≪高齢者と地域医療≫
高齢者の災害医療

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要旨

- 災害発生から数日以内の急性期では，高齢者は若年者と同様に外傷性疾患による死亡が多いが，亜急性期では従来から罹患する慢性疾患(高血圧，糖尿病，脳心血管疾患)の悪化，胃潰瘍，呼吸器感染症などが起こりやすく，ストレスや生活環境の悪化を背景として起こる震災関連死をいかに防止するかが鍵となる．
- 慢性期にはサバイバー・ギルトなどによる精神面の不安定さが目立つようになるため，孤独死や閉じこもり，無刺激による認知機能低下や廃用(生活不活発病)を予防しなければならない．精神面の管理をしながら，慎重に自立支援を行っていく必要がある．
- また，要介護高齢者の早期トリアージも重要であり，これらを円滑に行うためには多職種による広域医療連携の構築が必須である．

はじめに

本国は地震，台風，津波などの様々な災害が多い国である．高齢者は災害弱者といわれるように，その災害時において被災高齢者に対する医療対応は非常に重要である．今回，2011年3月11日14時46分に発生した東日本大震災(マグニチュード9.0)は，言い換えれば大「津波」震災といっても過言ではない．この未曾有の大震災は発生から約7ヵ月が経過した現在，大きな爪痕を残していると同時に，慢性期に向けて被災高齢者の様々な管理のむずかしさとも直面している．

「避難生活における被災高齢者の潜在的能力の喪失をどう防止するのか」，「災害時高齢者医療における円滑な医療初動のあるべき姿とは」，「大災害発生時に要介護高齢者に対してどう迅速に対応するのか」など，おそらく数多くの課題がみえてくる．それらの問題点に焦点を合わせて概説する．

今回の東日本大震災の特異性

1995年に発生した阪神淡路大震災と比較してみても，今回の東日本大震災の特異性がよく分かる．Fig. 1に示すように，阪神淡路大震災では8割が圧死・窒息死であり，死者数は6,434人に上ったが，逆に行方不明は3人のみであった．またDisaster Medical Assistance Team(DMAT)の創設の契機となった．さらに，地震による直接の死因ではなくその後の様々な疾患発症により死亡した方々が14%に上ったことから，「災害関連死」が

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Fig. 1. 阪神淡路大震災と今回の東日本大震災との比較

阪神淡路大震災では8割が圧死・窒息死であり死者数は6,434人に上ったが，逆に行方不明は3人のみであった．また「災害関連死」が改めて注目された．一方，今回の東日本大震災では死者9割超が水死(溺死・6割が60歳以上)という特徴から，今回のDMATは2〜4日で解散された．大震災からちょうど3ヵ月経過した時点で行方不明が8,069人と多い点も今回の震災の特異性であり，大津波地震による大きな影響を物語っている．
[阪神淡路大震災の写真は毎日新聞社サイトより引用(毎日 jp：http://mainichi.jp/select/jiken/graph/hansindaisinsai/)．東日本大震災の写真は筆者提供]

改めて注目された．

一方，今回の東日本大震災では死者9割超が水死(溺死・6割が60歳以上)という結果からも，ここ数十年間日本が経験したことのない大震災であったことは間違いない．また，この災害の特徴から今回のDMATは2〜4日で解散された．死者は大震災からちょうど3ヵ月経過した6月11日の時点で15,413人に上ると同時に，行方不明が8,069人という点が今回の震災の大きな特異性であり，津波地震による大きな影響を物語っている．今回は被災地がかなり広域に渡ったこともあり，避難者は最大48万人であり，震災関連死は524

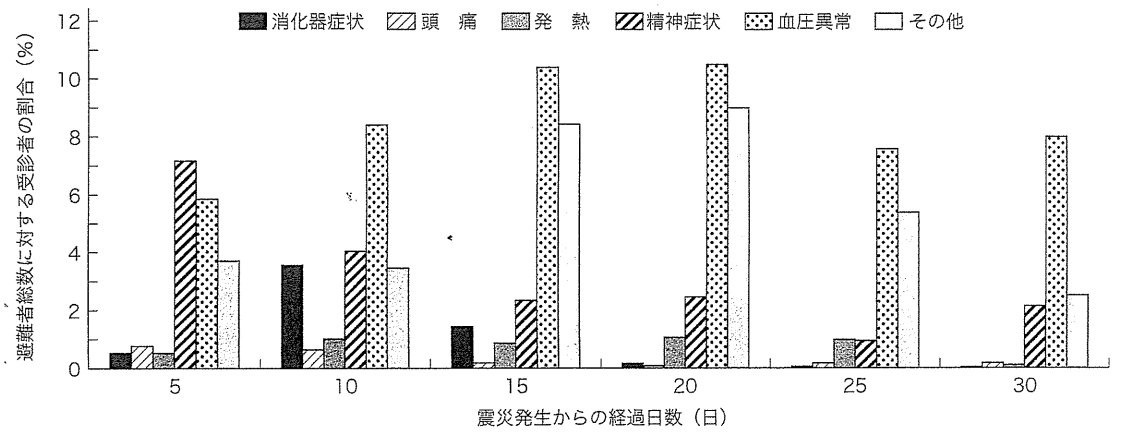

Fig. 2. 地震発生から5日間ごとの避難者総数に対する救護所疾患別受診者の割合
症状頻度のピークの時期は異なるものの，避難所においてはとくに血圧異常，発熱，精神症状は亜急性期の避難所に恒常的に認められ，対応が必要な症候であることがわかる．
［高齢者災害時医療ガイドライン（試作版）より参照．能登半島地震に関する解析データから］

人（5月13日時点）との報告がある．

また，阪神淡路大震災と比較して医療面における今回のもう一つの大きな違いは，1）被災地は従来から医師不足が問題であった地域であること，2）被災地の中核病院自体が数多く被災したことから，カルテなど多くの医療情報が失われてしまったこと，3）大規模災害時の通信手段が完全に途絶されてしまったことである．実際に，被災地の大学病院などには最初の数日間は現地からの情報の入手が困難であり，また大学病院の対策本部として怪我をした被災者の殺到を想定していたが，まったく想定外の経過をたどった．

経時的にみた高齢者災害時医療

1．急性期（災害発生後3日以内）

災害の質に大きく依存する．代表的な阪神淡路大震災では家屋倒壊および火災が中心であったため，急性期の犠牲者のほとんどは自宅における死亡（圧死・窒息死）であった．とくに戦前の木造住宅が比較的多く残存していた地域での死者が多く，年齢別では高齢者の死亡数が多いが，逆に若年者における死亡率も少なくないのが急性期の特徴である．しかし，前述したように，今回の東日本大震災では地震直後の大津波の影響で，9割以上の死者が溺死であった．

