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厚生労働科学研究費補助金

臨床研究基盤整備推進研究事業

厚生労働省多目的コホート班との共同による糖尿病実態及び発症要因の研究（若手医師・協力者活用に要する研究）

平成１８年度　総合研究報告書

主任研究者　門脇　孝

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（若手医師・協力者活用に要する研究）

主任研究者　　門脇　孝　　東京大学医学部附属病院　教授

研究要旨：本研究は、「厚生労働省多目的コホート班との共同による糖尿病実態及び発症要因の研究」（以下、コホート研究）の研究支援およびその応用的臨床研究を行うものである。コホート糖尿病研究は、従来から厚生労働省がん研究助成金「多目的コホートによるがん・循環器疾患の疫学研究」班（班長　津金昌一郎、以下「厚生労働省研究班による多目的コホート研究」と略す）が調査を行っている地域に、糖尿病の実態調査を加えることにより実施するものであり、同班との共同研究として1998年度から行っている。
(1)糖尿病調査とその解析：1998-2000および2003-2005年度に、質問紙及びHbA1cの測定により約24000名の対象者に対して糖尿病有病率を把握する。糖尿病の把握は老人保健法検診に含まれている血糖値（随時(空腹時を含む)）に加え、この質問紙法およびHbA1cの測定により把握する。ベースライン調査（1998-2000年度）、5年後調査（2003-2005年度）の2回の調査により、糖尿病発症率を把握する。さらに、これらを用い、前向きコホート研究、断面研究のデザインにより生活習慣等との関係を分析する。
(2)「厚生労働省研究班による多目的コホート研究」データとの包括的解析：「厚生労働省研究班による多目的コホート研究」データとの包括的解析を行い、糖尿病発症と生活習慣等との関係を明らかにする。
(3)採択された課題に関連する臨床研究：
さらに、申請する研究実施チームの整備により、これまでの研究成果などから得られた知見を実証する臨床研究を行う。

A. 採択された研究事業での研究概要

糖尿病の罹患者数は約740万人とわが国の高齢者における主要な疾患であり、糖尿病は心筋梗塞・脳卒中のリスク増大を介して日本人の健康寿命を短縮する最大の原因のひとつとなっている。今後の本格的な高齢化社会の到来を前にして、医療費の増大を抑制し国民の活力を維持するためには、糖尿病の実態を明らかにし、どの様な生活習慣などの環境因子が糖尿病を発症・進展させているかについて探索的な研究を行なうことの必要性がますます高まっている。

本研究は、厚生労働省研究班による多目的コホート研究によって得られたデータから糖尿病発症・進展において重要な役割を担っている生活習慣を網羅的・体系に解析するとともに、重要と考えられる生活習慣については個別に臨床試験を立ち上げその意義を明らかにすることを目的とする。本研究では、次のような成果が得られることが期待される。

(1) 糖尿病・メタボリックシンドロームを発症・進展させる生活習慣が明らかになる。更に、どのような生活習慣によってどの程度糖尿病・メタボリックシンドロームの発症リスクが上昇するかが明らかになる。本研究の成果を利用して将来的には、簡単な問診によって糖尿病・メタボリックシンドローム発症のハイリスク者をスクリーニングできるようなスコアリング法が開発されることが期待できる。

(2)糖尿病やメタボリックシンドロームの病態を簡便かつ早期・正確に診断するため

の臨床指標が明らかとなり糖尿病・メタボリックシンドロームの診断・治療における精度向上に寄与することが期待される。(1)(2)の成果は、糖尿病やメタボリックシンドローム診療のガイドラインや国の生活習慣病対策法を策定する際にも重要な基盤的データとなることが期待される。日本における糖尿病罹患者数の多さと糖尿病に伴う合併症による QOL(生活の質)低下、心筋梗塞・脳卒中による寿命の短縮を合わせて考えると、本研究による成果は社会的な波及効果が極めて高いと考えられる。

以下の(1)～(3)について、本研究の(a組)～(c組)のいずれかによって担当する。すなわち、これらのチームが調査・解析を実際に施行し、人的に支援した。

(1) 糖尿病調査とその解析(a組)ならびに(b組):1998-2000 年度に、質問紙及び HbA1c の測定により糖尿病有病率を把握する。5 年後(平成 2003-05 年度)にも同様の調査を行い糖尿病発症率を把握する。これらを用いて前向きコホート研究、断面研究のデザインにより生活習慣等との関係を分析する。全コホートにおいて糖尿病実態調査を行った。2000 年度に同様の調査(質問紙、血糖値、HbA1c の測定)を行う。対象者総数に対し、HbA1c およびこれで定義された糖尿病を曝露要因として、虚血性心疾患、脳卒中、癌等への危険因子としての役割を、「厚生労働省多目的コホート研究」班の疾患登録システムから得られた罹患データを用いて前向きコホート研究にて検討した。

(2)「厚生労働省研究班による多目的コホート研究」データとの包括的解析および採択された課題に関連する臨床研究(a組)～(c組):「厚生労働省研究班による多目的コホート研究」データとの包括的解析を行い、生活習慣等との関係を明らかにする。また本研究で、臨床試験を実施するためのチームを整備することにより、これまでの研究成果などから得られた知見を実証すると共にその簡便な診断法としてのバイオマーカーの臨床的意義を検討するための臨床研究を実施した。具体的には、①検査データ、嗜好と体格に関する研究(a組:野田):主研究で得られた検診などの検査データと、嗜好や体格との関係を検討した。対象は 600 人である。②運動と血糖コントロールに関する研究(b 組:高橋):主研究から得られた運動の重要性を教育入院の期間で検討した。20 例を対象とした。③糖尿病・メタボリックシンドロームの発症・進展や病態を予測可能な臨床指標の抽出(c 組:原):糖尿病・メタボリックシンドロームの発症・進展や病態を予測するための臨床指標として、特に脂肪細胞から分泌され糖尿病・メタボリックシンドロームの発症・進展に関わっていることが注目されているアディポカインについて、どのアディポカインが糖尿病・メタボリックシンドロームを診断するために有用かどうかの検討を行った。また、これまで糖脂質代謝によい影響を与えるとされている薬剤が実際にそのようなアディポカインを変化させているかを検証するための臨床試験(BCAT: Beneficial effect of Candesartan on Adiponectin Trial)を開始する。2型糖尿病における血圧のコントロールの目標値については、最近発表された「糖尿病治療ガイド(平成18年度版)」によると収縮期血圧 130mmHg・拡張期血圧 80mmHg とされている。血圧のコントロールに際してどの降圧薬を第一選択とすべきかについては規定されていない。本試験の試験薬である

