表1 HbA1c 値≦7% 群と HbA1c 値＞7%群における最適治療前後の血糖値比較

	HbA1c値≦7%群		HbA1c値>7%群		p=1vs.2	p=1vs.2
	最適治療前	最適治療後	最適治療前	最適治療後	最適治療前	最適治療後
HbA1c値	8.6±0.2	6.2±0.4	8.9±0.3	7.6±0.1	0.31	0.001
空腹時血糖(mg/dl)	174±5	117±2	175±7	119±3	0.92	0.63
朝食後血糖(mg/dl)	231±7	155±4	241±11	173±8	0.50	0.05
昼食前血糖(mg/dl)	166±7	112±3	184±10	130±6	0.20	0.002
昼食後血糖(mg/dl)	210±6	149±4	221±11	174±8	0.37	0.003
夕食前血糖(mg/dl)	172±6	124±3	190±10	161±9	0.15	0.001
夕食後血糖(mg/dl)	225±7	155±4	231±9	193±9	0.66	0.001
就寝時血糖(mg/dl)	197±7	136±3	213±9	164±8	0.22	0.001
食後血糖平均(mg/dl)	222±5	153±3	231±8	180±5	0.41	0.001
終日血糖(mg/dl)	196±5	135±2	208±7	159±4	0.25	0.001

Mean±S.E.M.

値をより改善するためには，FPG に加えて PPG も重要な治療ターゲットであることを示唆していた．

一方，Woerle ら[2] は，検討をさらに前進させ，プロスペクティブな介入試験を実施することで，HbA1c 値改善における PPG コントロールの重要性を明らかにした．本試験の対象は，血糖コントロールが不良（HbA1c 値≧ 7.5%）な糖尿病患者 164 例（平均年齢 62.4 ± 0.9 歳，平均罹患期間 8.4 ± 0.6 年）であり，症例ごとに最適と思われる治療が，3 カ月間にわたって積極的に施行された．治療の内容は，164 例中 basal-bolus 療法が 34 例（21%），インスリン分泌促進薬＋中間型インスリンが 34 例（21%），メトホルミン単独が 17 例（10%），メトホルミン＋中間型インスリンが 14 例（9%）などであった．検討の結果，73% の患者が HbA1c 値 7.0% 以下を達成した．HbA1c 値≦ 7.0% 群と HbA1c 値＞ 7.0% 群で，試験前後における血糖値の変化を比較すると，FPG は同等に低下しており，3 カ月後の群間有意差は認められなかった（**表 1**）．PPG に関しては，HbA1c 値＞ 7.0% 群よりも HbA1c 値≦ 7.0% 群のほうが大きく低下しており，3 カ月後の群間有意差が認められた（$p < 0.001$）．また，本検討における PPG 目標値（140mg/dl）を達成した患者の 94% で HbA1c 値が 7.0% 以下となっていた．一方，FPG 目標値（100mg/dl）を達成した患者のうち，HbA1c 値が 7.0% 以下になった割合は 64% でしかなかった．以上の結果から，FPG を低下させるだけでは HbA1c 値を 7.0% 以下へ改善するのが難しく，PPG コントロールの重要性が明らかにされた．

■ノボラピッド® による HbA1c 値の改善効果

従来の HI に比しノボラピッド® は，投与後速やかに単量体となって吸収され，かつ血中から消失する．このことにより，ノボラピッド® の皮下投与後における血中濃度推移を，生理的な食後のインスリン分泌パターンにより近づけることが可能となった．

Heinemann ら[3] の検討によると，ノボラ

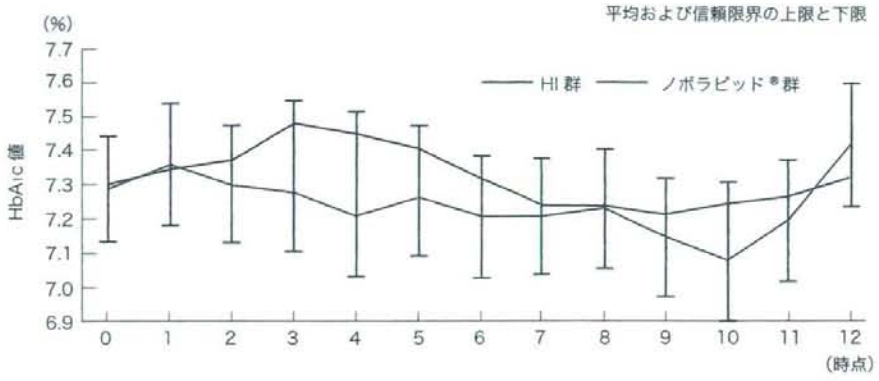


図1　2型糖尿病患者における切り替え後12カ月間のHbA1c値の推移

ピッド® またはHIを反復投与した後の最大血清インスリン濃度（Cmax）とCmax到達時間（Tmax）を求め，患者個人内および個人間での変動係数（CV）を算出した．その結果，ノボラピッド® 群はHI群に比し，CmaxおよびTmaxにおける個人間CVが有意に少ないことが示された（$p < 0.001$，Cmax：ノボラピッド® 群18%，HI群28%，Tmax：ノボラピッド® 群20%，HI群37%）．また，個人内CVについても，有意差は認められないもののノボラピッド® 群は，HI群に比して少ないことが示された（Cmax：ノボラピッド® 群14 ± 9%，HI群19 ± 8%，Tmax：ノボラピッド® 群15 ± 6%，HI群24 ± 10%）．このことによりノボラピッド® は，患者個人内および個人間でも作用のばらつきが少ないという利点が得られた．

このような特性をもつノボラピッド® だが，basal-bolus療法へ導入した際に，HbA1c値がどの程度改善されるのかは，過去にデータが示されていなかった．そこでわれわれは，糖尿病患者情報集積ソフト“CoDiC® ”により糖尿病マネジメント研究会（JDDM）に登録された2型糖尿病患者40,150例のうち，1日10単位以上で半年以上にわたりHIによるbasal-bolus療法継続中の患者647例を，ノボラピッド® に切り替えた群（ノボラピッド® 群，83例）と，HIを継続した群（HI群，564例）に分け比較検討を行った[4]．結果として，切り替え後1カ月および12カ月時点以外において，HbA1c値は，HI群に比しノボラピッド® 群が低値を示した（**図1**）．また，切り替え後の全時点を通して，HI群に比しノボラピッド® 群が平均的に有意に低値を示した（$p = 0.03$）．

また，Homeら[5]は，1型糖尿病患者753例を対象に無作為でノボラピッド® （ノボラピッド® 群，567例）またはHI（HI群，186例）を用いたbasal-bolus療法に割り付け，プロスペクティブな比較試験を実施した．結果として，ノボラピッド® 群では112例，HI群で

