

a result of renal failure, hyperglycemia or hypoglycemia. The history of macroangiopathy was obtained from medical records. Ischemic heart disease was classified as present when the patient had (i) a history of MI characterized by a typical clinical picture (chest pain, chest oppression and dyspnea), typical ECG alterations with occurrence of pathological Q waves and/or localized ST variations) and typical enzymatic changes (creatine phosphokinase); and (ii) a history of angina pectoris, positive treadmill ECG test or positive postload cardiac scintigram, confirmed by coronary angiography. Stroke was defined as clinical signs of a focal neurological deficit with rapid onset persisting ≥24 h, confirmed by either brain computed tomography or magnetic resonance imaging. No cases of asymptomatic lesions detected by brain imaging (i.e. silent infarction) were included. PVD was defined as the absence of dorsal pedal artery or posterior tibial artery pulsation and ankle–brachial index <0.8 or the presence of foot gangrene or ulcers.

All events related to diabetes were defined as any complications of cardiovascular events, fatal or non-fatal stroke, sudden death, renal death, diabetic foot complications and heart failure. All events included death unrelated to diabetes, as well as all events related to diabetes.

End-point validation

Possible clinical end-points were noted in the annual data sheets, with the diagnostic criteria for each end-point being predetermined. When an end-point was notified on a data sheet, the administrator requested full information from the data management and statistical analysis center, followed by a review by two clinical assessors of the event assignment committee. Two separate assessments for each end-point were entered on a special data sheet. If there was disagreement on the assessment, a final decision was made after discussions of the committee. The definition of the end-points is shown in the Appendix.

Statistical analysis and criteria for stopping the study

Differences in end-points (deaths or complications) between the two groups were analyzed using the log–rank test. Uni- and multivariate survival analyses were carried out using Cox proportional hazard regression models. All major analyses were according to assigned allocations (intention to treat), without exclusion of protocol deviants.

The Data and Safety Monitoring Committee examine the end-points annually and will stop the study when the difference in diabetes-related deaths or complications (disease) between the two groups becomes significant ($P < 0.001$, log–rank test).

Results

A total of 1173 outpatients with diabetes, aged over 65 years, were registered between March 2001 and February 2002. After randomization, 585 and 588 patients were allocated to intensive or conventional treatment, respectively. There were no significant differences between the two groups for age, sex, diabetes treatment, BMI, HbA1c, SBP and DBP, total cholesterol, triglycerides, HDL-C levels (Table 2), and number of risk factors (data not shown).

At baseline, the proportion of patients with a low ADL (TMIG Index of Competence ≤ 9), depressive symptoms (GDS-15 ≥ 5), or cognitive impairment (MMSE ≤ 23) were 13%, 28% and 4%, respectively. The prevalence of low ADL, depressive state and cognitive impairment was similar in the two groups (Table 2).

The dropout rate after 6 years was 8.9% (104 cases). HbA1c, total cholesterol, triglycerides, blood pressures and BMI at baseline and during follow up are shown in Table 3 and Figures 1–4. A small, but significant difference in HbA1c between the two groups was observed at 1 year after the start of intervention (7.9% *vs* 8.1%, $P < 0.05$), although this significant difference was not observed after the second year. Although SBP and DBP, total cholesterol and triglycerides levels tended to decrease by the sixth year compared with the baseline data in both groups, no significant differences in these variables were observed between the two groups during follow up (Figs 1–4). BMI and HDL-C levels did not change over the follow-up period in either group.

Table 4 shows the fatal and non-fatal events during follow up in the two groups. With the exception of coronary revascularization, there were no significant differences in fatal or non-fatal events between the groups ($P < 0.05$, log-rank test). Composite events (death as a result of diabetes, death unrelated to diabetes, coronary vascular events, stroke, total diabetes-related events and all events) were also similar in the two groups (Table 5).