カンデサルタンは優れた降圧作用があるとともに、インスリン抵抗性改善作用を持つアディポネクチンの血中レベルを増加させインスリン抵抗性を改善する作用があることが報告されており、インスリン抵抗性を基盤とする2型糖尿病やメタボリックシンドロームにおける血圧コントロール薬として最も好ましいと推測される。更にアディポネクチンは血中では様々な多量体構造をとっており、その中でも12量体～18量体の高分子量アディポネクチンが、最もアディポネクチンのインスリン抵抗性改善作用を強く持っていることが明らかになっている。我々は高分子量アディポネクチンを特異的に測定する方法を開発し、実際に高分子量アディポネクチンの絶対量あるいはその総アディポネクチンに対する比率が、総アディポネクチンに比べてもインスリン抵抗性と強く相関することを報告している。そこで、カンデサルタンがアディポネクチンの中でも高活性型である高分子量アディポネクチンの絶対量やその総アディポネクチンに対する比率を特に上昇させるかどうか、対照薬としてアムロジピンを用いた非盲検ランダム化比較試験にて明らかにする。また、実際にインスリン抵抗性を改善するか否かを、インスリン抵抗性の簡便な指標として臨床研究で頻用されているHOMA(homeostasis model assessment)の指標によって評価する。本試験の成果によって、2型糖尿病やメタボリックシンドロームにおける効果的な心血管疾患リスク低減法のガイドライン策定のための基礎的なデータが得られることが期待される。本臨床試験 BCAT に組み入れられる対象者は①年齢が20歳以上 70 歳未満で②2型糖尿病患者または境界型(IGT: impaired glucose tolerance)の条件を満たし、除外基準（①収縮期血圧が 140mmHg 以上または拡張期血圧が90mmHg 以上、②アンジオテンシンII受容体拮抗薬, アンジオテンシン変換酵素阻害薬, 長時間作用型 Ca チャネル遮断薬を既に服用中のもの、③インスリンによる治療を行なっているもの、④チアゾリジン誘導薬を服用中の者、⑤何らかの理由で空腹時採血が出来ない者、⑥HbA1c10%以上、⑦収縮期血圧が200mmHg 以上または拡張期血圧が110mmHg 以上、⑧腎不全(血清クレアチニンが男性で 2.0mg/dL 以上, 女性で 1.5mg/dL 以上)、⑨両側性腎動脈狭窄のある者または片腎で腎動脈狭窄のある者、⑩高カリウム血症、⑪カリウム保持性利尿薬、カリウム補給剤を投与中の者、⑫二次性高血圧症またはその疑いのある者、⑬肝不全、⑭薬剤過敏症の既往歴のある者、⑮妊婦または妊娠している可能性のある者）に当てはまらないものである。主要評価項目は試験終了時の(ア総アディポネクチン、高分子量アディポネクチン絶対量(HMW)ならびに高分子量アディポネクチンの総アディポネクチンに対する比率(HMWR)であり、主要な解析はカンデサルタン群とアムロジピン群とで両側 t 検定を行い、両群で差があるかどうか検討する。また、年齢、性別、BMI で調整した分散分析も同時に行い、これらの因子で調整後の差を検討することとした。

B. 採択された研究事業での研究実績

(1)糖尿病調査とその解析

平成 10～12 年度に行なった「厚生労働省研究班による多目的コホート」対象の健診受診者による糖尿病調査(ベースライン調査;対象者約2万5千人)の結果、糖尿病有病率を 51～70 歳では男性 13～15%、女性 6～9%と確定した。平成

15~17 年度に第 2 回目の糖尿病実態調査(5 年後調査)を全国 10 箇所で実施、終了した。

(2)「厚生労働省研究班による多目的コホート研究」データとの包括的解析および臨床研究

①嗜好と体格に関する研究(a組:野田):平成 2 年、7 年、12 年に行なわれた「厚生労働省研究班による多目的コホート(コホートⅠ)」のベースライン調査、5 年後調査、10 年後調査のアンケートの結果を用い、自己申告による 10 年間の糖尿病発症に対する危険因子を前向きコホート研究のスタディデザインによって分析した。その結果、年齢、BMI、糖尿病の家族歴は多重ロジステイック解析に予知男女とも糖尿病の発症と有意に正相関した。喫煙(過去の喫煙と現在 20 本以上の喫煙)も男女いずれにおいても糖尿病発症のリスクを有意に上げていた。男性では、1 日のエタノール摂取が23g(日本酒換算1合)以上のものにおいて、糖尿病発症のリスクが有意に上昇していた。とくに、痩せ型(BMI22 以下)の男性において 1 合/日以上の飲酒が 2 型糖尿病と正相関した。喫煙に関しては、BMI 22以上、特に 25 以上の男性において 2 型糖尿病の発症と相関が強く、障害喫煙量と糖尿病発症リスクとの間には容量・反応関係が認められた。さらに、そのリスクは禁煙により 10 年で非喫煙者とほぼ同等になることを見出した。

さらに、コーヒー摂取はコーヒー非摂取者に比し、その後の糖尿病発症が男女ともに有意に低かった(男性 0.83 (95%CI 0.70-0.99) 、 女性 0.76 (95%CI 0.61-0.94)。ベースライン調査のアンケートと健診データを用いた横断研究においては、コーヒー摂取(杯数、カフェイン換算)、総カフェイン摂取量は空腹時高血糖と有意な負の相関を示した(緑茶、紅茶、ウーロン茶は相関を示さなかった)。男女別に、コーヒーにや紅茶に砂糖を入れる習慣の有無と喫煙習慣を加えた解析を行ない、砂糖についての習慣、現在の喫煙習慣の要因を加えても、男性においてコーヒー摂取が空腹時高血糖と有意に相関した(砂糖に関する習慣、喫煙はいずれも有意な結果を示さなかった)。

②運動と血糖コントロールに関する研究(b 組:高橋):「厚生労働省研究班による多目的コホート研究」における運動について調査項目の妥当性の検討を行なっている。調査は、1)過去に行なったものと同一の質問表による調査を 2 度にわたって実施することにより、質問表の再現性について検討する。この際、「24 時間行動記録表」および「運動加速度計(ライフコーダ)」よる評価も同時に行い、それらの変動についても検討する、2)質問票から計算したエネルギー消費量を「24 時間行動記録表」および「運動加速度計(ライフコーダ)」で算出したエネルギー消費量と比較し、妥当性を検討する、というものである。その結果、「24 時間行動記録」による energy expenditure (EE: METs/day)の再現性はよいこと (Spearman's correlation coefficient = 0.91 ($p<0.0001$)や、質問票による EE と「24 時間行動記録」によるそれとの間には有意な相関(ρ =0.48～0.62)が認められること、「運動加速度計(ライフコーダ)」による EE と「24 時間行動記録」によるそれとの間の相関は低い(ρ =0.13)こと、などの知見を得ることができた。

③糖尿病・メタボリックシンドロームの発症・進展を予測するバイオマーカーの開発(c 組:原):これまでインスリン抵抗性

を増悪させると報告されているアディポカインについては、インスリン抵抗性と有意に相関するものは認めなかった。これとは対照的に,血中アディポネクチン値が、インスリン抵抗性やメタボリックシンドロームと有意に相関した。アディポネクチンは生体内では分子量の異なるいくつかの分子種として存在しているが、その中でも12～18量体の高分子量アディポネクチン(以下HMW(high molecular weight)アディポネクチンのインスリン感受性作用が最も強力であること、HMW-Adが形成されないようなアディポネクチン遺伝子変異保持者はいずれも2型糖尿病を発症していることなどから、HMWアディポネクチンが糖尿病の発症・進展に重要な働きを担っていることが推定されていた。そこで、HMWアディポネクチンがインスリン抵抗性・メタボリックシンドロームの病態をどの程度反映しているかを明らかにし、HMWアディポネクチンのメタボリックシンドローム病態診断法としての意義を検証するために、HMWアディポネクチンを特異的に測定することが出来るキットを利用して、糖尿病患者について総アディポネクチン、HMWアディポネクチンを測定した。HOMA-IRと総アディポネクチン、HMWアディポネクチンならびにHMWアディポネクチンの総アディポネクチンに対する比率であるHWWR（high molecular weight ratio）との相関を検討したところ、それぞれP= 0.0280、P= 0.0035、P = 0.0008と有意に相関を示したが、HMWRが最もインスリン抵抗性と強く相関した。HOMA-IRが2.5以上をインスリン抵抗性有としたときのインスリン抵抗性の診断に対するROC (receiver operator characteristics)曲線を描出したところ、総アディポネクチンの曲線下面積が0.615 [95%CI: 0.522 - 0.708]であったのに対してHMWRは0.713 [95%CI: 0.620 - 0.805]と有意にHMWRの方が大きく(P = 0.0160)、従ってHMWRが総アディポネクチンに比してもインスリン抵抗性の診断能が高いことが明らかになった。また、メタボリックシンドロームの診断能についてROC曲線を描出したところ、男性では総アディポネクチンの曲線下面積が0.730 [95%CI: 0.660 - 0.800]であったのに対してHMWRは0.806 [95%CI: 0.747 - 0.865]と有意にHMWRの方が大きく(P= 0.0025)、女性でも総アディポネクチンの曲線下面積が0.637 [95%CI: 0.532 - 0.742]であったのに対してHMWRは0.743 [95%CI: 0.659 - 0.828]と有意にHMWRの方が大きく(P= 0.0458)、従ってHMWRが総アディポネクチンに比してもメタボリックシンドロームの診断能が高いことが明らかになった。(*Diabetes Care* 29(6), 1357, 2006)。