2．亜急性期（災害発生後4日～3週間）

高齢者は不慣れな避難所生活を急に余儀なくされ，心身ともに疲弊しやすい．たとえば，避難所肺炎，衰弱，脱水を契機とした脳心血管疾患の発症，ADLの低下した要介護高齢者の避難所生活の困窮，インフルエンザの蔓延，栄養管理の不安定さなどが大きく関わる．

Fig. 2に能登半島地震（2007年3月25日発生）から5日間ごとの避難者総数に対する救護所受診者の割合を疾患別に示す[1]．各疾患・症候のピークをみると，頭痛は8日目，消化器症状は10日目，精神症状は7日目，発熱は11日目，血圧異常は15日目であり，また全期間にわたり受診があった．このことから，症状頻度のピークの時期は異なるものの，避難所においてはとくに血圧異常，発熱，精神症状は亜急性期の避難所に恒常的に認められ，対応が必要な症候であることがわかる．

とくに，急性期を免れたにしても，持病としての脳心血管疾患・高血圧・糖尿病などの慢性疾患の悪化，ストレス性胃潰瘍，肺炎を中心とした呼

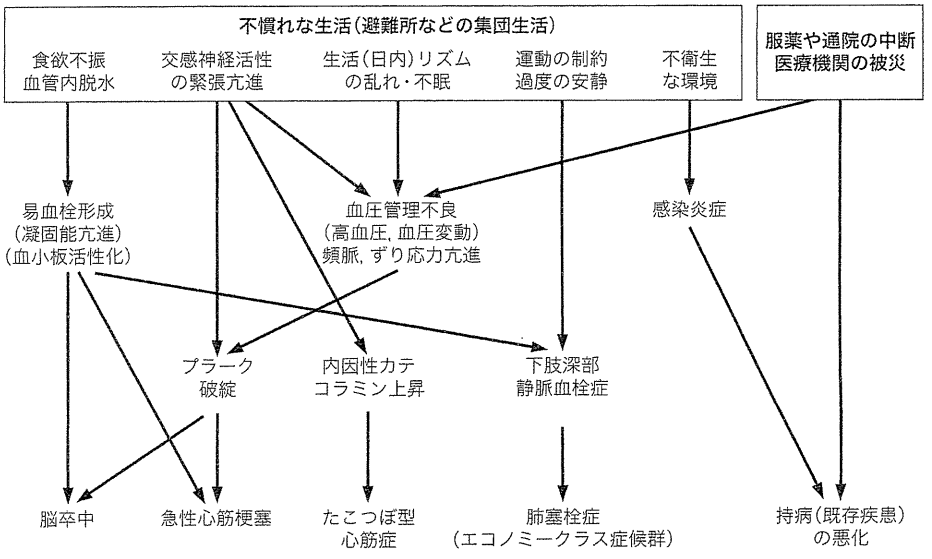

Fig. 3. 様々な要因により引き起こされる震災後関連疾患および震災関連死
降圧薬の中断や医療機関の被災などによっても血圧管理が不良となりやすいが，それらに加え，不慣れな避難生活を背景に精神的ストレスや交感神経活性などにより，さらに血圧管理が不良になりやすい．

吸器感染症などが起こりやすく，「震災後関連疾患」と呼ばれる．さらに精神的ストレスや生活環境の悪化が助長しやすく，これらによる死亡は「震災関連死」として位置づけられ，震災の死亡者の 1〜2 割は亜急性期以降に発生することが示されている．Fig. 3 に示すように，中でも高血圧管理の悪化は震災関連死への大きなトリガーとなりやすく，多くは定期的内服薬の中断および医療機関の被災による影響が大きい．また，高齢者の高血圧をさらに増悪もしくは管理をむずかしくさせる要素は数多くある．中でも，厳しい環境(猛暑や寒さ)への曝露，過剰労働など身体活動の増加，不眠・疲労などによる身体的要因に加え，心理的要因も非常に大きな影響を与える(Table 1)．

以上より，亜急性期における高齢者医療のポイントは，すでに罹患している慢性疾患に対する治療をいかに継続できるか，また，これら疾患の早期発見・早期治療を的確に行える医療体制をいかに迅速に構築するかが，「震災関連死」を最小限に抑えることにつながるのである．また，要介護高

Table 1. 大震災における高齢者高血圧管理をよりむずかしくさせる因子

- 薬剤の紛失による中断
- 診療所や医療機関への通院継続の中断・医療機関の被災(とくに今回は 300 以上の医療機関が休止・中止・廃業)
- 身体的要因
  - ①厳しい環境(猛暑や寒さ)への暴露
  - ②身体活動の増加…過剰労働
  - ③不眠，疲労
  - ④脱水
- 心理的要因
  - ①恐怖…断続的に続く余震への恐怖
  - ②悲しみ…家族の死亡
  - ③絶望…家屋倒壊，財産の喪失
  - ④不安…慣れない避難所生活，慢性疾病の増悪など将来への不安(失業，家計のひっ迫)

中でも高血圧管理の悪化は震災関連死への大きなトリガーとなりやすく，多くは薬剤の紛失など定期的内服薬の中断および医療機関の被災による影響が大きい．他にも，厳しい環境(猛暑や寒さ)への曝露，過剰労働など身体活動の増加，不眠・疲労などによる身体的要因に加え，心理的要因も非常に大きな影響を与える．

齢者に対する新たなトリアージも必須である．

3．慢性期（災害発生後4週間～5年）

慢性期に対応すべき被災高齢者の諸問題として，以下の点が提起されている．

①精神面の管理が非常に重要であり，高齢者の孤独死や無気力，潜在的能力の喪失などが起こりやすい．

②女性および高齢者が強いストレス反応を示しやすい．

③若い人たちは避難所を早々に離れ，高齢者ばかりが残りやすいことから，避難所に超高齢社会が形成され，結果的に住民による自治的な運営はむずかしい．

④震災後数年を経た後でも，被災高齢者の復興は様々な困難を伴いやすい．

中でも①の問題は非常に大きい．慢性期になると避難所から仮設住宅への入居に移っていくが，高齢者の仮設住宅における孤独死，孤独・虚無感を背景とした無気力や閉じこもり，また潜在的な能力の喪失などの問題は慢性期の大きな課題である．実際，仮設住宅に入ると，現実に戻りやすくなり，悲嘆・絶望・罪責（自分だけが生き残ったこと，家族を救ってあげられなかったこと（サバイバー・ギルト）など）の心境に陥りやすく，気力喪失や自殺企図へ向かう場合も少なくない．また，周囲への意識が薄れ無刺激になってしまうことから，認知機能低下や廃用性（生活不活発病）の点も懸念される．精神面の管理をしながら，慎重に自立支援を行っていく必要がある．