Discussion

The J-EDIT study has the potential to determine whether multiple risk factor intervention prevents aggravation of complications and quality of life, and reduces mortality in elderly diabetic patients. The study has three characteristics. First, it is a large-scale study of multiple risk factor intervention in elderly diabetic patients. No or very few elderly patients were included in the UKPDS[9,10] or Steno-2 Study.[12] Second, the multiple interventions involved control of blood pressure, serum lipids, bodyweight and blood glucose. The treatment goals in the intensive treatment group were similar

Table 2 Clinical characteristics of the participants at baseline

	Conventional treatment (n = 588)	Intensive treatment (n = 585)
General characteristics		
Age (years)	71.7 ± 4.7	71.9 ± 4.6
Male (%)	46.3	46.3
Duration of diabetes (years)	18.0 ± 9.9	16.7 ± 8.5
Body mass index (kg/m^2)	24.3 ± 7.3	24.0 ± 3.9
Waist (cm)	83.6 ± 9.9	84.3 ± 10.4
Waist-to-hip ratio	0.89 ± 0.07	0.90 ± 0.07
Smoking (%) (non-/ex-smoker/current smoker)	16:31:53	15:29:56
Smoking (package × years)	848 ± 762	789 ± 601
Family history of diabetes (%)	45.8	39.7
Systolic BP (mmHg)	137 ± 17	137 ± 16
Diastolic BP (mmHg)	75 ± 10	76 ± 10
Clinical status		
Ischemic heart disease (%)	16.3	14.9
Cerebrovascular disease (%)	12.4	13.3
Retinopathy (%)		
Stage 0	53.6	51.7
Stage 1	30.5	31.4
Stage 2	7.8	9.1
Stage 3	3.3	3.4
Stage 4	4.7	4.7
Nephropathy (%) (no/microalbuminuria/persistent proteinuria)	51:30:19	53:30:17
Loss or weakness of ATR (%)	56.8	57.1
Paresthesia (%)	18.5	22.3
Laboratory data		
HbA1c (%)	8.5 ± 0.9	8.4 ± 0.8*
Fasting plasma glucose (mg/dL)	170 ± 53	168 ± 49
Fasting insulin (mIU/mL)	10.9 ± 12.0	10.3 ± 9.6
Total cholesterol (mg/dL)	202 ± 34	203 ± 34
Triglycerides (mg/dL)	131 ± 70	137 ± 110
HDL-C (mg/dL)	56 ± 18	57 ± 19
Uric acid (mg/dL)	5.1 ± 2.0	5.1 ± 1.4
Blood urea nitrogen (mg/dL)	16.9 ± 5.9	17.2 ± 6.1
Creatinine (mg/dL)	0.93 ± 1.2	0.83 ± 0.36
Treatment		
Treatment of diabetes (diet/OHA/insulin)	9.0:60.7:30.3	8.7:61.0:30.3
Sulfonylurea drugs	54.6	56.0
α-Glucosidase inhibitors (%)	30.5	28.0
Biguanides (%)	16.4	15.5
Pioglitazone (%)	4.5	5.2
Glinides (%)	2.3	2.1
Antihypertensive drugs (%)	56.4	57.4
ACE inhibitors (%)	22.9	23.3
ARB (%)	10.1	9.3
Calcium blockers (%)	42.9	41.0
β-Blockers (%)	6.2	5.7
α-Blockers (%)	6.1*	3.4
Diuretics (%)	5.1	7.5
Antihyperlipidemic drugs (%)	40.2	36.8
Statins (%)	30.3	26.5
Fibrates (%)	3.4	3.9
EPA (%)	0.7*	2.7
Nicotinates (%)	1.3	1.4
Probucol	2.2	1.6
Antiplatelet drugs (%)	25.9	27.4
Aspirin (%)	13	15
Geriatric Assessment		
Barthel index (full score: 20)	19.8 ± 0.9	19.8 ± 0.8
Prevalence of any disabilities (%)	11	14
Functional abilities (TMIG index of competence) (full score: 13)	11.6 ± 2.2	11.6 ± 2.2
Geriatric depression scale (full score: 15)	4.3 ± 3.3	4.0 ± 3.2
Depressive symptoms (%) (Geriatric depression scale ≥5)	41	36
MMSE (full score: 30)	28.0 ± 2.4	27.8 ± 3.0
Cognitive impairment (%) (MMSE ≤23)	7	6
Visual impairment (%) (≤0.1)	9	12