更に、これまで糖脂質代謝によい影響を与えるとされている薬剤が実際にそのようなアディポカインを変化させているかを検証するための臨床試験(BCAT: Beneficial effect of Candesartan on Adiponectin Trial)については現在対象者について同意を得るための説明を行っているところである。

(倫理面への配慮)平成15年7月30日に厚生労働省によって策定された「臨床研究に関する倫理指針」を遵守して研究を遂行する。その具体的な配慮として、臨床研究を実施するに当たり、被験者の個人情報の保護のために、本研究で提供

される試料はすべて個人識別情報(カルテ番号，名前，住所など）を除き、連結可能匿名化した上で解析に利用される。連結可能のための対応表は他の一切のコンピューターと切り離された stand alone のコンピューターに専用の ID とパスワードよって厳重に保管される。また、当該コンピューターは民間警備会社によるセキュリティーシステムによって守られ、不特定多数の者の出入りができない専用の部屋に設置される。予測される試料提供者に対する危険や不利益に関して:試料提供は主として前腕の静脈からの採血によっており身体的危険はほとんどないといってよい。また提供された試料は解析に先立って速やかに匿名化されるので，試料等提供者の尊厳と人権は充分に保護されていると考えられる。

C.考察

家族歴、喫煙は男女いずれにおいても糖尿病発症のリスクを上昇させる。痩せ型(BMI22 以下)の男性においては 1 合/日以上の飲酒が2型糖尿病と正相関した。また、喫煙に関しては、肥満男性において 2 型糖尿病の発症と相関が強く、生涯喫煙量と糖尿病発症リスクとの間には容量・反応関係が認められた。さらに、そのリスクは禁煙により 10 年で非喫煙者とほぼ同等になる。さらに、コーヒー摂取はコーヒー非摂取者に比し、その後の糖尿病発症が男女ともに有意に低かった。HMW アディポネクチンならびに HMWR は糖尿病・メタボリックシンドロームの発症・進展を予測する臨床指標として有用である可能性が示唆された。

以上、男女とも糖尿病の家族歴、喫煙が、痩せ型の男性においては、飲酒は糖尿病の発症リスクを上昇させる。コーヒー摂取は逆に糖尿病の発症リスクを低下させる。また、HMW アディポネクチンの測定はインスリン抵抗性やメタボリックシンドロームの診断に有用であると考えられた。

D.健康危険情報

特になし

E.その他実施した臨床研究・治験の概要及び実績

２型糖尿病患者が摂取カロリーを見積もる正確性と血糖コントロールとの相関を、都内の２つの病院に通院する 46 人の男性、16 人の女性糖尿病患者(３３歳～７７才)を対象に検討した。摂取カロリーの見積もりが±10%以内の誤差で出来た人の割合は血糖コントロールが悪いほど低いという結果が得られ(*Diabetes Res Clin Pract.* 67(3):220, 2005)、栄養指導の重要性が示唆された。また小児肥満者の実態調査を都市部と非都市部で行った。1976 年から 1980 年にかけての調査では、肥満した学童の割合は男児では 6.1%であったのに対して、1996 年から 2000 年の調査では 11.1%に増加した。女児では同時期に 7.1%から 10.2%に変化した。都市部の女児では肥満の割合に有意な変化は認められなかった(Obesity Research 12(2), 2004)。

Ⅲ. 研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
KAZUO HARA, MD, PHD MOMOKO HORIKOSHI, MD, PHD TOSHIMASA YAMAUCHI, MD, PHD HIROKAZU YAGO OSAMU MIYAZAKI HIROYUKI EBINUMA YASUSHI IMAI, MD, PHD RYOZO NAGAI, MD, PHD TAKASHI KADOWAKI, MD, PHD	Measurement of the High–Molecular Weight Form of Adiponectin in Plasma Is Useful for the Prediction of Insulin Resistance and Metabolic Syndrome	Diabetes Care	29	1357-1362	2006
Yumi Matsushita[a],, Tetsuji Yokoyama, Takeshi Homma, Heizo Tanaka, Kazuo Kawahara	Relationship between the ability to recognize energy intake and expenditure, and blood sugar control in type 2 diabetes mellitus patients	Diabetes Research and Clinical Practice	67	220-226	2005
Trends in Childhood Obesity in Japan over the Last 25 Years from the National Nutrition Survey	Yumi Matsushita, Nobuo Yoshiike, Fumi Kaneda, Katsushi Yoshita, and Hidemi Takimoto	OBESITY RESEARCH	12	205-214	2004

Measurement of the High-Molecular Weight Form of Adiponectin in Plasma Is Useful for the Prediction of Insulin Resistance and Metabolic Syndrome

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OBJECTIVE — The high–molecular weight (HMW) form of adiponectin, an adipocyte-derived insulin-sensitizing hormone, has been reported to be the most active form of this hormone. We investigated whether measurement of plasma HMW adiponectin levels, using our newly developed enzyme-linked immunosorbent assay system for selective measurement of human HMW adiponectin level, may be useful for the prediction of insulin resistance and metabolic syndrome.

RESEARCH DESIGN AND METHODS — A total of 298 patients admitted for diabetes treatment or coronary angiography served as study subjects. Receiver operator characteristic (ROC) curves for the HMW ratio (HMWR; ratio of plasma level of HMW adiponectin to that of total adiponectin) and plasma total adiponectin levels were plotted to predict the presence of insulin resistance and metabolic syndrome.

RESULTS — The area under the ROC curve (AUC) of the HMWR values to predict the presence of insulin resistance was significantly larger than that of plasma total adiponectin level in total subjects (0.713 [95% CI 0.620–0.805] vs. 0.615 [0.522–0.708], $P = 0.0160$). The AUC for the HMWR values to predict the presence of metabolic syndrome was significantly larger than that for plasma total adiponectin levels in men (0.806 [0.747–0.865] vs. 0.730 [0.660–0.800], $P = 0.0025$) and in women (0.743 [0.659–0.828] vs. 0.637 [0.532–0.742], $P = 0.0458$).

CONCLUSIONS — The HMWR value has better predictive power for the prediction of insulin resistance and metabolic syndrome than plasma total adiponectin level.