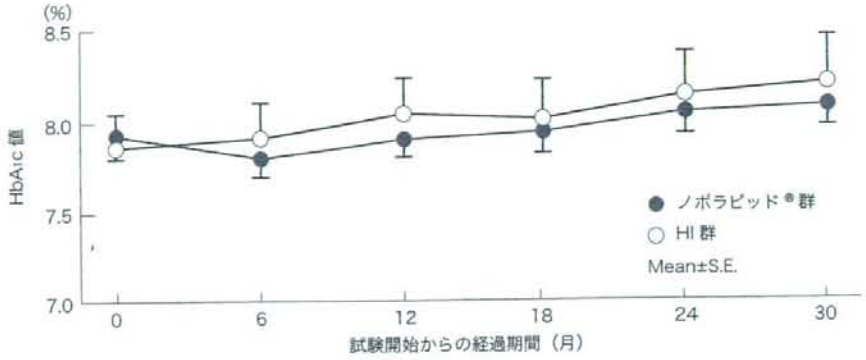


図2　1型糖尿病患者における HbA1c 値の推移（30カ月）

は91例において30カ月後までの追跡がなされ，HbA1c 値は，ノボラピッド® 群のほうが有意に低値を示した（p=0.035，**図2**）．

■まとめ

従来のHIに比して，ノボラピッド® は，「食直前投与が可能」「効果発現が速やか」であることから，QOLの向上と食後高血糖の良好なコントロールが期待できる．また，われわれのJDDMでの調査[6]において，超速効型インスリンアナログを用いたbasal-bolus療法が，HIを用いたbasal-bolus療法より臨床で多く使われていることが示された．このことから，ノボラピッド® をはじめとする超速効型インスリンアナログの治療効果に，多くの専門医が期待していることが推測できる．

このようなプロフィールをもつノボラピッド® を再現性の高いベーサルインスリンと組み合わせることで，よりよいbasal-bolus療法が可能になると考えられる．

文　献

1）Monnier, L., Lapinski, H. et al.：Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients. *Diabetes Care*, **26**：881～885, 2003.
2）Woerle, H. J., Neumann, C. et al.：Impact of fasting and postprandial glycemia on overall glycemic control in type 2 diabetes Importance of postprandial glycemia to achieve target HbA1c levels. *Diabetes Res. Clin. Pract.*, **77**：280～285, 2007.
3）Heinemann, L., Weyer, C. et al.：Variability of the metabolic effect of soluble insulin and the rapid-acting insulin analog insulin aspart. *Diabetes Care*, **21**：1910～1914, 1998.
4）高井昌彦，田中紀子・他：強化インスリン療法における2型糖尿病に対する超速効型インスリン（インスリン アスパルト）の有効性に関する研究（JDDM5）―ヒトインスリンとの比較検討―．*Prog. Med.*, **26**：168～173, 2006.
5）Home, P. D., Hallgren, P. et al.：Pre-meal insulin aspart compared with pre-meal soluble human insulin in type 1 diabetes. *Diabetes Res. Clin. Pract.*, **71**：131～139, 2006.
6）金塚　東，川井紘一・他：2型糖尿病患者における薬物療法に関する実態調査（I）―薬物療法と使用薬剤―．糖尿病，**49**：409～415, 2006.

CoDiC®:Surveillance of clinical management of diabetes in Japan (2 nd report)

CoDiC®データ解析からみた糖尿病専門施設における治療実態(2)

2型糖尿病におけるインスリン療法の現状と血糖コントロール状況について

小林　正・山﨑　勝也・金塚　東・糖尿病データマネジメント研究会

□はじめに

糖尿病データマネジメント研究会(Japan Diabetes Clinical Data Management Study Group；以下JDDMと略す)は，多施設共同で糖尿病の臨床研究を進め，糖尿病医療の質を向上させることを目的に2001年に設立された[1]．現在の会員施設は72医療機関(23病院，49クリニック)，データベース登録患者数は約75,000例に上る．JDDMでは，これまでに糖尿病診療データ管理ソフトであるCoDiC®を用いて全国の糖尿病診療を専門とする施設のデータを集計・解析し，糖尿病診療に関する実態調査を報告してきた[2-4]．

今回はJDDM会員施設において2005年5～7月に受診した患者データをもとに，2型糖尿病患者におけるインスリン使用状況を調査するとともに，HbA_{1c}値6.5%未満を達成するためのより適切なインスリン療法について考察した．

□対象と方法

JDDM会員61施設において，CoDiC®にデータ登録された2型糖尿病患者のうち，2005年5～7月に受診し診療情報の得られた2型糖尿病患者35,404例を対象とした．今回の解析に使用するため集計したデータは，(1)2005年5～7月受診時の臨床検査値と処方内容，(2)インスリン新規導入から12カ月間の臨床検査値と処方内容，(3)インスリン導入後，最初にインスリン処方変更を行った時点から12カ月間の臨床検査値と処方内容，である．

なお，糖尿病の診断および糖尿病型の分類は日本糖尿病学会委員会報告にもとづき行った[5]．HbA_{1c}は各施設でHPLC法により測定し，「日本糖尿病学会糖尿病関連検査の標準化に関する委員会勧告」にもとづき標準化した[6]．

□結果

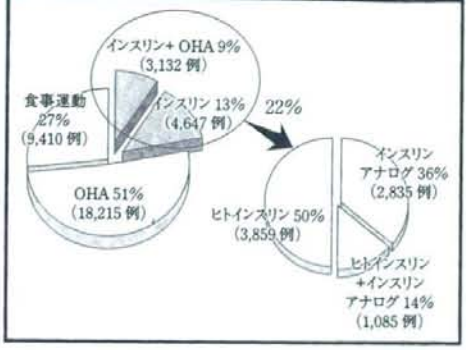
1．2005年5～7月における2型糖尿病患者のインスリン治療状況

対象患者35,404例のうち，インスリン療法を行っている患者総数は7,779例で，全体の約22%であった(Box 1)．このうち，インスリン療法単独の患者は13%(4,647例)，インスリンと経口糖尿病薬(以下OHAと略す)併用患者は9%(3,132例)であった．ヒトインスリン製剤の併用を含めると，インスリンアナログ製剤がインスリン使用例の50%(3,920例)を占めていた．また，インスリン新規導入時の製剤選択に限ると，2005年度ではインスリンアナログ製剤の選択率は57%(インスリンアナログのみ47%，ヒトインスリン併用10%)に上った．