ARB, angiotensin II receptor blockers; ACE, angiotensin-converting enzyme; ATR, Achilles tendon reflex; BP, blood pressure; EPA, eicosapentenoic acid; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; OHA, oral hypoglycaemic agents; TMIG, Tokyo Metropolitan Institute of Gerontology. *P < 0.05.

Table 3 Changes in bodyweights, glycated hemoglobin A1c, serum lipids, and blood pressure at baseline and during the follow-up period

	Conventional treatment							Intensive treatment						
Follow up (years)	0	1	2	3	4	5	6	0	1	2	3	4	5	6
BMI (kg/m^2)	23.6	23.6	23.6	23.4	23.5	23.5	23.4	23.9	23.8	23.8	23.8	23.8	23.7	23.5
HbA1c (%)	8.5	8.1	8.0	7.9	7.9	7.9	7.8	8.4	7.9	7.8	7.8	7.8	7.8	7.7
TC (mg/dL)	202	200	199	195	193	190	190	202	196	198	194	190	188	188
TG (mg/dL)	112	111	109	108	103	101	101	114	110	110	108	110	104	104
HDL-C (mg/dL)	56	56	55	56	55	55	54	57	54	54	55	55	55	55
SBP (mmHg)	137	137	135	135	135	135	134	138	136	136	133	134	136	134
DBP (mg/dL)	75	74	73	72	72	72	71	74	73	74	72	71	71	71

BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Table 4 Comparison of fatal events and non-fatal events during the 6-year follow-up period in the conventional and intensive treatment groups

		Number	*P*-value
Fatal event	Myocardial infarction	12	0.083
	Sudden death	13	0.993
	Stroke	6	0.656
	Death due to renal failure	3	0.084
	Death due to hyper/hypoglycemia	1	0.322
	Malignancy	37	0.506
	Pneumonia	10	0.525
	Others	13	0.570
	Subtotal	95	0.291
Nonfatal event	Myocardial infarction	17	0.998
	Angina pectoris	21	0.517
	Coronary revascularization	18	0.0282
	Hospitalization due to heart failure	15	0.190
	Stroke	63	0.281
	Diabetic ulcer or gangrene	12	0.564
	Subtotal	146	
Total		241	

Table 5 Comparisons of composite events (death due to diabetes, death unrelated to diabetes, coronary vascular events, stroke, total diabetes-related events and all events) in the conventional and intensive treatment groups

	No. events	*P*-value (log–rank test) Conventional *vs* intensive
Death due to diabetes	35	0.8495
Death not related to diabetes	59	0.2991
Coronary vascular events	55	0.9868
Stroke	67	0.2915
All events related to diabetes	155	0.5573
All events	206	0.2239

Death due to diabetes was defined as sudden death or death from atherosclerotic coronary heart disease (myocardial infarction or heart failure due to ischemia) or stroke, death due to renal failure, hyperglycemia or hypoglycemia. All events related to diabetes were defined as any complications of cardiovascular events, fatal or non-fatal stroke, sudden death, renal death, diabetic foot complications and heart failure. All events included death unrelated to diabetes, as well as all events related to diabetes.