被災高齢者の精神症状と対応◎

被災高齢者では，1）急な避難所生活への環境の激変，2）罪悪感や虚無感などの精神状態の変化，3）認知症合併など，精神的影響が出やすい．被災高齢者に認められる精神疾患のきっかけとして，急激な環境変化，親族や近親者の死，財産の消失などが大きく影響し，心理的反応として様々な気分障害が惹起されてしまう．また，新たに出現する精神障害の他に，従来持ち合わせていた認知症の悪化も高頻度で報告されている[2]．

阪神淡路大震災において，被災高齢者（65歳以上）の震災後6ヵ月間までの受診内容に関して，精神疾患を中心とした後ろ向き調査によると，認知症の増悪や顕在化，せん妄，うつ病などの気分障害，幻覚・妄想状態，急性ストレス障害（Acute Stress Disorder：ASD）などの不安障害，睡眠障害などが多く報告されている[3]．また，地震発生後1週間以内に認知症患者の43%に症状の変化があり，震災前には軽度の認知症であった例に症状悪化例が多かった[4]．さらに，半年後から数年間にわたり，心理外傷後ストレス障害（Post-Traumatic Stress Disorder：PTSD）の遷延化が認められる．また，うつ病の発症にも気を配る必要がある．うつ傾向になると，自殺の危険性が増えるだけではなく，精神運動抑制による全身衰弱（横になったまま動けない，何も考えられない，仮性認知症と判断される，など），廃用症候群などのリスクも急増するため，精神面と身体面をバランスよく配慮することが求められる．

被災前の医療を可能な限り継続するために◎

1．平時の医療情報やお薬手帳の重要性

大災害時には普段のお薬手帳などをもって避難することはなかなかむずかしい．しかし，高齢者に対して自分自身の医療情報も含めた準備を普段から幅広く啓発し，しっかりとした「防災心」を教育しておく必要もある．

また，災害発生急性期において，一避難所では具体的に巡回してきた医療班や巡回保健師などの診療行為や注意点が記録に残されていないことが少なくない．著者は今回の東日本大震災でもその問題の重要性を改めて認識した．被災地の実地医療が普及するまでの急性期では，いわゆる「情報をつなぐ医療」が重要になる．そのためには，医師からコメディカル，そしてボランティアまでの多職種にわたる円滑な連携が鍵となる．

2．災害関連死および災害後関連疾患の予防

突然の災害発生による精神的ストレスが脳心血

管疾患の発症を著明に増加させることは明らかであり，男性では約 1.6 倍，女性では約 2.7 倍の増加との報告もある[5~7]．前述のように，災害関連死（震災関連死）は災害による直接死ではなく災害後に疾患発症もしくは増悪となり死亡に至ることを指し，阪神淡路大震災では死者全体の約 14% を占め大きく注目された．多くは高齢者であり，60 歳以上が 9 割であったと報告されている．新潟県中越地震では全体の 76% が震災関連死とみられている．今回の震災においても，5 月 13 日の時点で 3 県において少なくとも 524 人（宮城県 347 人，福島県 123 人，岩手県 54 人）が報告されている．地震直後から 2 週間までに 197 人（全体の 41%）が死亡したとされる．年代別にみても，65 歳以上の高齢者が全体の 90% 近くを占めている．

死因は脱水の関与する急性心筋梗塞や脳卒中など循環器系疾患と肺炎などの呼吸器系の疾患が多くを占めることが報告されており[8]，東日本大震災でも循環器系疾患と呼吸器系疾患が全体の 62% を占めている．また，それ以外に車内泊による静脈血栓塞栓症やエコノミークラス症候群，タコツボ型心筋症なども大震災では報告が少なくない[9,10]．よく経験する実例として，避難所生活におけるプライバシー欠如，環境衛生の不良，疲労などに加えて，断水（水洗トイレの使用不可）や慣れない環境に対する躊躇・不慣れもあり，トイレを控えるために水分摂取量をあえて制限してしまい，血管内脱水を背景とした脳心血管疾患の発症につながってしまう．この現象は今回の東北地方でも同じように起こっており，より具体的な，そしてきめの細かい避難所生活サポートを展開していく必要がある．

医療班および周囲の者は高齢者に対して，あえて水分摂取と（下肢を中心とした）適度な運動を促さなければならない．また，薬剤（抗血栓薬）の安定した供給と管理も必須である．震災後に warfarin を中止している患者や服用中でも治療域に達していない無効例が避難所で散見される．その状況を改善するためには，医療者が意識的に warfarin 服用者を拾い上げていくことと，PT-INR の簡易迅速測定装置コアグチェック XS を活用していく必要がある．

慢性期に向けての高齢者災害時医療

1．避難所医療に加え，災害時『在宅医療』の原点を改めて見直す

避難所での医療だけでなく，「在宅高齢者」もいかに守るかが重要である．実際，どうにか杖や歩行器で歩いていた高齢者や家族が送り迎えしていたような高齢者が家に閉じこもり気味になっている現実がある．自宅でも脱水傾向に陥り，また寝たきりから褥瘡へと向かう．今回の東日本大震災のもう一つの特徴として，被災地の数多くの中核病院も同時に被災してしまったことである．その中でも，ある病院では被災した中，「訪問診療と訪問リハビリテーション」を重視した診療スタイルに移行し，多職種（医師・看護師に加え，理学療法士，作業療法士，言語聴覚士，事務職員など）がチームを組み訪問診療を行っている．

今回，大都市圏ではない地域における大災害だからこそ，改めて災害時在宅医療の原点に立ち返る必要があるであろう．慢性期には『地域に根付いた医療』こそが被災高齢者の管理だけでなく，その家族の安心にまでつながる．

2．要介護高齢者に対する避難誘導システムの確立・啓発・普及

今回の大震災においても要介護・支援高齢者の対応が大きな問題となっている．避難所，福祉避難所，特別養護老人ホームも含めた施設入所，訪問在宅医療，医療機関（大学・病院・診療所），そして被災地外の後方支援などとの連携が今まで以上に必要とされ，今後，災害時にはどの高齢者がどの選択肢（施設）に円滑に運ばれるのかをあらかじめ検討しておく必要があるであろう．長期的な円滑さを求めて，「系列を超えた横の広域医療連携」が必須である．