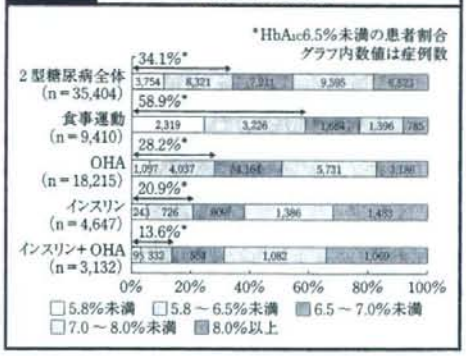
Box 2に対象患者のHbA_{1c}値の分布を示す．HbA_{1c}値6.5%未満の患者の割合は，対象患者全体では34.1%(12,075/35,404例)であったが，インスリン療法患者20.9%(969/4,647例)，OHA併用の

受付日：2007年2月10日
受理日：2007年5月7日

Box 1 2005年5～7月の治療法別患者数と比率



Box 2 治療法別 HbA_{1c} 値コントロール分布と6.5%未満の患者割合



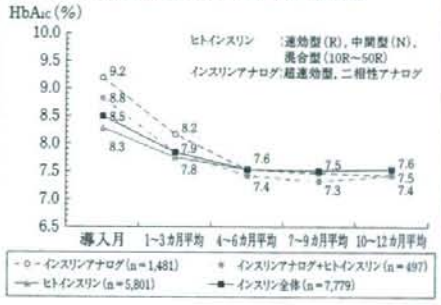
インスリン療法患者13.6%(427/3,132例)と，インスリン使用例では達成率が低くなった．

2．インスリン新規導入時からの HbA_{1c} 値推移

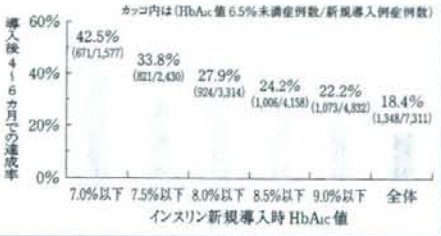
2005年5～7月にインスリン処方歴のあった2型糖尿病患者7,779例について，インスリン新規導入から10～12カ月後までの HbA_{1c} 値推移を検討した(Box 3 A)．新規導入時の平均 HbA_{1c} 値は8.5%であり，前年調査時(8.8%)に比べ若干早くなっていた．導入から4～6カ月で7.6%まで低下したが，その後はほぼ横ばいに推移し10～12カ月には7.6%となった．インスリン導入時 HbA_{1c} 値を製剤別にみると，ヒトインスリン製剤8.3%，インスリンアナログ製剤9.2%，インスリンアナログ+ヒトインスリン製剤8.8%と違いはあったが，4～6カ月後にはいずれも7.4～7.6%に低下し，10～12カ月後まで同程度で推移した．

Box 3 インスリン新規導入時の HbA_{1c} 値推移と6.5%未満達成率

A. インスリン新規導入時の平均 HbA_{1c} 値推移



B. インスリン新規導入時の HbA_{1c} 値と4～6カ月後の6.5%未満達成率(累積)



次にこれらの患者について，新規導入時 HbA_{1c} 値と4～6カ月後の HbA_{1c} 値6.5%未満達成率の関係について検討した(Box 3 B)．新規導入例全体の達成率は18.4%(1,348/7,311例)であったが，導入時 HbA_{1c} 値が低いほど6.5%未満達成率は高く，導入時 HbA_{1c} 値7.0%以下の患者では42.5%(671/1,577例)を示した．

また，4～6カ月後における HbA_{1c} 値6.5%未満達成率とインスリン投与回数の関連を検討したところ，1日1～2回投与が17.0%(840/4,948例)であったのに対し，1日3～4回投与は21.8%(509/2,334例)であり，頻回投与でより達成率が高い傾向を認めた．

3．インスリン処方変更時からの HbA_{1c} 値推移

上記7,779例のうち，2004年1月以降に処方変

更のあった2,659例について，処方変更から10～12カ月のHbA$_{1c}$値推移を検討した(Box 4 A)．処方変更時の平均HbA$_{1c}$値は8.0%であった．処方変更後4～6カ月で7.7%に低下したが，それ以降はほとんど変化なく10～12カ月まで推移した．処方変更後のHbA$_{1c}$値の推移を，ヒトインスリン，インスリンアナログ，インスリンアナログ+ヒトインスリンに分け検討したが，いずれも同様の推移を辿り，ヒトインスリンとインスリンアナログで特に違いは認めなかった．

処方変更後4～6カ月後におけるHbA$_{1c}$値6.5%未満達成率の検討では，対象患者全体で14.4%(482/3,339例)であった．また，新規導入時と同様に，処方変更時HbA$_{1c}$値が低いほど達成率は高く，処方変更時HbA$_{1c}$値が7.0%以下であった患者では41.3%(309/749例)に達した(Box 4 B)．

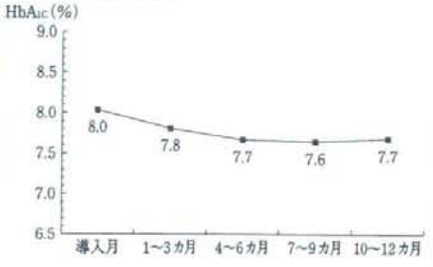
血糖コントロールに対するインスリン投与回数の影響を検討するため，処方変更前に1日2回投与を実施していた患者について，変更後「2回投与のまま」，「3回投与に変更」，「4回投与に変更」に層別し，処方変更後4～6カ月のHbA$_{1c}$値6.5%未満を調べた．その結果，「2回投与のまま」10.6%(102/963例)，「3回投与に変更」13.5%(47/348例)，「4回投与に変更」15.5%(24/155例)であり，新規導入時と同様に，投与回数が増加するほど達成率は高くなる傾向が認められた．

□考察

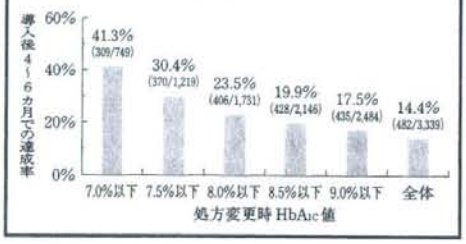
日本糖尿病学会では，糖尿病による血管障害の発症・進展抑制の観点から，糖尿病治療の血糖コントロール目標はHbA$_{1c}$値6.5%未満が望ましいとしている．また，過去の大規模臨床試験の結果からもHbA$_{1c}$値6.5%未満の血糖コントロールが合併症の進展を遅れさせることは既に報告されている[7]．しかしながら，これまでおよび今回のJDDMによる調査結果からわかるとおり，治療中の2型糖尿病患者の3人に1人程度，更にインスリン療法においては5人に1人程しかこの目標を達成できていないという実態が浮かび上がっている．この理想と現実の乖離を解消するためには，HbA$_{1c}$値6.5%未満を達成した「成功事例」の治療実態を把握し，それをもとにして，適切な時期に