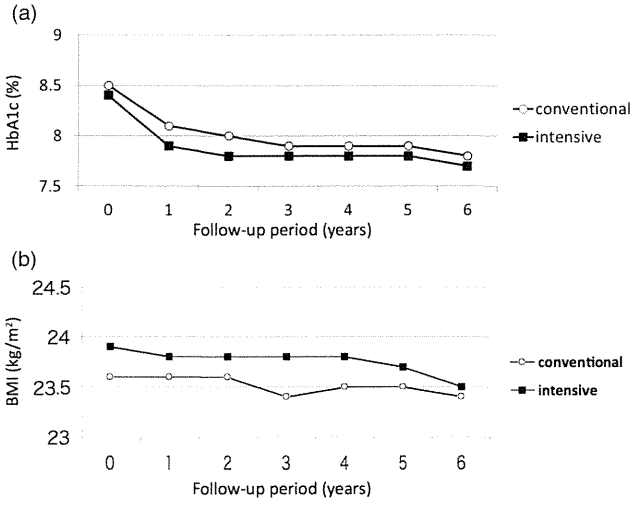

Figure 1 Clinical course of (a) glycated hemoglobin A1c (HbA1c) and (b) body mass index (BMI) in the conventional and intensive treatment groups.

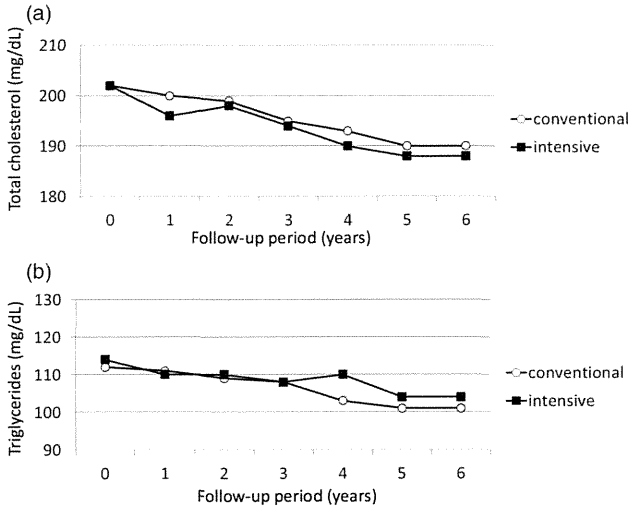

Figure 2 Clinical course of (a) total cholesterol and (b) triglycerides in the conventional and intensive treatment groups.

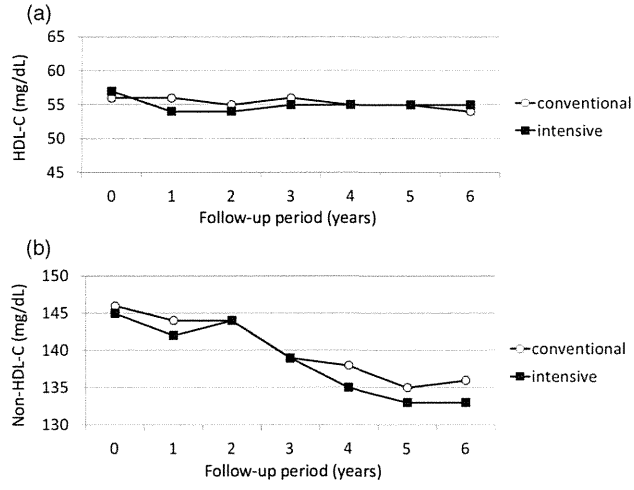

Figure 3 Clinical course of (a) high-density lipoprotein cholesterol (HDL-C) and (b) non-HDL-C in the conventional and intensive treatment groups.

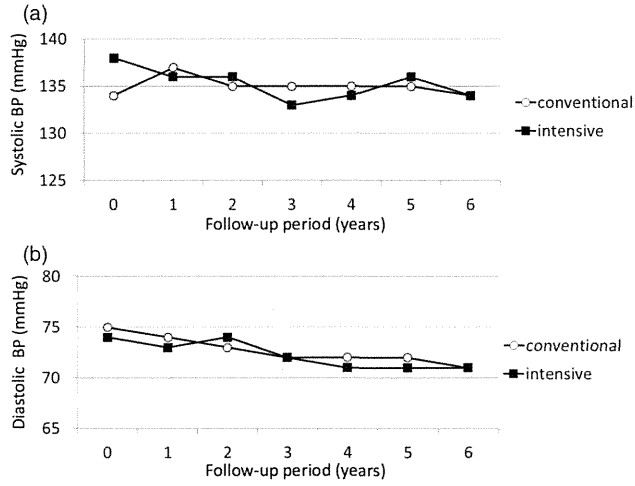

Figure 4 Clinical course of (a) systolic and (b) diastolic blood pressures (BP) in the conventional and intensive treatment groups.