おわりに

今回，東日本において史上最大の大震災が発生し，今までに経験したことのない津波により大きな爪痕を残した．避難所での避難者の年齢構成は6割以上が高齢者といわれており，震災列島であるわが国において高齢者災害時医療に対しては大きな課題がまだ山積みである．行政，自治体，そして様々な医療機関や組織・団体により，幅広い広域連携を平時から想定・構築し，そして災害発生後には可及的速やかにそれを実行する必要がある．それらにより，被災高齢者を災害後関連疾患や災害関連死から守り，そして潜在的能力の喪失を予防することにつながると考えられる．

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Predictive Factors for Hospitalized and Institutionalized Care-giving of the Aged Patients with Diabetes Mellitus in Japan

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ABSTRACT

To identify predictive factors for hospitalized and institutionalized care-giving among a group of aged patients with diabetes mellitus in Japan, retrospective chart review was performed in 288 diabetic subjects aged 65 years or older. Independent variables, based on the chart review, were age, sex, diagnosis, diabetic control and complications. Comprehensive geriatric assessment was performed to obtain information on the functional capacity and demographic variables, including physical and mental function, and socioeconomic status. 131 diabetic patients were considered as frail elderly and characterized for their higher age, longer duration of diabetes, higher frequency of insulin use, lower cognitive function, and lower QOL, in comparison with those of non-frail patients. All non-frail diabetic patients were independently treated at their homes, while 38 subjects out of 131 frail diabetic patients were hospitalized or institutionalized. Apparent clinical features of hospitalized/institutionalized patients were higher age, higher serum creatinine, and higher prevalence of stroke episodes, advanced cognitive decline and absence of key caregiver in the family members, in comparison with those of in-home frail diabetic patients. The predicted probabilities from the multivariate logistic regression analysis in predicting hospitalized and institutionalized care-giving were as follows: $\text{Log } p/(1 - p) = -19.801x_1 - 54.269x_2 + 721.405$; where x_1 = cognitive function (score), x_2 = social support (score). Receiver operating characteristic curve analysis revealed a satisfactory discrimination for hospitalized and institutionalized care-giving in frail diabetic elderly with 92.9% of sensitivity and 91.4% of specificity, when the cutoff point of the model was set at 0.992. We concluded that cognitive decline and low social support are the predictive for hospital and institutional care-giving, and that demographic and mental information as well as diagnostic data should be analyzed to predict the hospitalization/institutionalization among frail diabetic elderly.

INTRODUCTION

Successful management of diabetes mellitus in the elderly population is a major public health challenge. The aging population (over 65 years) now makes up 23.1% of the overall

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population in Japan, and the prevalence of diabetes in this population is over 16% (1). Along with the increasing duration of diabetes in the elderly, diabetes-related complications frequently occur and propagated: not only vascular complications such as diabetic foot, retinopathy, and nephropathy, but also age-associated illness and frail homeostasis, which produce a high rate of disablement and decay of quality of life. The complexity of physical and mental disability, coupled with the vulnerability to frailty often disturbs the day to day diabetes self-management at their homes. In the previous reports (2-4), diabetes is a significant predictor for the institutionalization among the frail elderly; the aged diabetic patients are 1.8 times more likely to enter a nursing home (2). Therefore, for the achievement of successful medical treatment of diabetic elderly, the cooperative long-term caregiving should be conducted, involving community-based and institutional care services.

Japan moved toward socialization of care for the frail elderly by initiating public, mandatory long-term care insurance in 2000. Everyone aged 65 and older is eligible for benefits based strictly on physical and mental disability. The long-term care insurance covers chronic-care beds in hospital, institutional and community-based caregiving. By improving the health outcomes, community-based caregiving can reduce the cost of the frail elderly, and the ability to identify patients who are at high risk for hospitalization and institutionalization could be useful not only in setting the medical treatment of the frail elderly, but also in developing policy for the long-term care insurance. Several studies have looked at factors that might predict hospitalization among populations of community dwelling older adults (5, 6) hospitalized patients (7), and those with dementia (8). However, information on the hospitalized and institutionalized care-giving of frail elderly with diabetes is scarce.

The present study attempts to identify predictive factors for hospitalized and institutionalized care-giving among the elderly with diabetes. For this purpose, we reviewed the charts of diabetic elderly who were treated at the Kobe University Hospital. Relationship between medical, functional and demographic variables of the diabetic elderly and the subsequent hospitalization and institutionalization was examined.

MATERIAL AND METHODS

Participants

Retrospective medical chart of 288 patients aged 65 years or older with known diabetes mellitus (164 women; mean age, 72.8± 7.7 years) were reviewed. This study was conducted from 2006-2009. The institutional review boards of Kobe University Hospital approved the research protocol, and written informed consent was obtained from each patient and his or her family members. All subjects met the criteria of diabetes from Japan Diabetes Society (9). At entry into this study, geriatricians routinely examined all patients to estimate diabetic control and complications, and assessed the functional and socioeconomic status. Professionals in neurology, psychiatrics, orthopedics, urology, and ophthalmology examined their specific problems.

Among 288 diabetic elderly, 131 patients were considered as frail elderly by their chief physicians. In this study, frail elderly was defined as persons who are vulnerable and at high risk of a range of adverse health outcomes, such as dependency, institutionalization, falls, injuries, acute illness, hospitalization, slow recovery from illness and mortality, and also included persons who have relatively preserved physical function, but easily become supported or cared condition (so-called ''specified elderly individuals'') in the modified Japanese long-term care insurance (10). Frail diabetic patients often had nonlocalizing or

constitutional symptoms such as weakness, fatigue, poor appetite, undernutrition, and/or dehydration.

Measurements of diabetic control and complications

Glycemic control and diabetes-related complications were analyzed by data chart. Fasting and postprandial blood glucose and HbA1c examined diabetic control in each individual. Information on duration of diabetes and on pharmacological therapeutics for diabetes was obtained. Diabetic retinopathy was classified into three subclasses, normal, nonproliferative, and proliferative diabetic retinopathy. Diabetic neuropathy was diagnosed by subjective symptoms and by objective examinations; autonomic function was tested by beat to beat variation test and Schellong test, and conduction velocity of the peripheral nerve was measured. Based on these observations, diabetic peripheral neuropathy was classified into three subclasses, normal, asymptomatic, and symptomatic neuropathy. Renal complication of diabetes was estimated by quantification of serum creatinine and Urea-N in dialyzed and non-dialyzed patients. Abnormal findings in electrocardiogram, chest X-ray, and cardio-echogram diagnosed coronary artery disease and congestive heart failure. Previous stroke episodes were re-evaluated by neurological examinations and presence of the cerebral vascular disease was investigated by MRI brain scanning.