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Adiponectin (also known as ACRP30, GBP28, and AdipoQ) is a hormone secreted exclusively by adipocytes (1–4). Adiponectin replenishment has been found to ameliorate the abnormalities of metabolic syndrome, including insulin resistance, hyperglycemia, and dyslipidemia, in a murine model of obesity-linked metabolic syndrome associated with decreased adiponectin levels (5). Adiponectin-deficient mice (6,7) have been demonstrated to show features of metabolic syndrome, such as insulin resistance, glucose intolerance, dyslipidemia, and hypertension. In humans, decreased plasma adiponectin levels have been demonstrated in patients with obesity, diabetes, and coronary artery disease (8–10), all of which are linked to insulin resistance. Moreover, the degree of hypoadiponectinemia has been reported to be correlated with the degree of insulin resistance (11,12), and hypoadiponectinemia has been shown to be closely associated with the clinical phenotype of metabolic syndrome (13,14). The gene encoding adiponectin (*APM1*) has been mapped to chromosome 3q27, which has been reported to be linked to type 2 diabetes and metabolic syndrome by genome-wide scans in Japanese (15), American, (16), and French-Caucasian (17) populations. A single nucleotide polymorphism in the adiponectin gene was shown to be associated with hypoadiponectinemia, insulin resistance, and increased risk of type 2 diabetes (18,19), indicating that adiponectin may play a crucial role in the regulation of insulin sensitivity and glucose and lipid metabolism and that reduced plasma adiponectin levels caused by genetic and environmental factors may lead to the development of insulin resistance, type 2 diabetes, and metabolic syndrome (20). Indeed, a recent study demonstrated that individuals with high plasma adiponectin levels had a substantially lower relative risk of developing type 2 diabetes, even after adjustment for conventional risk factors, such as BMI (21,22).

We have reported that adiponectin forms multimers and is present in the serum as a trimer, hexamer, or as a high–molecular weight (HMW) form (23). The HMW isoform binds most avidly to its receptors and stimulates AMP-activated protein kinase, one of the key molecules mediating the metabolic actions of adiponectin (Y. Hada, T.Y., H. Waki, K.H.,

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Abbreviations: AUC, area under the curve; HMW, high molecular weight; HMWR, HMW ratio; HOMA-IR, homeostasis model assessment of insulin resistance; IDF, International Diabetes Federation; ROC, receiver operator characteristic.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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H.Y., O.M., H.E., T.K., unpublished observations). Mutations in the adiponectin gene that cause impaired multimerization and decreased plasma HMW adiponectin levels have been found to be associated with insulin resistance and type 2 diabetes (23), suggesting that alterations in plasma HMW adiponectin level may be more relevant in the prediction of insulin resistance than those in plasma total adiponectin levels. Indeed, a recent study has shown that the ratio of the plasma level of HMW adiponectin to that of total adiponectin level (HMWR) is significantly more useful for monitoring the improvement of insulin sensitivity in response to thiazolidinediones in cases of type 2 diabetes (24). The HMWR value has been also shown, by oral glucose tolerance tests, to be more significantly inversely correlated with 2-h glucose levels than total adiponectin level (25). However, in this study, the adiponectin multimers were separated by velocity sedimentation/gel filtration and quantified HMW adiponectin level by Western blotting. In the present study, we investigated the clinical usefulness of measurement of plasma HMW adiponectin level using a newly developed method, as compared with that of plasma total adiponectin level by analyzing the sensitivity or specificity of total adiponectin levels, HMW adiponectin levels, and HMWR values for the prediction of insulin resistance and metabolic syndrome. This study is the first to demonstrate the clinical usefulness of measuring HMW adiponectin levels in making precise prediction of insulin resistance and metabolic syndrome.

RESEARCH DESIGN AND METHODS

— The subjects of this study were 298 patients admitted to Tokyo University Hospital for the treatment of diabetes or coronary angiography. The present study was conducted according to the principles outlined in the Declaration of Helsinki. Informed consent was obtained from each of the study subjects. The protocol of the study was approved by the ethics review committee of Tokyo University School of Medicine.

Height, weight, hip, waist, fasting plasma glucose, serum insulin, serum total cholesterol, triglyceride, HDL cholesterol, and LDL cholesterol levels were measured the morning after an overnight fast. We modified the diagnostic criteria of the National Cholesterol Education Program Adult Treatment Panel III for metabolic syndrome (26) by adopting a cutoff level for the waist circumference of 85 cm in men and 90 cm in women, in accordance with the recommendations for the Japanese population by the International Diabetes Federation (IDF) (27). The homeostasis model assessment of insulin resistance (HOMA-IR) (28) was determined in 171 subjects (110 men and 61 women); however, it could not be assessed in subjects being treated with insulin or in some of the subjects admitted for coronary angiography. We defined subjects with a HOMA-IR of >2.5 as having insulin resistance. This cutoff has been adopted in the Japanese guideline for the treatment of diabetes. We analyzed the relationship between total adiponectin levels or HMWR values and severity and extent of coronary atherosclerosis using the score by Gensini (29). Subjects with a history of percutaneous coronary intervention were excluded from this analysis. Because thiazolidinediones have been reported to exhibit direct antirestenotic effects in the vasculature (30) and have protective effects against coronary artery disease (31), after the prescription of thiazolidinediones was incorporated into the model in addition to the conventional risk factors for atherosclerosis, stepwise regression analysis was done to analyze the relationship between HMWR values and Gensini score. The measurement method for plasma HMW adiponectin level is described elsewhere (H.E., O.M., H.Y., K.H., T.Y., T.K., unpublished observations) and coefficients of variations of the assay were 5.3% for total adiponectin and 3.3% for HMW adiponectin level.

Statistical analyses

The values of the clinical parameters were expressed as means ± SD. All statistical analyses were performed using JMP for Windows software (version 4.0; SAS Institute, Cary, NC). The significance of differences in plasma total adiponectin levels, HMW adiponectin levels, and HMWR values was analyzed by ANOVA. ROC curves were plotted and compared using the Stata software (College Station, TX). P values <0.05 were considered to denote statistical significance.

RESULTS

— As shown in online appendix Table 1 (available at http://care.diabetesjournals.org), there is no difference in the proportion of the subjects who took at least one of the drugs potentially affecting plasma adiponectin levels, such as thiazolidinediones, biguanide, ACE inhibitors, and angiotensin receptor blockers, between subjects with and without metabolic syndrome (68 [42.5%] vs. 54 [39.1%], $P = 0.686$).

Correlations between patient characteristics and plasma total adiponectin and HMW adiponectin levels and HMWR values

Women had higher plasma total adiponectin levels (5.59 ± 0.31 vs. 4.55 ± 0.22 μg/ml, $P = 0.0069$), HMW adiponectin levels (2.19 ± 0.14 vs. 1.54 ± 0.11 μg/ml, $P = 0.0003$), and HMWR values (35.9 ± 1.1 vs. 29.9 ± 0.8%, $P = 0.00001$) than men. There was an inverse correlation between BMI and plasma total adiponectin levels ($r = -0.29$, $P = 0.0001$), HMW adiponectin levels ($r = -0.27$, $P = 0.0001$), and HMWR values ($r = -0.13$, $P = 0.012$). In multivariate analysis taking into account BMI, sex, and the interaction between sex and BMI, sex and BMI were independently correlated with plasma total adiponectin levels ($P = 0.0001$ and 0.0025, respectively), plasma HMW adiponectin levels ($P = 0.0001$ and 0.0001, respectively), and HMWR values ($P = 0.0075$ and 0.0001, respectively). However, since there was no interaction between sex and BMI for these three different measurements of plasma adiponectin ($P = 0.29$, 0.23, and 0.34, respectively), the inverse correlation between BMI and plasma total adiponectin level, plasma HMW adiponectin levels, or HMWR values were not affected by sex. Plasma total adiponectin level, plasma HMW adiponectin levels, and HMWR values did not vary with age in either sex (data not shown).