Box 4　インスリン処方変更時のHbA$_{1c}$値推移と6.5%未満達成率

A. 2004年1月以降に処方変更のあった2,659名の平均HbA$_{1c}$値推移



B. インスリン処方変更時のHbA$_{1c}$値と4～6カ月後の6.5%未満達成率(累積)



おける治療の変更を検討することが重要と考え，今回の調査を行った．

本調査において，2型糖尿病患者のインスリン療法を行っている患者の割合は22%と，前年(2004年)調査時と同程度であった[4]．インスリン単独療法，OHAとの併用の患者割合についても前年と変化はみられなかった．しかし，インスリン製剤別でみると，インスリンアナログ製剤の使用割合は毎年増加し，本調査では50%(ヒトインスリン製剤併用を含む)を占め，すでにインスリン製剤の主流はアナログ製剤へと移行していることが明らかとなった．2001年にインスリンアナログ製剤が上市されてから，4年足らず(調査時点)で急速に普及してきた状況から考えて，今後2～3年で，インスリンアナログ製剤使用者が大部分を占める可能性がある．ただし，患者によってはヒトインスリン製剤のほうが良好なコントロールが得られる例や，QOLが高いといった例もあるの

で，個々の患者に合った適切な製剤を選択することが大切である．

血糖コントロール状況については**Box 2**に示すとおり，全体を通してHbA_{1c}値6.5%未満の達成患者の割合は，前年調査とほぼ同等であった[6]．われわれは，OHA併用のインスリン療法患者では，OHA単独やインスリン製剤単独に比べ血糖コントロールが不良であることを既に報告しているが[8]，前年調査および本調査でも同様の結果となっている．この理由については不明であるが，今後は患者背景や治療状況などの詳細を解析し，コントロール不良の原因を検討することが治療の改善には必要である．

Box 3 Aに示すとおり，インスリン新規導入患者の平均HbA_{1c}値は8.5%であり，4～6カ月後に7.6%まで低下しその後同程度で推移した．導入時のHbA_{1c}は製剤間で差があり，ヒトインスリン製剤投与例とインスリンアナログ製剤投与例では0.9%もの差があった．それにもかかわらず，いずれの製剤を用いても4～6カ月後以降は同レベルのHbA_{1c}に収束しそれが持続した．このような経過を取る理由は明らかでないが，インスリン新規導入時は血糖コントロールが不良であるため糖毒性が存在すると考えられ，初期は糖毒性の解除によりHbA_{1c}値7.5%程度までは改善すると推測することができる．また，4～6カ月後までのHbA_{1c}値低下量はインスリンアナログ製剤投与例でより大きいことから，インスリン導入当初はインスリンアナログ製剤を選択したほうが，HbA_{1c}値をより改善する効果が高いと考えられる．しかし，本検討は実態調査であるため，ヒトインスリン製剤とインスリンアナログ製剤のHbA_{1c}を改善する効果については更なる検討が必要である．

4～6カ月後以降にHbA_{1c}値の低下が頭打ちになってしまう原因は，今後検討の必要がある課題だが，患者の膵β細胞機能が関係しているかもしれない．2型糖尿病患者のβ細胞量は健康者に比べ，50%以上減少しているとされ[9,10]，インスリン増量による低血糖や患者コンプライアンスの低下が起こりやすく，それを避けたことが一因となっている可能性が考えられる．つまり，患者全体としてはHbA_{1c}値7.5%付近に収束していたが，β細胞量がある程度維持されていた患者では6.5%未満を達成し，よりβ細胞が疲弊していた患者では8%以上になったことも推測できる．もちろん，血糖コントロールを左右する要因はβ細胞機能だけではないので，患者背景やインスリン投与方法の違いなども含め今後検討していく必要がある．

インスリン新規導入例では，HbA_{1c}値が低い患者ほどHbA_{1c} 6.5%未満達成率が高く，7.0%以下で変更した患者の達成率は42.5%であった．この傾向はインスリン処方変更例においても同様に認められ，7.0%以下で変更した患者では41.3%の達成率であった．このように，インスリン新規導入例ではできるだけ早期導入すること，インスリン処方変更例でもできるだけ早期に変更することが，HbA_{1c} 6.5%未満を達成するために重要であることが確認された．IDFは2型糖尿病のGlobal Guideline[11]において，HbA_{1c} 7.5%を超えたときをインスリン導入の目安としているが，本調査においても，この考え方を概ね支持する結果となった．IDFのGlobal Guidelineでは処方変更時期について触れてはいないが，本調査の処方変更時の平均HbA_{1c}は8.0%であった．一方，EASD/ADAの共同勧告[12]では新規導入，処方変更ともにHbA_{1c} 7.0%を目安としている．このことから，日本においても今後インスリン新規導入ならびに処方変更の目安となるHbA_{1c}値の確立が望まれるところである．もちろん，インスリン導入，処方変更の時期は，単にHbA_{1c}値のみで決定できるわけではない．BMI，罹病期間などの患者背景，インスリン分泌能，患者コンプライアンス，患者のQOLなどを総合的に検討した上で行うべきである．また，罹病期間が短く，HbA_{1c}が低いほど内因性インスリンの分泌が保持されている可能性が高いので，その点を考慮したインスリン投与量の調整も適宜必要である．

インスリン投与回数とHbA_{1c}の関連については，新規導入，処方変更いずれの場合にも3回ないしは4回投与例でHbA_{1c} 6.5%未満達成率が高かった．すなわち，従来から考えられているように，2型糖尿病であっても強化インスリン療法が

望ましいことが確認された.

以上の結論として，本調査結果により，糖尿病専門施設における2型糖尿病患者のインスリン治療実態が明らかとなった．また，インスリン投与患者でHbA_{1c}値を6.5%未満に近づけるためには，「新規導入，処方変更のいずれにおいても，より早期(すなわちHbA_{1c}値がより低値のとき)に行うこと」，「強化インスリン療法を行うこと」，が望ましいと考えられた.