to those in the Steno-2 Study[12] and considerably stricter than those in the UKPDS[9,10] (Table 1). Third, outcome in the study included ADL, cognitive function, depressive mood, well-being and the diabetic-specific psychological state, important components for geriatric assessment of elderly people.

The treatment groups in the study had similar general characteristics, diabetic complications, atherosclerotic disease, blood pressure, metabolic risk factors and prevalence of drug therapy for diabetes, hypertension, and hyperlipidemia, with the prevalence of micro- and macrovascular complications being 50% and 15%, respectively. As patients with poor diabetes control were selected, the prevalence of drug-treated hypertension and hyperlipidemia was high (47% and 65%, respectively). Mean HbA1c level at baseline was 8.5%, lower than that of the UKPDS, but still worthy of improvement. The prevalence of patients with SBP ≥ 130 mmHg (70%), DBP ≥85 mmHg (14%), serum total cholesterol ≥ 200 mg/dL (52%), triglycerides ≥ 150 mg/dL (30%), HDL-C ≤ 40 mg/dL (15%) or BMI ≥ 25 (34%) was also high, showing a need for intervention. The high prevalence and presumably high rate of deterioration of complications and potential risk factors show that the present study had a good chance of determining whether multiple risk factor intervention prevented the development and progression of complications. Therefore, we included both primary and secondary prevention trials.

The oral hypoglycemic drugs differed from those used in previous studies. Oral hypoglycemic drugs might be more beneficial than sulfonylurea drugs for preventing cardiovascular disease in patients with type 2 diabetes. α-Glucosidase inhibitors also prevent cardiovascular disease and progression of carotid atherosclerosis,[21–23] whereas metformin use is associated with lower cardiovascular morbidity and mortality, and attenuated progression of carotid atherosclerosis compared with sulfonylurea therapy.[24,25] Thiazolidinediones attenuate carotid atherosclerosis and restenosis after coronary stent implantation in patients with type 2 diabetes.[26,27]

We did not observe any significant differences in fatal or non-fatal cardiovascular events and composite events, including diabetes-related mortality, between the two treatment groups over the follow-up period. Although we observed significant improvements in HbA1c and LDL-C during the first 2 years in the intensive treatment group, there were no differences in HbA1c, lipid or blood pressure after that time. The similar values in atherosclerotic risk factors in both groups during follow up might account for the same prevalence of events, including cardiovascular and stroke, in the two groups. The results show it is difficult to markedly reduce HbA1c, blood pressure and lipid levels in elderly diabetic patients. The high prevalence of depressive and hypoglycemic symptoms at baseline in our cohort was notable. The intention of physicians to avoid hypoglycemic events and psychological barriers to providing elderly patients with extremely strict glucose control might explain the difficulties associated with aggressive intervention. In fact, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, aggressive glucose control was reported to lead to increased mortality in patients with longstanding diabetes.[28] Cardiovascular autonomic abnormalities, arrhythmia and hypercoagulability as a result of hypoglycemia might be responsible for increasing mortality during aggressive treatment. In addition, elderly patients do not accept the increase in the number of oral drugs or the initiation of insulin therapy.

In conclusion, preliminary analysis in the present study showed no significant differences in fatal or non-fatal events between the intensive and conventional treatment groups. However, as the levels of blood lipids, SBP and HbA1c tended to decrease during the follow-up period, further detailed analysis of the data might clarify to what extent treatment of risk factors influences functions and quality of life in elderly diabetic patients.

Acknowledgments

We thank all patients, physicians, and staff who took part in the J-EDIT study.