Assessment of functional and socioeconomic status

Information on physical, mental, and demographic status among the aged diabetic patients was collected through personal interviews and supplemented by corroborative data from nursing staff. Comprehensive Geriatric Assessment Form, a standardized data sheet was completed by the physicians and clinical psychologists (11, 12). Geriatric assessment consisted of following 8 examinations, which were shown to be important predictors of institutionalization (4): physical measurements, basic activities of daily living (ADLs), instrumental ADLs, cognitive function, quality of life (QOL), depression, and socioeconomic status. Functional measurements included visual acuity, auditory acuity, communication, and bladder incontinence. Each of the dichotomous variables was coded so that 3=normal, 2=slightly disturbed, 1=severely disturbed, 0=functionally disrupted. Ability of communication was tested to ask every subject to read a short paragraph and answer questions about the paragraph. Basic ADLs were determined using the Barthel index, including the ability for bathing, dressing, toileting, transferring, and eating. Instrumental ADLs were estimated by Roken score, established in the Tokyo Metropolitan Geriatric Hospital, Japan (13), which referred to going outside the home, shopping for groceries, preparing meals, managing finances, reading the newspapers and magazines, interests in health management, and communicating to family members and friends. For the self-administered screening instruments for depression, we used geriatric depression scale-15 (14). For measuring the cognitive function, mini-mental state examination (MMSE) was used (15). QOL was tested by the questionnaires of Morale scale of the Philadelphia Geriatric Center (16). To evaluate the socioeconomic status, we used the elderly diabetes impact scales (17). For caregiving conditions, 8 positive questionnaires and 4 negative questionnaires were asked, to know presence of and relationship with a key caregiver. Information on economical status was obtained from the patients and their caregivers, and coded so that 4=excellent, 3=good enough for daily life, 2=partially shortened, 1=asking for assistance.

Statistical analysis

Data were reported as mean ± SD. Two-tailed Student's t-test and χ^2 test were used to compare the variables between the frail and non-frail diabetic groups, and between the

institutionalized and in-home diabetic patients. Logistic regression analysis was employed to determine the predictive factors for institutionalization in frail diabetic elderly. Any significant items were entered into a multivariate logistic regression, using stepwise selection with an inclusion criteria of $p < 0.05$ and exclusion criteria of $p > 0.1$. Using a developed model, a receiver operating characteristic (ROC) curve was constructed to test the relationship between sensitivity and specificity using varying cutoff points of the model for predicting hospitalized/institutionalized care-giving. The area under the curve was calculated. Statistical analysis was performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). The level of significance was set at $p < 0.05$ for all statistical analyses.

RESULTS

Clinical characteristics of frail diabetic patients were shown in Tables I-III. Frail elderly were significantly older and had longer duration of diabetes than non-frail diabetic patients. However, there was no significant difference in gender (Table I). Type 1 diabetes was significantly frequent in the frailty group. Insulin user was more predominant in frail subjects than in non-frail patients. In the frail diabetic patients, HbA_{1c} levels were significantly higher than those in the non-frail group.

Table I. Clinical profiles of the non- frail and frail diabetic elderly

	Non-frail	Frail
Number (M/F)	157 (68/89)	131 (56/75)
Age (year)	70.3±6.3	75.3±9.0*
Duration of diabetes (years)	13.8±9.3	18.1±12.6*
Type 1 diabetes (%)	1.6	10.2 *
Insulin use (%)	22.9	43.5 *
HbA_{1c} (%)	7.4±1.4	7.9±1.1 *
Fasting blood glucose (mg/dl)	162±60	168±73

Data are presented as mean± SD. Student's t-test and χ^2 test were used to compare the variables between non-frail and frail patients. * $P<0.05$.

Underlying causes of the frailty in 131 aged diabetic patients were shown in Table II. Most common complication among the frail subjects was cognitive impairment including all types of dementia (30.5%), followed by visual disturbances (15.3%), depression (13.7%), cerebrovascular disease (13.7%), and end-stage renal disease (12.2%). MMSE of the frail diabetic subjects was 21.0±4.5, as shown in Table III, and thirty-two subjects of the frail diabetic patients were diagnosed as dementia. Visual disturbance was mostly due to diabetic retinopathy and/or cataracts. Coronary artery disease, congestive heart failure, and Parkinsonism were also frequently observed in the frail subjects. 5 frail patients had orthopedic disturbances such as hip and knee joints instability.

Table II. Underlying causes of frailty in 131 diabetic elderly

	Number (%)
Cognitive decline and Dementia	40 (30.5)
Visual disturbances	20 (15.3)
Depression and Other psychiatric disorders	18 (13.7)
Cerebrovascular disease	18 (13.7)
End-stage renal disease	16 (12.2)
Coronary artery disease and congestive heart disease	9 (6.9)
Parkinsonism	5 (3.8)
Orthopedic disturbances	5 (3.8)

Incidence of frailty is shown as a number of patients (%).

TableIII. Comprehensive geriatric assessment in non-frail and frail diabetic elderly

	Non-frail	Frail
Number (M/F)	157 (68/89)	131 (56/75)
Physical measurements (/12)	11.9 ± 0.3	11.3 ± 0.9
Basic ADL (/20)	19.6 ± 2.2	18.1 ± 3.0
Instrumental ADL (/13)	10.6 ± 2.3	9.9 ± 3.1
Cognitive function (/30)	24.8 ± 2.7	21.0 ± 4.5*
QOL (/17)	12.4 ± 3.1	11.3 ± 3.2*
Depression (/15)	4.2 ± 2.2	4.1 ± 3.5
Social support (/12)	9.3 ± 1.3	7.3 ± 3.3
Economic status (/4)	3.2 ± 0.4	3.2 ± 0.9

Data are presented as mean± SD. Student's t-test and χ^2 test was used to compare the variables between non-frail and frail patients. * $P<0.05$. Functional measurements included visual acuity, auditory acuity, communication, and bladder incontinence. Basic ADL and instrumental ADL were determined using the Barthel index and the Roken score, respectively. For measuring the cognitive function, mini-mental state examination was used. QOL was tested by the questionnaires of Morale scale of the Philadelphia Geriatric Center. Screening of depression was evaluated by geriatric depression scale-15. To evaluate the socioeconomic status, the elderly diabetes impact scales was used.

Demographic and functional status was assessed by comprehensive geriatric assessment (Table III). Of the physical measurements, visual acuity was slightly depressed in the frail subjects, other functional measurements including auditory acuity, communication, and bladder incontinence, were not different between non-frail and frail subjects (data not shown).