CoDiC®を用いたデータ解析を継続することによって，多数例における糖尿病治療の実態が次々と明らかとなってきている．今後もCoDiC®を用いた臨床データの集積を進めることにより，臨床研究だけではなく，実地臨床，地域医療，糖尿病教育，ガイドライン作成など糖尿病医療のさまざまな領域に貢献できるものと考えている．M

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文　献

1) 金塚　東，糖尿病データマネジメント研究会(JDDM)(2004)ITを利用した糖尿病データマネジメント—CoDiC®登録データにみる日本での糖尿病診療の実態—．糖尿病学2004．診断と治療社，東京，pp 154−160
2) Kobayashi M, Yamazaki K, Hirao K, et al(2006)The status of diabetes control and antidiabetic drug therapy in Japan—A cross-sectional survey of 17,000 patients with diabetes mellitus(JDDM 1). Diabet Res Clin Pract 73：198−204
3) 金塚　東，川井紘一，平尾紘一，他(2006)2型糖尿病患者における薬物療法に関する実態調査(I)—薬物療法と使用薬剤—．糖尿病49：409−415
4) 小林　正，山崎勝也，金塚　東，他(2006)CoDiC®データ解析からみた糖尿病専門施設における治療実態．糖尿病診療マスター4：751−755
5) 糖尿病診断基準検討委員会(1999)糖尿病の分類と診断基準に関する委員会報告．糖尿病42：395−404
6) 富永真琴，牧野英一，芳野　原，他(2003)第7回ヘモグロビンA$_{1c}$精度管理調査について．糖尿病46：961−965
7) Yasuo Ohkubo, Hideki Kishikawa, et al(1995)Intensive insulin therapy prevents the progression of diabetic

microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diab Res Clin Pract 28：103－117
8) Kanatsuka A, Kobayashi M(2003)The relation between the phenotypes and the efficacy of drug(s)in type 2 diabetic patients : CoDiC-based analyses on the clinical data obtained at multiple instructions. Diabetologia 47 (Suppl 1) ：A 358
9) Lebovitz HE(1999)Insulin secretagogues: old and new. Diabetes Reviews 7：139－153
10) Butler AE, Janson J, Bonner-Weir, et al(2003)：β cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes 52：102－110
11) International Diabetes Foundation(2005)Glucose control：insulin therapy. *In*：Grobal Guideline for Type 2 Diabetes, International Diabetes Foundation, Brussels, pp 39－42
12) Nathan DM, Buse JB, Davidson MB, et al(2006)Management of hyperglycemia in type 2 diabetes : a consensus algorithm for the initiation and adjustment of therapy. Diabetes Care 29：1963－1972

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Six-month multicentric, open-label, randomized trial of twice-daily injections of biphasic insulin aspart 30 versus multiple daily injections of insulin aspart in Japanese type 2 diabetic patients (JDDM 11)

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ABSTRACT

To evaluate glycemic control using convenience-oriented biphasic insulin analog compared with intensified insulin therapy, we conducted a 6-month multicentric, open-label, randomized trial in Japanese insulin-naïve patients with type 2 diabetes mellitus. A total of 160 adult patients at 19 centers were randomized into two groups: those who received twice-daily injections of biphasic insulin aspart 30 and those on three-times-daily injections of insulin aspart with or without NPH insulin (multiple daily injections). At 6 months, mean HbA_{1c} decreased by approximately 2.5% in both groups. Reduction of HbA_{1c} on both regimens was better in patients whose prior therapy before starting the study was only diet and exercise (−5.0%) than in patients who were previously taking oral antidiabetic agents (−1.0%). No incidence of major hypoglycemia was observed in either regimen. These results suggest that convenience-oriented insulin therapy using biphasic insulin analog is as useful as intensified insulin therapy with insulin analog for the treatment of type 2 diabetes mellitus over 6 months. Furthermore, early induction of insulin therapy in individuals hitherto using only diet and exercise may provide good glycemic control. This study suggests that convenience-oriented biphasic insulin aspart 30 might be a useful option for the treatment of type 2 diabetes mellitus, especially for insulin-naïve patients over 6 months, although it should be changed to another regimen when expected efficacy is not obtained.

1. Introduction

Many studies have shown that strict glycemic control is one of the most important factors in the management of diabetes mellitus to prevent risk of death from diabetic complications and cardiovascular diseases. The Diabetes Control and Complication Trial (DCCT) [1] showed that intensified insulin therapy using a regimen consisting of three-times-daily

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injections of regular insulin with or without NPH insulin provides better glycemic control than convenience-oriented insulin therapy using twice-daily human insulin in patients with type 1 diabetes mellitus. Furthermore, Ohkubo et al. [2] reported similar results in patients with type 2 diabetes mellitus.

The increasing incidence of type 2 diabetes mellitus in Japan is believed to reflect shifting diet and lifestyle changes among the general population. As a result, it is increasingly necessary to select therapeutic regimens that not only effectively maintain glycemic control but also allow diabetic patients to pursue many daily activities; in large numbers of insulin-requiring diabetic patients, multiple-daily injection regimens are not desirable. In this regard, in many outpatients overall glycemic control attained with twice-daily injection regimens may be as effective as that with multiple injection therapy [3,4].

Recently, rapid-acting and biphasic insulin analogs have been made available and are being widely used for the treatment of type 2 diabetes mellitus. These insulin analogs are very convenient tools for adjusting to the variety of lifestyles of today's diabetic patients. However, among modern insulin analog therapies it is not known whether rapid-acting analog plus NPH insulin or twice-daily biphasic insulin analog provides better glycemic control.

In 2001, the Japan Diabetes Clinical Data Management Study Group (JDDM) was established to promote clinical research on diabetes in Japan [5]. Data on patients at healthcare institutes across Japan are collected in the CoDiC® database, a data collection and diabetes management information system developed by the JDDM [5]. The CoDiC® system enables researchers to perform many multicentric, randomized clinical studies in Japan. Using this database, we performed a multicentric, open-label, randomized trial comparing glycemic control using twice-daily injections of biphasic insulin aspart 30 versus three-times-daily injections of insulin aspart with or without NPH insulin in insulin-naïve patients with type 2 diabetes mellitus.

2. Subjects and methods

2.1. Subjects

This was a 6-month, randomized controlled trial analyzing data on adult type 2 diabetic patients recruited at 19 centers in Japan. The definition of type 2 diabetes mellitus was based on the criteria in the "Report of the Committee of Japan Diabetes Society (JDS) on the Classification and Diagnostic Criteria of Diabetes Mellitus" [6]. These criteria are almost identical to those described by WHO [7]. Subjects had to have $HbA_{1c} \geq 8.0\%$ for ≥3 months irrespective of using oral antidiabetic agents and indication for starting insulin therapy. Patients with soft drink ketoacidosis were excluded. Subjects were randomized to receive either twice-daily injections of biphasic insulin aspart 30 or three-times-daily injections of insulin aspart with or without NPH insulin (multiple daily injections). Oral antidiabetic agents that stimulate insulin secretion such as sulfonylureas and short-acting insulin secretagogues were discontinued and other insulin preparations disallowed during the study. Doses of insulin analogs were adjusted to achieve target $HbA_{1c} < 7.0\%$ at the discretion of each investigator.

Participating clinics and hospitals were JDDM affiliated and the clinical data of all patients were standardized and stored on personal computer using CoDiC® software [5]. The clinical data were collected from each institute on CD-R storage media and analyzed by SPSS® software (SAS Institute, Cary, NC). Data received at the central analytic center were treated on an anonymous basis. JDDM operates as an intermediate organization under the supervision of a central analytical center and ethics committee. Informed consent was obtained from all participants at each institute in accordance with the Japanese Ministry of Health, Labour and Welfare's guideline for the ethics of clinical study.