HMWR value predicted insulin resistance more precisely than plasma total adiponectin level

Insulin resistance is closely linked with metabolic syndrome and is often observed even in the early stage of metabolic syndrome (32). We investigated the correlation between insulin resistance and each of the three different measurements of plasma adiponectin. The total adiponectin level was inversely correlated with the HOMA-IR ($P = 0.0280$) in 171 men and women, consistent with the results of previous studies (11,12); the HMW adiponectin levels ($P = 0.0035$) and HMWR values ($P = 0.0008$) were also inversely correlated with HOMA-IR. In 110 men, there was a significant inverse correlation between HOMA-IR and

plasma HMW adiponectin levels (P = 0.0083) and HMWR values (P = 0.0010), while there was only a tendency toward inverse correlation between HOMA-IR and plasma total adiponectin levels (P = 0.0613). In 61 women, tendencies were found for decreased plasma total adiponectin levels and for HMW adiponectin levels or HMWR values to be associated with increased HOMA-IR values. HMWR values were significantly and inversely correlated with HOMA-IR, even after adjusting for age, sex, and BMI (P = 0.0304) or adjusting for BMI alone (P = 0.0389) in 171 men and women, suggesting that correlation between HMWR values and HOMA-IR was independent of the association between BMI and HOMA-IR. In contrast, the statistically significant association between total adiponectin and HOMA-IR disappeared after adjusting for age, sex, and BMI (P = 0.227) or adjusting for BMI alone (P = 0.249) in 171 men and women. These results are again consistent with the superiority of HMWR values over total adiponectin level to predict the presence of insulin resistance. We then plotted ROC curves to compare the power of plasma total adiponectin level and HMWR value to predict the presence of insulin resistance (Fig. 1). The AUC of HMWR values was significantly larger than that of plasma total adiponectin levels (0.713 [95% CI 0.620–0.805] vs. 0.615 [0.522–0.708], P = 0.0160) (Fig. 1), suggesting that the HMWR value had better predictive power for the prediction of insulin resistance than plasma total adiponectin level. When a cutoff value of 35% was used, the HMWR value predicted the presence of insulin resistance with a sensitivity of 72% and specificity of 66%. On the other hand, at a cutoff level of 4.2 μg/ml, plasma total adiponectin diagnosed insulin resistance with a sensitivity of 56% and specificity of 63%. When stratified according to sex, there was a significant difference between the AUCs for plasma total adiponectin levels and HMWR values in men (0.713 [0.605–0.821], P = 0.048 vs. 0.624 [0.514–0.733], P = 0.048), while we could detect no such difference in women (0.794 vs. 0.665, P = 0.09).

Correlation between the number of risk factors and plasma total adiponectin levels, HMW adiponectin levels, or HMWR values

We then investigated the association between the number of risk factors defining the prediction of metabolic syndrome (see RESEARCH DESIGN AND METHODS) in the subjects and plasma total adiponectin levels, HMW adiponectin levels, and HMWR values. The plasma total adiponectin levels (P = 0.0001), HMW adiponectin levels (P = 0.0001), and HMWR values (P = 0.0001) decreased as the number of risk factors present increased; this tendency was observed irrespective of sex (data not shown).

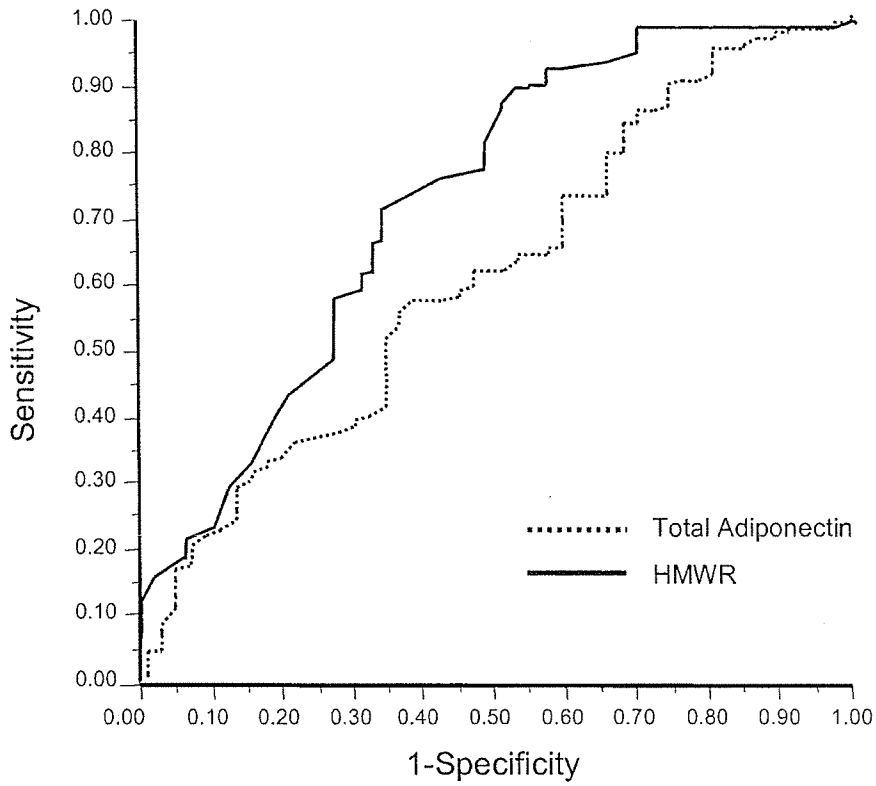

Figure 1—*ROC curves of plasma total adiponectin levels and HMWR values for the prediction of insulin resistance, defined as a HOMA-IR index >2.5 (n = 171). The AUC for the HMWR values was significantly larger than that for plasma total adiponectin levels (0.713 [95% CI 0.620–0.805] vs. 0.615 [0.522–0.708], P = 0.0160).*

ROC curves for models to predict the presence of metabolic syndrome

We performed an ROC analysis to quantify the power of the HMWR values to make a prediction of metabolic syndrome. ROC curves for plasma total adiponectin levels and HMWR values to discriminate between subjects with and without metabolic syndrome were plotted for total subjects (data not shown), men (Fig. 2*A*), and women (Fig. 2*B*). The areas under the curve for plasma total adiponectin level and HMWR values were then compared to determine whether the HMWR value had a better predictive power for the prediction of metabolic syndrome than plasma total adiponectin level. The AUC for the HMWR values was significantly larger than that for plasma total adiponectin levels in all subjects (0.780 [95% CI 0.736–0.824] vs. 0.692 [0.632–0.751], P = 0.039) (data not shown), in men (0.806 [0.747–0.865] vs. 0.730 [0.660–0.800], P = 0.0025) (Fig. 2*A*), and in women (0.743 [0.659–0.828] vs. 0.637 [0.532–0.742], P = 0.0458) (Fig. 2*B*). When a cutoff value of 32.0% for men and 40.2% for women was adopted to maximize the sensitivity (%) plus specificity (%), HMWR value predicted the presence of metabolic syndrome with a sensitivity of 83.2% and specificity of 62.0% in men and a sensitivity of 77.4% and specificity of 55.0% in women.

We have undertaken the subgroup analyses in both diabetic and nondiabetic subjects. In both groups, AUCs for the HMWR values to predict metabolic syndrome were larger than those for total adiponectin levels (type 2 diabetic group: 0.815 [95% CI 0.755–0.875] vs. 0.676 [0.616–0.736], P = 0.0013; nondiabetic group: 0.843 [0.743–0.943] vs. 0.751 [0.651–0.851], P = 0.00475).