Basic ADLs and instrumental ADLs tended to decrease in the frail diabetic patients, which did not reach statistical significance in this study. MMSE of the frail diabetic patients was significantly lower than that of non-frail subjects. Depression was screened by the GDS-15, in which more than 5 positive answers were reported to indicate the possible geriatric depression (18). Scores of GDS-15 in frail and non-frail diabetic patients of this study were not elevated. Although an association between diabetes and depression has been recently postulated (19), our diabetic patients did not seem depressive, but rather in reasonably self-satisfactory condition. QOL was measured by Philadelphia Morale scale, and an average QOL was reported approximately 4 through 7 (20). QOL of our frail diabetic patients was slightly lower than that of non-frail diabetic patients. Socioeconomic status was not different between non-frail and frail diabetic elderly.

Table IV. Clinical profiles of in-home and institutionalized patients with diabetes mellitus

	In-home	Hospitalized/ Institutionalized
Number (M/F)	93 (40/53)	38 (16/22)
Age (year)	73.0±9.2	81.2±4.9*
DM duration (years)	17.8±13.3	18.7±10.9
HbA_{1c} (%)	7.8±1.0	8.2±1.3
Blood glucose (mg/dl)		
Fasting	165±77	173.7±68
Postprandial	259±76	285±80
Insulin use (%)	45.2	39.5
Proliferative retinopathy (%)	38.0	44.0
Symptomatic neuropathy (%)	75.5	69.7
Dialysis treatment (%)	11.4	23.7
Serum creatinine (mg/dl)	1.3±1.4	2.4±2.8*
Cerebrovascular diseases (%)	12.0	41.1*
Coronary artery disease and heart failure (%)	21.1	27.3
Peripheral vascular disease (%)	9.5	23.1

Data are presented as mean± SD. Student's t-test and χ^2 test were used to compare the variables between in-home and institutionalized patients. *P<0.05. Diabetic retinopathy was classified into three subclasses, normal, nonproliferative, and proliferative diabetic retinopathy. Diabetic neuropathy was diagnosed by subjective symptoms and by objective examinations. Previous stroke episodes were re-evaluated by neurological examinations and presence of the cerebral vascular disease was investigated by MRI brain scanning. Abnormal findings in electrocardiogram, chest X-ray, and cardio-echogram diagnosed coronary artery disease and congestive heart failure.

All of 157 non-frail diabetic patients were independently living at their homes, whereas thirty-eight out of 131 frail diabetic patients (29%) required hospitalized/institutionalized care-giving. Next, we compared the medical, functional, and demographic variables of in-home and of hospitalized/institutionalized patients among frail diabetic subjects (Tables IV and V). Hospitalized/institutionalized patients were older than in-home subjects, while difference in gender was not significant (female gender was 57.0% and 57.9% in in-home and hospitalized/institutionalized patients, respectively). Blood glucose and HbA_{1c} levels were considerably higher in the hospitalized/institutionalized patients, but the difference in the glycemic control did not reach statistical significance. Prevalence of proliferative retinopathy and symptomatic neuropathy tended to be equally common among frail diabetic patients. In contrast, diabetic nephropathy was more propagated in the hospitalized/institutionalized diabetic patients. One fourth of the

hospitalized/institutionalized patients received dialysis treatment, and mean concentration of serum creatinine was significantly higher in hospitalized/institutionalized patients than in in-home patients. Of the macroangiopathic disease, cerebrovascular disease was more prevalent in the hospitalized/institutionalized patients, while coronary artery disease and peripheral vascular disease were not different between in-home and hospitalized/institutionalized patients.

Comprehensive geriatric assessment in the hospitalized/institutionalized patients with diabetes demonstrated that physical measurements including visual acuity, auditory acuity, communication, and bladder incontinence were not different, compared with those of in-home patients (data not shown). Basic and instrumental ADLs tended to decrease in the frail diabetic subjects with hospitalized/institutionalized care-giving, however, which did not reach statistical significance in the study. (Table V). In the super-old individuals aged 85 or over, basic ADL of the hospitalized/institutionalized patients was significantly impaired than that of in-home frail elderly (13.1±3.4 and 16.8±4.5, respectively) and instrumental ADL of the hospitalized/institutionalized patients was also lower than that of in-home frail elderly (5.2±4.0 and 9.0±4.2 in the respective group, $P<0.05$). In contrast, basic and instrumental ADLs of young-old (65-74 years old) and old-old (75-84 years old) were not altered between in-home and hospitalized/institutionalized patients. Cognitive function of the hospitalized/institutionalized patients was more seriously impaired than that of in-home frail elderly. However, scores of GDS-15 and Morale scale were similar in the in-home and hospitalized/ institutionalized patients. Social support for the hospitalized/institutionalized patients was significantly decreased and the presence of a caregiver in their family members was apparently lower in the hospitalized/institutionalized patients than in in-home patients (50.0% and 90.0%, respectively). Economic status did no differ between the in-home and the hospitalized/institutionalized elderly with diabetic mellitus.

Table V. Comprehensive geriatric assessment in the in-home and institutionalized patients

	In-home	Hospitalized/ Institutionalized
Number(M/F)	93 (40/53)	38 (16/22)
Physical measurements (/12)	11.3±0.9	11.2±1.0
Basic ADL (/20)	18.4±2.7	17.3±3.5
Instrumental ADL (/13)	10.3±3.0	9.0±3.5
Cognitive function (/30)	22.2±4.2	17.7±3.6*
QOL (/17)	11.4±3.1	10.9±3.6
Depression (/15)	4.0±3.2	4.4±4.1
Social support (/12)	8.7±1.9	2.4±2.2 *
Economic status (/4)	3.3±0.7	2.4±1.6

Data are presented as mean± SD. Student's t-test and χ^2 test was used to compare the variables between in-home and institutionalized patients. * $P<0.05$. Physical measurements, basic ADL, instrumental ADLs, cognitive function, QOL, depression, socioeconomical support were determined as described for Table III.

Finally, to develop a model for predicting the hospitalized/institutionalized care-giving in frail diabetic elderly using stepwise selection, clinical variables that were shown to be different at $p < 0.05$ (Tables IV and V) were entered into a multivariate logistic regression. This showed that cognitive dysfunction and low social support were predictive factors for hospitalization/institutionalization in frail diabetic elderly subjects. The predicted probabilities from the multivariate logistic regression analysis in predicting hospitalized/institutionalized care-giving were as follows: $\text{Log } p/(1 - p) = -19.801x_1 - 54.269x_2 + 721.405$; where x_1 = MMSE (score), x_2 = social support (score). ROC analysis revealed a satisfactory discrimination for hospitalization/institutionalization in frail diabetic elderly subjects with a sensitivity of 92.9% and a specificity of 91.4%, when the cutoff point of the model was set at 0.992.