The registration number for this clinical trial was UMIN000000890. This study was financially supported by Research Grants for Longevity Sciences from the Ministry of Health and Labour, and Welfare (H12-Choju-016, H15-Chojyu-016, H17-Choju-Ordinal-013) and the Japan Foundation for Aging and Health.

Conflict of interest

There is no conflict of interest. The Japanese Elderly Diabetes Intervention Trial (J-EDIT) Study Group has not cleared any potential conflicts.

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Appendix

1. Atherosclerotic coronary heart disease (CHD) death – either or both of the following categories:

A. Death with consistent underlying or immediate cause plus either of the following:
   (1) Preterminal hospitalization with definite or suspected myocardial infarction (MI).
   (2) Previous definite angina or definite or suspected MI when no cause other than atherosclerotic CHD could be ascribed as the cause of death.

B. Sudden and unexpected death (requires all three characteristics).
   (1) Deaths occurring within 1 h with or without the onset of severe symptoms.
   (2) No known non-atherosclerotic acute or chronic process or event that could have been lethal.
   (3) An unexpected death of a person who was not confined to their home, hospital or other institution as a result of illness within 24 h before death.

2. Criteria for non-fatal MI – any one or more of the following categories using the stated definition:

A. Diagnostic electrocardiogram (ECG) at the time of the event.
B. Ischemic cardiac pain and diagnostic enzyme profile.
C. Ischemic cardiac pain and equivocal enzymes and equivocal ECG.
D. A routine ECG diagnostic for MI while the previous ECG was not.

3. Angina pectoris

The participants must report pain or discomfort with all of the following characteristics:

(1) The site must include the sternum at any level.
(2) It must occur during a form of exertion or stress and must usually last at least 30 s.
(3) It must on most occasions disappear within 10 min or less from the time of resting or decrease the intensity of exertion.
(4) It must usually be relieved in 2–5 min by nitroglycerine (does not apply if participant has never taken nitroglycerine).

In the case of angina pectoris at baseline, chest pain or discomfort should disappear or be controlled at entry. Reappearance or exacerbation of chest pain or discomfort and fulfilling points (1)–(4) were considered as an event. Subjects with uncontrolled angina pectoris at entry were not enrolled in the study.

4. Cerebrovascular disease

A diagnosis required all of the following:

(1) History of recent onset of unequivocal and objective findings of a localizing neurological deficit documented by a physician.
(2) Findings persist longer than 24 h.
(3) The neurological findings were not referable to an extracranial lesion.
(4) Findings of computed tomographic (CT) or magnetic resonance image (MRI) taken within 3 weeks after onset, or autopsy records classifying the cerebrovascular disease into cerebral hemorrhage, cerebral infarction, or subarachnoidal hemorrhage. Cerebral infarction was defined as a stroke accompanied by CT and/or MRI scan(s) that showed an infarct in the expected area, and also on the basis of clinical findings of stroke, for which there was evidence of cerebral infarction at autopsy. Cerebral or subarachnoid hemorrhage was classified on the basis of evidence obtained on CT or MRI scans or at autopsy, excluding hemorrhagic conversion of infarction.

In the case of cerebrovascular disease at baseline, the appearance of new unequivocal and objective findings of a localizing neurological deficit documented by a physician that persisted longer than 24 h was considered as an event and classified on the basis of evidence obtained on CT or MRI scanning or at autopsy. Cerebral infarction without obvious neurological symptoms shown by CT or MRI scans taken incidentally was not considered as an event.

5. Composite events

Death as a result of diabetes was defined as sudden death or death from atherosclerotic CHD (MI or heart failure as a result of ischemia) or stroke, death as a result of renal failure, hyperglycemia or hypoglycemia. All events related to diabetes were defined as any complications of cardiovascular events, fatal or non-fatal stroke, sudden death, renal death, diabetic foot complications and heart failure. All events included death unrelated to diabetes, as well as all events related to diabetes.