We have also plotted ROC curves for

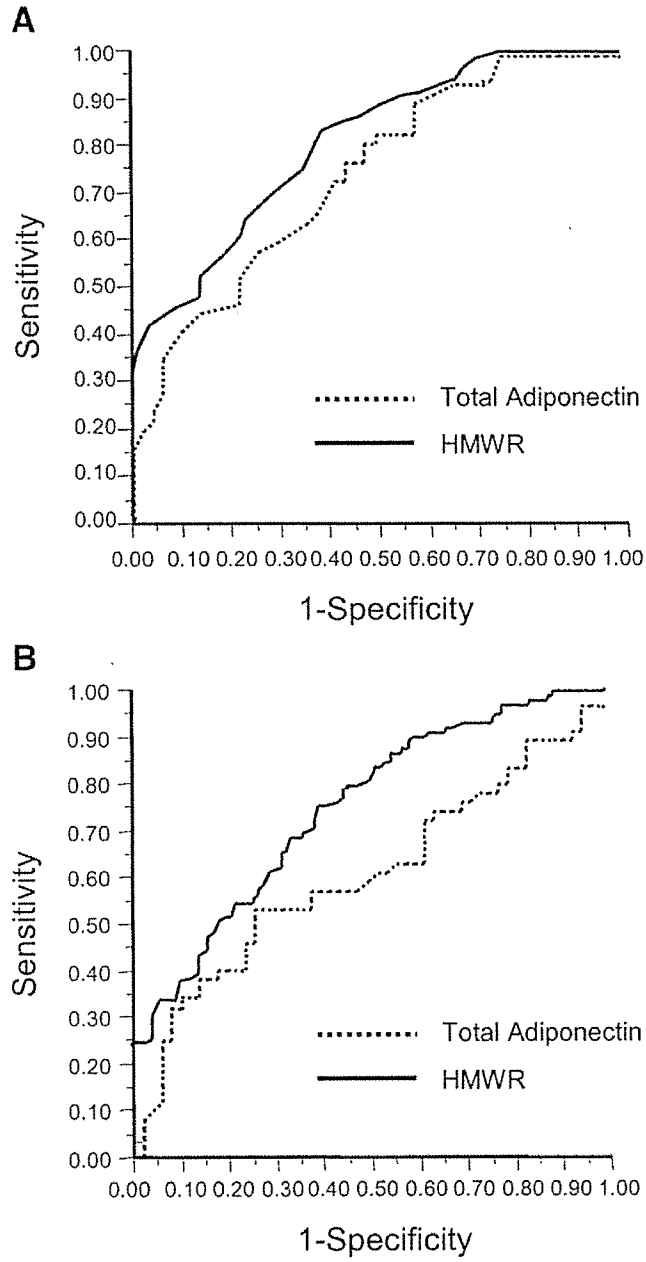

Figure 2—*ROC curves of plasma total adiponectin levels and HMWR values for prediction of metabolic syndrome in men (A) (n = 193) and women (B) (n = 105). Prediction of metabolic syndrome was based on the criteria of the National Cholesterol Education Program Adult Treatment Panel III for prediction of metabolic syndrome. The AUC for the HMWR values was significantly larger than for total adiponectin in both men (0.806 [95% CI 0.747–0.865] vs. 0.730 [0.660–0.800], P = 0.0025) and women (0.743 [0.659–0.828] vs. 0.637 [0.532–0.742], P = 0.0458).*

total adiponectin levels and HMWR values to predict metabolic syndrome defined by newly announced IDF criteria (27). Indeed, HMWR values were more predictive of metabolic syndrome defined by IDF than total adiponectin levels in total subjects (0.733 [95% CI 0.693–0.773] vs. 0.680 [0.640–0.720], P = 0.0037).

HMWR value predicts the presence or absence of metabolic syndrome independently of plasma total adiponectin level

The HMWR values varied substantially even among subjects with similar total adiponectin levels in plasma. The present ROC analysis suggested the possibility that the HMWR value may be useful for predicting the presence of metabolic syndrome among subjects with similar plasma levels of total adiponectin. We examined whether the HMWR values were different between subjects with and without metabolic syndrome after stratifying the subjects into quartiles of plasma total adiponectin levels. HMWR values were significantly lower in all the quartiles of total adiponectin in subjects with metabolic syndrome than in those without, suggesting that the HMWR value may be useful for the prediction of metabolic syndrome, irrespective of plasma total adiponectin level.

The relationship between HMWR value and the severity of coronary artery disease

We analyzed the relationship between total adiponectin levels or HMWR values and severity and extent of coronary atherosclerosis using the score by Gensini (29). Gensini scores were significantly associated with age (P = 0.0022), prescription of thiazolidinediones (P = 0.0443), and HMWR values (P = 0.0437). Subjects with lower HMWR value had higher Gensini score, suggesting that HMWR value might be associated with the onset and development of coronary artery disease independently of age and prescription of thiazolidinediones. Total adiponectin level was not correlated with Gensini score before and after adjustment for the conventional risk factors for atherosclerosis and prescription of thiazolidinediones.

CONCLUSIONS— Prediction of metabolic syndrome, defined by the presence of a cluster of metabolic abnormalities, including impaired glucose metabolism, high BMI and abdominal fat distribution, dyslipidemia, and hypertension, is very important because of its association with the subsequent development of type 2 diabetes and cardiovascular disease (28). Because of the epidemic of obesity and a sedentary lifestyle worldwide, metabolic syndrome is becoming increasingly commonly recognized. According to the National Cholesterol Education Program (NCEP) definition, roughly one-fourth of middle-aged men and women in the U.S. have metabolic syndrome (33). Development of a method for convenient prediction of metabolic syndrome in daily clinical practice presents a major challenge for physicians and public health policy makers facing

the epidemic of obesity and a sedentary lifestyle.

There is a mounting body of evidence to suggest that adiponectin is an insulin-sensitizing hormone and that the plasma level of this hormone is the best predictor of the subsequent development of type 2 diabetes among the various plasma biomarkers (34). Recently, however, it has been reported that adiponectin forms a wide range of multimers in plasma and that mutations in the adiponectin gene that inhibit the formation of HMW adiponectin are closely associated with the subsequent development of type 2 diabetes. Therefore, it was considered that HMW adiponectin value might be an attractive biomarker for the prediction of insulin resistance and metabolic syndrome. Indeed, the present study demonstrated that the AUC of HMWR values was significantly larger than that of plasma total adiponectin levels and that the sensitivity of the HMWR value for predicting the presence of metabolic syndrome reached 80%. Thus, this study is the first to demonstrate that HMWR value is more closely associated with insulin resistance and the presence of metabolic syndrome than plasma total adiponectin level.

The present study provided evidence of the usefulness of a newly developed method of measurement of plasma HMW adiponectin level as a convenient and sensitive biomarker for the prediction of insulin resistance and metabolic syndrome.

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Relationship between the ability to recognize energy intake and expenditure, and blood sugar control in type 2 diabetes mellitus patients

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Abstract

To investigate the association between an individual's ability to recognize his/her energy intake and energy expenditure with the status of diabetes mellitus (DM) control, we conducted a cross-sectional study using data from 62 outpatients with type 2 DM (46 men and 16 women), aged 33–77 years, from two hospitals in Tokyo in 1999. A dietitian–interviewer asked the patients to estimate their probable energy intake and expenditure in recent days (self-estimated energy intake and expenditure, respectively). Subsequently, a dietary survey was conducted to estimate the patient's energy intake by a self-recorded method with a dietitian's interview for three continuous business days; the physical exercise levels were measured using a pedometer with multiple-memory accelerometers for one week. The percentage of subjects whose self-estimated energy intake was within ±10% of the dietary survey-based energy intake became significantly lower as the control status worsened (35.6, 12.9, and 11.1% in the first, second, and third tertile groups of HbA_{1c}, respectively; $P = 0.015$). Similar but non-significant results were observed for the energy expenditure ($P = 0.35$). Since the control status of DM was worse among patients who could not recognize their amount of caloric intake and expenditure, a training program to improve such recognition ability may be needed.
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Keywords: Energy intake; Energy expenditure; Dietary therapy; Type 2 diabetes mellitus; Self estimation

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1. Introduction

Non-pharmacological therapies for diabetes mellitus (DM), including a low-calorie diet, weight loss, and regular vigorous exercise, are the essential approaches regardless of whether pharmacologic agents are prescribed [1]. DM patients are instructed to understand their caloric intake and energy expenditure, and are requested to balance these factors in order to control their disease. To learn the skills to perform this, DM patients are educated about their energy intake and energy expenditure [2]. Since the patients need to self-administer their energy intake and energy expenditure in their daily life, it is reasonable to speculate that the status of DM control may depend on the patients' ability to recognize their energy intake and energy expenditure. For example, if a patient underestimates the amount of what he/she eats, it may result in excessive caloric intake. To date, however, no studies have examined the effect of this recognition ability on the status of DM control.