DISCUSSION

This study first indicated that factors to predict hospitalized/institutionalized care-giving of frail diabetic elderly are cognitive decline and low social support, namely absence of a caregiver in the family members. These results indicated that cognitive dysfunction with changes in self-care behavior and treatment of diabetes may increase the use of care beds in hospital and institutional caregiving when social support is limited. In contrast, clinical features of frailty of diabetic elderly including aging, longer duration of diabetes, insulin use and decreased QOL were not critical for hospitalized/institutionalized care-giving.

Of the physical measurements, visual activity, auditory acuity, communication, and bladder incontinence did not differ between in-home and hospitalized/institutionalized frail diabetic patients. Basic and instrumental ADLs of the hospitalized/institutionalized super-old patients aged 85 or over were significantly impaired, but ADLs of the overall frail subjects were not changed in this study, which presumably due to the relatively preserved physical activities of the younger frail diabetic elderly. Our results in diabetic subjects were consistent to the previous reports that ADLs were not significantly associated with nursing home replacement (2), at least in the young-old and old-old diabetic populations. Among the general population, physical and mental disabilities have consistently been found to be the primary predictor for nursing home placement (2, 6-8, 21). However, in the selected frail elderly, the relative importance of functional limitations was lessened or even insignificant if caregiver conditions were taken into account (22). Follow-up of frail subjects recruited to the National Long-Term Care Survey (2-year mortality: 22%; 2-year nursing home replacement rate: 8%) showed that caregiver burden was the strongest predictor among the variables and that ability to perform ADLs was not associated with institutionalization (21). Follow-up studies of demented individuals (1.5-year nursing home placement rate: 51%) also indicated that the predictive power of caregiver burden was stronger than ADL level of the care receivers (22).

Recent population-based cohort studies have suggested that older subjects with diabetes have an increased risk of dementia (23, 24). A critical review of 19 controlled studies concluded that sufficient evidence exists to link cognitive dysfunction with type 2 diabetes (24). We have reported the characteristics of cognitive dysfunction of Japanese diabetic patients (25-27). In this study, we found that lower MMSE was closely related to hospitalized/institutionalized care-giving in frail diabetic elderly. Our results confirmed to earlier studies that found that cognitive impairment is important in predicting institutionalization (3, 4). Sinclair et al. provided evidence that demonstrates that subjects with lower MMSE required significantly more assistance with personal care behavior, and were more likely to have been institutionalized (28). In addition, physical function was more

compromised in those with cognitive impairment. In this connection, it should be noted that our hospitalized/institutionalized patients were not so severely demented and maintained relatively preserved physical activities. However, even mild to moderate cognitive decline often disturbs the treatment of diabetes, including medication, exercise and diet therapy. Importantly, chronic hyperglycemia further worsens the cognitive dysfunction vice versa. Thus, it would seem more likely that the cognitive deterioration leads to poor self-management of diabetes, resulting in the increased need for hospitalized/institutionalized care-giving.

Another critical factor for hospitalized/institutionalized care-giving in diabetic elderly was caregiver issues, namely increased caregiver burden. Tsuji et al (2) pointed out three caregiver characteristics for the strong predictors of the nursing home placement: living separate from the patients, having time conflicts attribute to work, and being stressed by caregiving. In addition, they suggested that having a secondary caregiver in the family tended to decrease and using a formal caregiver tended to increase the risk of nursing home replacement (2). Although these findings were obtained in the general frail elderly in the defined area of southeast Baltimore, U.S., we felt that this was the case in Kobe, Japan. Therefore, clinicians must be alert to caregivers' burden, and have to pay much attention to use a formal caregiver under the long-term care insurance.

A major limitation of this study among diabetic elderly is the nature of the study population, who entered into this study at the Kobe University Hospital. Elderly subjects participating in research are likely to have lots of health problems, including a series of diabetes-related complications and age-associated illness. On the other hand, most diabetic elderly recruited in this study were highly motivated for receiving careful medical follow-up of diabetes. In fact, our diabetic patients seemed in reasonably self-satisfactory conditions and not depressive. These characteristics of our diabetic population were advantageous to investigate the possible risk factors of hospitalized/institutionalized care-giving, although we have to be cautious to consider the risk in general diabetic population. Second limitation is the reliability to assess physical activity, because we obtained information on ADLs from the patients themselves. Patients with dementia often overestimate their functional abilities. In this respect, it should be mentioned that the capacity for self-observation is considerably preserved in patients with mild to moderate dementia, although a decline in patient self-reporting on this issue is less dramatic than that seen in family reports (29, 30).

As noted, Japan started mandatory long-term care insurance in 2000. In respect of long-term care insurance, institutionalization is defined as entry into nursing homes or health facilities for the elderly and hospitalization is defined as entry into designated care beds in hospitals. In the nursing homes, frail elderly can be placed for long, but with limited medical facilities. Health facilities for the elderly can provide rehabilitation toward the independent self-care management for the frail elderly. Medical treatment can be provided in the care beds in hospitals, but only for the limited term. For the institutionalized patients with diabetes, medical follow-up for glycemic control and diabetes-related complications is additionally required, when compared with that for non-diabetic frail elderly. In particular, diabetes-specific medical requirements such as daily insulin injection, continuous dialysis therapy, and functional rehabilitation are often limiting factors for the institutionalization. These medical requirements for institutionalization in the frail elderly with diabetes should be overcome in near future.

Conclusively, cognitive decline and low social support are the predictive factors for hospitalized/institutionalized care-giving in diabetic elderly. We believe the current study emphasizes an obvious but critical fact, when caring for disabled and dependent diabetic

patients, clinicians should be sensitive to the people on whom they depend. The present study also indicated that the subsequent risk for hospitalization/institutionalization could be predicted at the time of entry into in-home care program by comprehensive understanding of risk, including medical problems, mental status, and social factors of the frail diabetic elderly.

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ORIGINAL ARTICLE: BIOLOGY

Effects of insulin and amyloid β_{1-42} oligomers on glucose incorporation and mitochondrial function in cultured rat hippocampal neurons

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Aim: The molecular basis for impaired glucose metabolism in patients with Alzheimer's disease (AD) has not been fully clarified. We tested whether insulin and amyloid (A)β_{1-42} oligomers would regulate glucose metabolism and energy homeostasis directly in cultured rat hippocampal neurons and evaluated possible interactions between insulin signaling and Aβ_{1-42} oligomers.

Methods: Dissociated hippocampal neurons were prepared from Wistar rat embryos at day 21 of gestation and cultured for 14 days. Cultured neurons were exposed to insulin (1 μM) for 30 min, and Aβ_{1-42} oligomers (1 μM) were added to culture media for 10–30 min. The glucose uptake of cultured neurons was measured by enzymatic fluorescence assay using 2-deoxy-d-glucose (2DG), and adenosine triphosphate (ATP) contents were quantified using a luciferin/luciferase luminescence assay.