2.2. Measurement and standardization of data

HbA_{1c} was measured by HPLC method. Normal range for HbA_{1c} was defined as 4.3–5.8%. Postprandial plasma glucose was assessed after breakfast or lunch by hexokinase method. Measurement of each parameter assessed in this study was standardized at all institutions.

2.3. Statistical analyses

Statistical analyses were conducted using SPSS® version 13.0J for Windows software (SAS Institute). Mean intergroup values of HbA_{1c} were subjected to repeated measurement analysis of variance and non-paired t-test. The intergroup differences of the time taken until values of 7.0% or 6.5% of HbA_{1c} were achieved were analyzed by life table analysis—Wilcoxon (Gehan) test. All data are expressed as mean ± S.D. and P-value <0.05 were considered significant.

3. Results

A total of 160 patients were equally randomized to the two treatment groups. At baseline, demographic and clinical characteristics were comparable between the two groups (Table 1). Fifty of the 80 patients (62.5%) in the multiple daily

Table 1 – Baseline characteristics of patients (mean ± S.D.)

	Twice-daily injection group	Multiple daily injection group
Number of patients, *n*	80	80
Prior therapy, *n*		
Diet/exercise only	39	41
Oral antidiabetic agents	41	39
Sex (M/F), *n*	47/33	49/31
Age (years)	58.5 ± 11.3	57.9 ± 11.9
Duration of diabetes (years)	9.5 ± 10.7	12.2 ± 13.3
HbA_{1c} (%)	10.5 ± 2.1	10.7 ± 2.1
Postprandial plasma glucose (mg/dL)	298.6 ± 114.2	293.3 ± 113.6
Body weight (kg)	62.5 ± 12.9	62.1 ± 12.2
BMI (kg/m^2)	23.7 ± 4.1	23.7 ± 4.2

Table 2 – Reasons for discontinuation (number of patients)

Reasons	Twice-daily injection group	Multiple daily injection group
Defined as type 1 diabetes	1	1
Changed hospitals or clinics	11	10
Improved glycemic control	1	1
Less of an improvement in glycemic control than was expected	8	6
Worse compliance	2	1
Death of the patient	1	0
Total number	24	19

injection group used NPH insulin in addition to insulin aspart. In all, 56 of 80 patients (70.0%) in the twice-daily injection group and 61 of 80 patients (76.3%) in the multiple daily injection group completed the study. The reasons for discontinuation are summarized in Table 2 and are similar in the two treatment groups. At 6 months, in the two groups mean HbA_{1c} changed from 10.2 ± 2.1% to 7.6 ± 1.3% and from 10.4 ± 2.0% to 7.8 ± 1.8%, respectively. There was no statistical difference between the two groups. Mean HbA_{1c} steadily decreased by approximately 2.5% at 6 months versus baseline in both groups (Fig. 1). At the end of the study, 32.1% and 17.9% of patients in the twice-daily injection group and 32.8% and 16.4% in the multiple daily injection group achieved $HbA_{1c} < 7.0\%$ and <6.5%, respectively. The figures were not very different between the two groups. Besides, the times taken to achieve $HbA_{1c} < 7.0\%$ or <6.5% at the end of the trial between the two groups were not different ($P = 0.661$, $P = 0.954$, respectively). Among patients whose therapy prior to starting the study consisted only of diet and exercise (early induction of insulin subgroup) mean HbA_{1c} changed from 12.2 ± 1.8% to 7.2 ± 1.3% in those who took twice-daily injections and from 12.0 ± 1.8% to 7.5 ± 2.0% in those who took multiple daily injections over the 6-month treatment period; no difference in

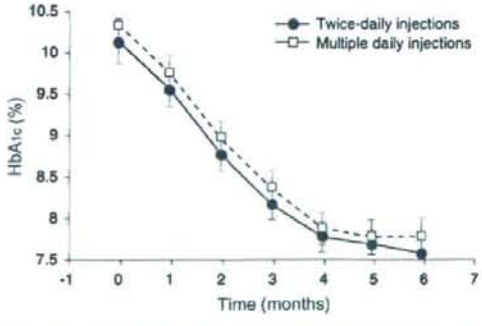

Fig. 1 – Mean (±S.E.) HbA_{1c} in patients taking twice-daily injections (●, $n = 56$) or multiple daily injections (□, $n = 61$). Mean HbA_{1c} steadily decreased to an approximately 2.5% reduction at 6 months. No statistical difference was noted between the two groups.

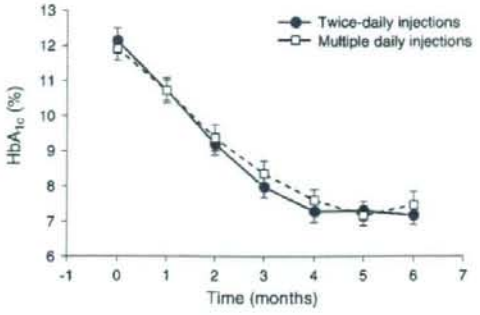

Fig. 2 – Mean (±S.E.) HbA_{1c} in patients who were not previously receiving oral antidiabetic agents before study entry. Twice-daily injections (●, $n = 24$); multiple daily injections (□, $n = 28$). HbA_{1c} decreased by approximately 5.0% at 6 months. No statistical difference was noted between the two groups.

this parameter was observed between the two treatment groups (mean reduction: −4.9 ± 2.4% and −4.5 ± 2.4%, respectively; Figs. 2 and 3). Among patients who were previously taking oral antidiabetic agents prior to starting the study, mean HbA_{1c} changed from 8.8 ± 0.7% to 8.0 ± 1.2% in those who took twice-daily injections, and from 9.1 ± 1.0% to 8.0 ± 1.6% in those who took multiple daily injections over 6 months. Again, there was no difference noted between the two treatment groups (mean reduction: −0.8 ± 1.2% and −1.1 ± 1.3%, respectively; Figs. 3 and 4). In the twice-daily injection group, the duration of diabetes among patients with early induction of insulin (6.58 ± 8.17 years) was significantly shorter than in patients who had been previously taking oral antidiabetic agents (10.99 ± 7.04 years) ($P = 0.034$). While in the multiple daily injection group, there was no statistical difference in the durations between the two subgroups (10.05 ± 13.59 years and 12.43 ± 8.58 years, respectively). Comparing these two prior treatment subgroups, however, the decrease of HbA_{1c} among early induction of insulin patients was significantly ($P < 0.001$) greater than that observed in patients who were previously taking oral antidiabetic agents (Fig. 3).