We analyzed the association between an individual's ability to recognize his/her energy intake and energy expenditure with the status of their DM control, and discussed strategies to control DM in the context of the results.

2. Materials and methods

2.1. Subjects

We recruited consecutive outpatients with type 2 DM, aged 33–77 years, from two hospitals in Tokyo from April to August 1999. Two patients who had restricted physical exercise because of severe diabetic nephropathy were excluded. In total, 46 men and 16 women were enrolled in this study. When the subjects were diagnosed as type 2 DM, their physician instructed them to consume 25–30 kcal/day per kg of the standard body weight (defined as the body weight that corresponds to BMI = 22 kg/m^2), and to exercise more than 160 kcal/day or more than 10,000 foot steps. Then, a dietary survey (a one-week food record method) was conducted to assess the patients' dietary intake and a dietitian pointed out the problems of the patients' dietary intake based on the survey data. Informed consent was obtained from all subjects.

2.2. Survey items

The body height and weight were measured using a calibrated scale, and the BMI was defined as the weight/height^2 (kg/m^2). The body composition (body fat and lean body mass) was measured using the bioelectrical impedance method (Tanita, TBF-300).

To quantitatively measure physical exercise levels, the subjects wore a pedometer with multiple-memory accelerometers (Suzuken, Life Corder). This was a very small and light device (approximately 40 g), and was fixed at the first lumbar vertebra position of the subject's waist for one week. The device has an accelerometer sensor inside, and records the number of foot steps and 10-level exercise intensity every 4 s based on the amplitudes and frequencies of acceleration in the vertical direction, and calculates energy expenditure with and without exercise, taking into account the subject's gender, age, body height, and weight [3–7]. The exercise intensity calculated by the Life Corder has been shown to correspond with daily activities estimated by a time-motion study and to be correlated with overall energy expenditure as determined by the whole-body indirect calorimetry or breath gas analysis [3,6,8]. A one-day energy expenditure calculated by a living behaviors survey and a 24-h cardiograph has also been shown to be correlated with the exercise intensity recorded by a Life Corder [5,8].

For three continuous business days while wearing the Life Corder, the subjects themselves recorded what they ate (the self-recorded method). These three days were selected as normal business days (days with special diet because of social events were excluded). Dietitians reviewed the dietary records, and interviewed the subjects in detail about the foods he/she had eaten during the three days. The portion size was also determined by this interview with the aid of food models. Subsequently, the total and fat energy intake was calculated based on the fourth Standard Tables of Food Composition in Japan [9], and the mean values for these three days were used for the analysis. Hereafter, the energy intake and expenditure estimated by the self-recorded method and the Life Corder are referred to as the 'survey-based energy intake' and 'accelerometer-recorded energy expenditure,' respectively.

In advance of the dietary and physical exercise surveys, a dietitian–interviewer who was blinded to the subjects' DM control status asked the patients to estimate their usual energy intake and energy expenditure (hereafter referred to as the 'self-estimated energy intake (or expenditure)') by simply asking "how many calories do you think you usually take per day (in kcal)?" and "how many calories do you think you usually expend per day (in kcal)?" The smoking and alcohol drinking status were also reported in this interview. The levels of hemoglobin A_{1c} (HbA_{1c}) were measured using a non-fasting blood sample.

2.3. Statistics

The subjects were classified into three groups: ≤6.6% (group L), 6.7–7.5% (group M), and ≥7.6% (group H) according to the tertiles of their HbA_{1c} levels. Among these groups, the mean HbA_{1c} was compared by an analysis of covariance (ANCOVA) with a calculation of the least square means and standard errors (LSMs ± S.E.s). A ratio comparison was conducted using a logistic model adjusted for gender, age, and the receipt of pharmacological therapy.

The ability of a patient to recognize his/her energy intake (expenditure) was categorized as a "close match" when the self-estimated energy intake (expenditure) was within ±10% of the survey-based (accelerometer-recorded) method, as a "rough much" when it was within ±20%, as a "poor match" when it was beyond ±20%, and as "unable" when the patient could not answer. The relationship between the ability to recognize energy intake and energy expenditure and the status of DM control (as assessed by the HbA_{1c} levels) were analyzed by the proportional odds model, where the dependent variable was the tertile groups of HbA_{1c} (L, M, and H); the independent variables were the recognition ability ("close match," "rough much," "poor match," and "unable") and other potential confounders.

All statistical analyses were performed using SAS software (Version 8.2, SAS Institute).

3. Results

The basic characteristics of the study subjects are shown in Table 1. The mean age was 58.1 ± 9.5 years,

Table 1
Basic characteristics of the study subjects according to HbA_{1c} levels and status of self-estimated energy intake and expenditure

	All subjects	HbA_{1c} (tertiles)				Self-estimated energy intake				Self-estimated energy expenditure			
		Group L (≤6.6%)	Group M (6.7–7.5%)	Group H (7.6%≤)	*P* for trend	Close/rough match[a]	Poor match[a]	Unable[a]	*P* for trend	Close/rough match[a]	Poor match[a]	Unable[a]	*P* for trend
Number of subjects	62	20	21	21		24	17	21		17	23	22	
Percentages of women	25.8%	15.0%	33.3%	28.6%	0.33	25.0%	11.8%	38.1%	0.35	23.5%	17.4%	36.4%	0.32
Age[b]	58.1 ± 9.5	60.4 ± 8.9	58.0 ± 9.1	56.0 ± 10.4	0.39	56.3 ± 8.7	58.5 ± 10.1	59.8 ± 10.0	0.21	55.2 ± 9.4	59.8 ± 8.7	58.5 ± 10.3	0.32
Disease duration[b,c]	1.89 ± 0.98	1.68 ± 1.00	1.87 ± 1.06	2.11 ± 0.88	0.03	1.82 ± 0.82	1.90 ± 1.12	1.97 ± 1.08	0.61	1.66 ± 1.06	2.06 ± 0.91	1.89 ± 1.00	0.55
HbA_{1c}(%)[b]	7.2 ± 1.0	6.1 ± 0.5	7.1 ± 0.3	8.3 ± 0.6	–	7.0 ± 1.0	7.1 ± 1.2	7.5 ± 0.8	0.11	7.0 ± 1.0	7.3 ± 1.0	7.2 ± 1.1	0.62
Pharmacological therapy	53.2%	40.0%	52.4%	66.7%	0.09	45.8%	47.1%	47.6%	0.90	52.9%	39.1%	50.0%	0.91

[a] See text for definition.
[b] Mean ± standard deviation.
[c] Natural logarithm of 1 + disease duration (years).