Results: Aβ_{1-42} oligomers did not suppress 2DG uptake, reflecting the activities of glucose transporters and/or hexokinase, but led to disrupted ATP contents in the presence and absence of monocarboxylates (lactate/pyruvate). Insulin and C-peptide did not change glucose uptake or ATP concentrations.

Conclusion: The primary target of Aβ_{1-42} oligomers might be mitochondria, which could explain the reduced cerebral glucose levels in patients with AD. Moreover, insulin signaling was not directly linked to glucose metabolism or energy homeostasis in cultured rat hippocampal neurons. **Geriatr Gerontol Int 2011; 11: 517–524.**

Keywords: 2-deoxyglucose, Alzheimer's disease, adenosine triphosphate, insulin, mitochondria.

Introduction

Alzheimer's disease (AD) is a late-onset, progressive, age-dependent neurodegenerative disorder, characterized clinically by the impairment of cognitive functions, and changes in behavior and personality.[1–4] Clinical studies using the positron emission tomography tracer fluoro-2-deoxy-d-glucose (2DG) in patients with AD have demonstrated that glucose metabolism is impaired in the cerebral cortex. The hypometabolism is most prominent in the posterior cingulate and parietotemporal regions in early stages, and spreads to the prefrontal cortex as the disease progresses.[5–8]

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To date, the molecular basis for reduced glucose uptake in AD has not been fully clarified. Biochemical analyses of autopsied brains from patients with AD indicate impaired activities of enzymes involved in anaerobic glycolysis, such as hexokinase and glucose-6-phosphate dehydrogenase (G6P-DH), and reduced expression of several isoforms of the glucose transporter.[9] Pharmacological experiments have demonstrated that amyloid-β (Aβ) in the millimolar range prohibited glucose uptake in primary cultured neurons,[10,11] suggesting decreased levels of nonoxidative glycolysis. On the other hand, Parihar *et al.* have shown that mRNA expression levels of mitochondrial-encoded genes (subunit 5 of complex I and cytochrome oxidase) are reduced in the temporal cortex of patients with AD, suggesting the importance of altered mitochondrial function for reduced glucose incorporation in this disease.[12]

Recently, Aβ oligomers have attracted considerable attention for their pivotal roles in the development and progression of cognitive decline in the early stage of AD. They have been implicated as primary candidates for initiating the deterioration of synaptic function, composition and structure.[13,14] However, little is known about the impacts of Aβ oligomers on glucose metabolism and energy homeostasis.

It has been postulated that insulin might be involved in regulating glucose and energy metabolism, synthesis of neurotransmitters and modulation of synaptic plasticity as well as metabolism of Aβ and tau in AD pathogenesis. Deficiency of insulin's effects in the brain is closely associated with cognitive dysfunction. Several epidemiological studies have indicated that insulin-resistant disorders, including obesity, metabolic syndrome and diabetes, are risk factors for developing AD.[15–17] However, the effects of insulin on glucose and energy metabolism in the brain are still controversial. Zhao *et al.* have reported a molecular link between insulin resistance and AD pathogenesis in that insulin receptor signaling in neurons is strikingly sensitive to disruption by Aβ oligomers.[18] However, the pathways involved in glucose utilization and adenosine triphosphate (ATP) synthesis by insulin and Aβ oligomers have not been investigated.

The current study addressed whether insulin and $A\beta_{1-42}$ oligomers would regulate glucose metabolism and energy homeostasis in cultured rat hippocampal neurons. We wished to evaluate whether possible interactions of insulin signaling and $A\beta_{1-42}$ could cause impaired glucose metabolism in patients with AD. We found that neuronal glucose incorporation was not altered after stimulation with insulin and $A\beta_{1-42}$ oligomers, whereas mitochondrial function was significantly affected by $A\beta_{1-42}$ oligomers.

Methods

Preparation and characterization of Aβ1–42 oligomers

$A\beta_{1-42}$ was purchased from Peptide Institute (Osaka, Japan). The oligomers were prepared as described.[19] Briefly, the $A\beta_{1-42}$ peptide was dissolved in dimethylsulfoxide (DMSO) at 2 mM and then diluted 1:10 in sterile phosphate-buffered saline (PBS), vortexed for 30 min at room temperature and centrifuged at 15 000 *g* for 1 h at 4°C. The supernatant (200 μM) was aliquoted (25 μl) and snap frozen at –20°C.[19] Unless stated differently, aliquots were diluted in culture medium to a final concentration of 1 μM immediately before use. $A\beta_{42-1}$, a reverse amyloid beta peptide, was also obtained from Peptide Institute, treated similarly and used for the control experiments.

Oligomerization of $A\beta_{1-42}$ was confirmed by gel electrophoresis. Samples (18 μL) were mixed with a 4 × Nu Page sample buffer (Invitrogen, San Diego, CA, USA) and incubated at 70°C for 10 min. The sample was briefly centrifuged at room temperature for 2 min and applied to a 12% Nu-Page Bis-Tris gel (Invitrogen). The samples were electrophoresed at 100 V for 2 h, transferred to a nitrocellulose membrane at 100 V for 1 h and blocked with 5% milk in Tris-buffered saline containing 0.05% Tween-20 for 1 h at room temperature. The blots were probed with 6E10 (1:1000; Chemicon International, Temecula, CA, USA) – a monoclonal antibody against amino acid residues 1–16 of Aβ – overnight at room temperature, followed by incubation with horseradish peroxidase-conjugated antimouse antibody (1:5000) for 2 h at room temperature. Then, membranes were developed with enhanced chemiluminescence reagents (GE Healthcare Japan, Tokyo, Japan)[20] and visualized using a Kodak X-Omat 1000 processor (Kodak Japan, Tokyo, Japan). Molecular mass was estimated using Rainbow molecular weight markers (Bio-Rad, Tokyo, Japan).

Primary hippocampal neuronal cultures

All animals were treated according to the guidelines for animal experimentation of Kobe University School of Medicine. Dissociated embryonic hippocampal neurons were prepared from Wistar rat embryos at day 21 of gestation. Neurons were dissociated from fetal hippocampi in Hank's balanced salt solution containing 0.5% glucose, 2% sucrose, 1 mM sodium pyruvate and 15 mmol/L 2-(4-[2-hydroxyethyl]-1-piperazinyl) ethanesulfonic acid, and then centrifuged for 1 min at 15 000 *g*. Cells were plated onto poly-d-lysine-coated dishes at a density of 5×10^5 cells/mL in B27-neurobasal medium (B27-NBM). Cultured neurons were incubated with B27-NBM for 14 days.[21]