Statistically, the BMI in the two groups increased from 23.8 ± 4.1 kg/m^2 to 25.2 ± 4.0 kg/m^2 ($P < 0.0001$) and from 24.0 ± 4.2 kg/m^2 to 24.8 ± 4.5 kg/m^2 ($P < 0.0001$), respectively, at the end of the 6-month trial. The change in BMI during 6 months in the twice-daily injection group (1.47 ± 1.82 kg/m^2) was more than that in the multiple daily injection group (0.69 ± 1.04 kg/m^2) ($P = 0.013$), while, the mean BMI at the baseline and the end of the 6-month trial was not statistically different in the two treatment groups.

No major hypoglycemic episode was observed in either treatment group. Of the 24 patients in the twice-daily injection group and 19 patients in the multiple daily injection group who discontinued the study, most withdrew because of improvement or deterioration of glycemic control or were transferred to another clinic and hence lost to follow-up.

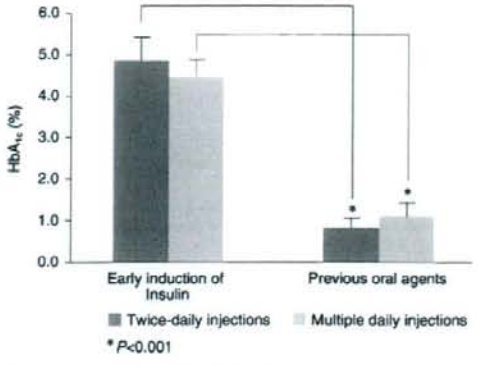

Fig. 3 – Decrease of HbA_{1c} in the two treatment groups according to whether they underwent early induction of insulin therapy or had previously received oral antidiabetic agents. Those who underwent early induction of insulin therapy exhibited significantly greater decrease of HbA_{1c} than those previously taking oral antidiabetic agents in both treatment groups irrespective of whether they were assigned twice-daily or multiple daily injections ($P < 0.001$).

4. Discussion

In this study mean HbA_{1c} decreased by approximately 2.5% after patients had received either twice-daily injections of biphasic insulin aspart or multiple daily injections of insulin aspart with or without NPH insulin at 6 months. These results are comparable to those of previous studies that suggested that glycemic control using twice-daily injection regimens may be as good as that achieved with multiple daily injection therapy in certain patients [3,4]. In our study, including data on a total of 43 patients who discontinued early, we performed an intent-to-treat analysis of the results obtained in all 80 patients initially randomized to each treatment group. In this analysis we obtained the same results as seen in the protocol-compatible analysis. Also the reasons for discontinuation were similar in both treatment groups. The cause of death of the patient in the twice-daily injection group, which occurred within one month, was an acute myocardial infarction. In the twice-daily injection group, out of eight patients who showed less of an improvement in glycemic control than was expected, five of them added oral antidiabetic agents and three of them changed to multiple injections of insulin therapy. In the multiple daily injection group, out of six patients who showed less of an improvement in glycemic control than was expected, three added oral antidiabetic agents, two changed NPH insulin to insulin gulargine and one replaced insulin asprat with NPH insulin. Therefore our results suggest that in insulin-naïve patients convenience-oriented insulin therapy using biphasic insulin analog is as effective as insulin therapy using rapid-acting insulin analog plus NPH insulin, at least over the first 6 months of treatment.

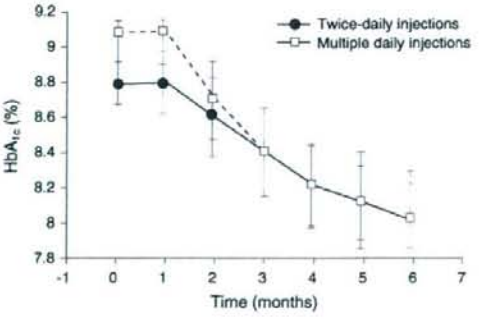

Fig. 4 – Mean (±S.E.) HbA_{1c} in patients who were previously receiving oral antidiabetic agents before study entry. Twice-daily injections (●, $n = 32$); multiple daily injections (□, $n = 33$). HbA_{1c} decreased by approximately 1.0% at 6 months. No statistical difference was noted between the two groups.

Modern rapid-acting insulin analog has been shown to elicit better reduction of HbA_{1c} than regular insulin [8,9]. Furthermore, the former exerts glucose-lowering effects more rapidly than the latter [10]. However, although it is recommended to inject regular insulin 30 min before meals, many patients inject this formulation just before meals [11]. Hence because rapid-acting insulin analog is formulated to allow injection just before meals, in the real world it may be more effective against postprandial hyperglycemia than regular insulin. It has been reported that biphasic insulin aspart 30 significantly improves postprandial hyperglycemia as compared with premixed human insulin 30/70 on a twice-daily regimen, while overall blood glucose control was similar [12]. These results suggest that not only rapid-acting insulin analog but also biphasic insulin analog effectively controls postprandial hyperglycemia.

In our subgroup analysis, HbA_{1c} was reduced to a greater extent in patients who did not previously receive treatment with oral antidiabetic agents (early induction of insulin subgroup) versus those who did take these drugs regardless of whether they were in the intensive regimen or convenience regimen group over 6 months. The early insulin induction subgroup had a shorter duration of diabetes, though there was no statistical difference in the multiple injection group. This suggested that the shorter duration might contribute to the reserve of beta-cell function. Plasma glucose level gradually rises with progressive deterioration of beta-cell function during the natural course of diabetes [13,14]. Treatment with sulfonylureas, a widely prescribed class of oral hypoglycemic agents, has been associated with beta-cell apoptosis [15] in type 2 diabetic patients and increases postprandial secretion of beta cell-derived amylin, a component of islet amyloid characteristic of type 2 diabetes [16]. Amylin deposition in rat pancreas has also been shown to stimulate apoptosis of beta cells [17]. Treatment with insulin, on the other hand, reduces amylin concentration [16]. Moreover, UKPDS showed that insulin injections are the most powerful tool available so far to achieve satisfactory long-term metabolic control in the majority of diabetic patients who are not sufficiently controlled by diet and/or oral agents [13]. The DCCT showed that intensive insulin therapy is more effective at conserving residual beta-cell function than conventional therapy in patients with type 1 diabetes [18]. In newly diagnosed patients

with type 2 diabetes, induction of euglycemia with just 2 weeks of intensive insulin therapy was sufficient to allow long-term glycemic control without medication for a period of ≤3 years [19]. Therefore beta-cell rest is important for beta-cell preservation and insulin therapy given at an early stage of type 2 diabetes might be a useful option for patients who fail diet therapy alone. However, many diabetic patients resist accepting insulin therapy because of the invasiveness of injections in comparison with taking oral antidiabetic agents. In these individuals, twice-daily injections using biphasic insulin analog instead of intensive insulin therapy might be a more acceptable choice when starting insulin therapy.