Table 2
Comparison of the anthropometric measurements, energy intake, energy expenditure, and smoking and alcohol drinking habits among patients in the tertile groups of HbA_{1c}

	HbA_{1c} (tertiles)			
	Group L (≤6.6%) (LSM ± S.E.)	Group M (6.7–7.5%) (LSM ± S.E.)	Group H (≤7.6%) (LSM ± S.E.)	*P* for trend
Anthropometric measurements				
Height (cm)	162.3 ± 1.1	163.6 ± 1.0	161.2 ± 1.1	0.939
Weight (kg)	64.6 ± 1.9	62.6 ± 1.8	60.4 ± 1.8	0.145
BMI (kg/m^2)	24.5 ± 0.7	23.3 ± 0.7	23.3 ± 0.7	0.160
Body fat (%)	23.2 ± 1.3	21.4 ± 1.3	20.8 ± 1.3	0.205
Lean body mass (kg)	49.5 ± 1.1	49.2 ± 1.0	47.6 ± 1.0	0.249
Energy intake				
Total energy intake (kcal/day)	1883 ± 85	1814 ± 81	1698 ± 82	0.197
Per standard body weight (kcal/kg/day)	32.3 ± 1.5	31.0 ± 1.4	29.8 ± 1.4	0.241
Instructed value (kcal/kg/day)	27.7 ± 0.5	27.9 ± 0.5	28.3 ± 0.5	0.087
Fat energy ratio (%)	26.0 ± 1.3	26.8 ± 1.2	26.6 ± 1.3	0.815
Energy expenditure				
Total energy expenditure (kcal/day)	1983 ± 37	1972 ± 35	1876 ± 35	0.035
Physical activity intensity (METs)	1.348 ± 0.018	1.348 ± 0.017	1.327 ± 0.017	0.221
Energy expenditure by exercise (kcal/day)	276.0 ± 21.7	252.1 ± 20.6	238.3 ± 21.0	0.097
Number of steps (steps/day)	9030 ± 686	9049 ± 652	8809 ± 665	0.521
Smoking and alcohol intake				
Prevalence of current smoking	51.4%	64.5%	49.1%	0.872
Alcohol consumed (ethanol g/day)	29.9 ± 8.9	26.3 ± 9.0	21.5 ± 9.0	0.461

The values are expressed as least squares means (LSM) ± standard error (S.E.) by analysis of covariance (ANCOVA) and percentage values by a logistic regression model, adjusted for gender, age, and the receipt of pharmacological therapy.

and females represented 27.4% of the subjects. The higher the HbA_{1c} value, the longer the disease duration was. The percentage of patients undergoing pharmacological therapy was higher in the higher HbA_{1c} groups. There were no significant differences in these variables among the recognition ability groups of self-estimated energy intake and expenditure.

The anthropometric measurements, energy intake (survey-based), energy expenditure (accelerometer-recorded), and smoking and alcohol drinking habits are compared among the tertile groups of HbA_{1c} adjusted for gender, age, and receipt of pharmacological therapy (Table 2). The patients' weight, BMI, and percent body fat were slightly lower in the poorly controlled group H, but these differences were not significant. The survey-based energy intake was slightly lower in group H, although again this was not significant ($P = 0.197$ for trend), whereas the fat energy ratio was very similar among the three groups. Despite the mean recommended energy intake of 27.7, 27.9, and 28.3 kcal (per kg of the individual's standard body weight) in groups L, M, and H, respectively, the mean energy intake was higher than these values in all groups. The mean fat energy ratio exceeded the recommended value of ≤25% in all groups. The accelerometer-recorded total energy expenditure (LSM ± S.E.) was significantly higher in the well-controlled group ($P = 0.035$ for trend). The energy expenditure due to exercise showed a similar tendency, although it was not significant ($P = 0.097$). When expressed as metabolic equivalents (METs), there was no significant difference in the physical activity intensity among the three groups. There were also no significant differences in the amount of smoking or alcohol intake among the three groups.

The relationship between the ability to estimate energy intake and expenditure and the control status of DM is shown in Fig. 1. With respect to energy intake, the percentage of subjects who scored a "close match" became significantly poorer as the control status worsened (35.6, 12.9, and 11.1% in groups L, M, and H, respectively), whereas the percentage of

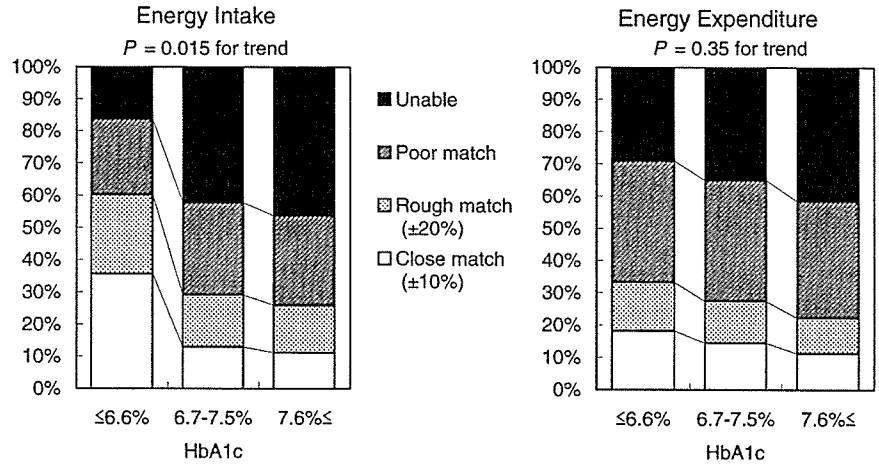

Fig. 1. Relationship between the ability to estimate energy intake and expenditure and the control status of DM. The percentage and *P*-values are adjusted for gender, age, and the receipt of pharmacological therapy with the use of a proportional odds model. The ability of a patient to recognize his/her energy intake (expenditure) was categorized as a "close match" when the self-estimated energy intake (expenditure) was within ±10% of the survey-based (accelerometer-recorded) method, as a "rough much" when it was within ±20%, as a "poor match" when it was beyond ±20%, and as "unable" when the patient could not answer.

subjects giving an "unable" response increased (16.4, 42.4, and 46.3%, respectively) ($P = 0.015$ for trend). Similar results were shown for the energy expenditure, but differences across the groups were not statistically significant ($P = 0.35$).

4. Discussion

Previous studies on DM patients have shown inconsistent findings about the relationship between the status of blood sugar control and the patient's knowledge of lifestyle-related factors: blood sugar control improves as knowledge increases [10–16]; improvements in blood sugar control can be achieved even without changes in knowledge [17,18]; and improvements in blood sugar control may not occur even with increased knowledge of lifestyle-related factors [19–26]. Although an educational program for DM patients is an essential approach for the management of this disease, these inconsistent findings suggest that some of the DM patients may not be able to comply with the recommended lifestyle changes, even after they acquire the knowledge about diet and physical exercise through the educational program.

There may be various reasons why DM patients do not comply with the dietary therapy and exercise. In this study, we hypothesized that the patients needed the ability to recognize their energy intake and energy expenditure for the good control of DM, and for adequate compliance with their therapy schedules. Given that the DM patients are advised by their physicians and dietitians about dietary intake and physical exercise, and can understand it, the patients may not necessarily comply with this advice. Even when the patients do try to comply, because of their inability to recognize how many calories they actually consume and expend, there are often errors. In fact, one study regarding the estimation of caloric intake in DM patients [27] reported that 30% of the subjects were able to accurately estimate their food energy, 20% of them overestimated it, and 50% of them underestimated their caloric intake. Our results (shown in Fig. 1) clearly indicated that the patients in the better control group were able to more accurately recognize their energy intake. A similar finding was also observed for the energy expenditure but it was not statistically significant. Thus, it is possible that the patients who cannot recognize the amount of caloric intake and physical exercise do not adequately comply with their nonpharmacological therapy schedule, and this eventually results in the poorly controlled status of DM. It may be more effective to improve the patients' ability to comprehend their energy intake and energy expenditure through an educational program.