Both regimens used in this study were generally safe. There was no incidence of major hypoglycemia observed in either treatment group.

In summary, the present results suggest that not only intensified insulin therapy with insulin analog but also convenience-oriented insulin therapy using biphasic insulin analog is a useful option for the treatment of type 2 diabetes mellitus, at least over 6 months. The convenience-oriented twice-daily regimen might conceivably contribute to compliance in certain patients, especially those with highly active lifestyles. Selection of therapy should be made after careful assessment of risk–benefit in each patient.

Acknowledgment

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Appendix A

The following members of JDDM participated in this study (in alphabetical order):

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Dr. Noriharu Yagi (Yagi Internal Medicine Clinic)
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REFERENCES

[1] The Diabetes Control Complication Trial Research Group, The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus, N. Engl. J. Med. 329 (1993) 977–986.
[2] Y. Ohkubo, H. Kishikawa, E. Araki, T. Miyata, S. Isami, S. Motoyoshi, et al., Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study, Diabetes Res. Clin. Pract. 28 (1995) 103–117.
[3] M. Small, S. MacRury, A. Boal, K.R. Paterson, A.C. MacCuish, Comparison of conventional twice-daily subcutaneous insulin administration and a multiple injection regimen (using the NovoPen™) in insulin-dependent diabetes mellitus, Diabetes Res. 8 (1988) 85–89.
[4] H. Yki-Jarbinen, M. Kauppila, E. Kujansuu, K. Lahti, T. Marjanen, L. Niskanen, et al., Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus, N. Engl. J. Med. 327 (1998) 1426–1433.
[5] M. Kobayashi, K. Yamazaki, K. Hirao, M. Oishi, A. Kanatsuka, M. Yamauchi, et al., The status of diabetes control and antidiabetic drug therapy in Japan—A cross-sectional survey of 17,000 patients with diabetes mellitus (JDDM 1), Diabetes Res. Clin. Pract. 73 (2006) 198–204.
[6] T. Kuzuya, S. Nakagawa, J. Satoh, Y. Kanazawa, Y. Iwamoto, T. Kobayashi, et al., The Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus. Report of the committee on the classification and diagnostic criteria of diabetes mellitus, Diabetes Res. Clin. Pract. 55 (2002) 65–85.
[7] K.G. Alberti, P.Z. Zimmet, Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1. Diagnosis and classification of diabetes provisional report of a WHO consultation, Diabetic Med. 15 (1998) 539–553.
[8] P.D. Home, A. Lindholm, A. Riist, European Insulin Aspart Study Group, Insulin aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial, Diabetic Med. 17 (2000) 762–770.
[9] P. Raskin, A. Riis, R.A. Guthrie, L. Jovanovic, L. Leiter, Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes, Diabetes Care 23 (2000) 583–588.
[10] J. Brange, A. Volund, Insulin analogs with improved pharmacokinetic profiles, Adv. Drug Deliv. Rev. 35 (1999) 307–335.
[11] L.N. Jorgensen, F.S. Nielsen, Timing of pre-meal insulin in diabetic patients on a multiple daily injection regimen. A questionnaire study, Diabetologia 33 (1990) A116.
[12] B.O. Boehm, O.D. Home, C. Behrend, N.M. Kamp, A. Lindholm, Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in type 1 and type 2 diabetic patients, Diabetic Med. 19 (2002) 393–399.
[13] UKPDS 33, Intensive blood glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes, Lancet 352 (1998) 837–853.
[14] J. Levy, A.B. Atkinson, P.M. Bell, D.R. McCance, D.R. Hadden, Beta-cell deterioration determines the onset and rate of progression of secondary dietary failure in type 2 diabetes mellitus: the 10-year follow-up of the Belfast Diet Study, Diabetic Med. 15 (1998) 290–296.

[15] T. Mandrup-Poulsen, Beta-cell apoptosis, stimuli and signaling, Diabetes 50 (Suppl. 1) (2001) S58–S63.
[16] J. Rachman, M.J. Payne, J.C. Levy, B.A. Barrow, R.R. Holman, R.C. Turner, Changes in amylin and amylin-like peptide concentrations and beta-cell function in response to sulfonylurea or insulin therapy in NIDDM, Diabetes Care 21 (1998) 810–816.
[17] S.E. Kahn, D.A. D'Alessio, M.W. Schwartz, M.W. Fujimoto, J.W. Ensinck, G.J. Tarborsky Jr., et al., Evidence of cosecretion of islet amyloid polypeptide and insulin by beta-cell, Diabetes 39 (1990) 634–638.
[18] The Diabetes Control and Complication Trial Research Group, Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the Diabetes Control and Complication Trial. A randomized, controlled trial, Ann. Intern. Med. 128 (1998) 517–523.
[19] H. Ilkova, B. Glaser, A. Tunckale, N. Bagriacik, E. Cerasi, Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients by intensive insulin treatment, Diabetes Care 9 (1997) 1353–1356.

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Original Article

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Prevalence of albuminuria and renal insufficiency and associated clinical factors in type 2 diabetes: the Japan Diabetes Clinical Data Management study (JDDM15)

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Abstract

Background. Microalbuminuria is widely accepted as the first clinical sign of diabetic nephropathy. However, normoalbuminuric type 2 diabetic patients who have renal insufficiency (RI), i.e. low estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, exist. We explored the prevalence of such patients and associated clinical factors.

Methods. We investigated the distribution of patients when stratified by albuminuria stages and chronic kidney disease (CKD) stages in a large-scale population of Japanese type 2 diabetic patients ($N = 3297$), and the common and independent factors for albuminuria and low eGFR.

Results. The proportion of subjects with low eGFR was 15.3% (506/3297), which was 11.4% among those with normoalbuminuria (NA) (262/2298), 14.9% among those with microalbuminuria (105/705) and 47.3% among those with macroalbuminuria (139/294). There were 262 patients with NA and low eGFR, and 63.4% of them had neither diabetic retinopathy nor neuropathy. They were older and included a higher proportion of women and patients with hypertension, hyperlipidaemia and cardiovascular disease (CVD), and fewer smokers compared with those with NA and preserved eGFR. Multiple logistic regression analysis revealed that factors commonly associated with RI and albuminuria were hypertension, CVD and proliferative retinopathy. Factors independently associated with RI were age, duration of diabetes, A1C (negative), hyperlipidaemia, smoking (negative) and macroalbuminuria, whereas those associated with albuminuria were male sex, BMI, A1C, simple retinopathy and RI.

Conclusions. A significant proportion of type 2 diabetic patients have normoalbuminuric RI. Renal disease in type 2 diabetes could be heterogeneous, implying the possibility of involvement of renal atherosclerosis and lipid toxicity.

Keywords: chronic kidney disease; glomerular filtration rate; normoalbuminuria; renal insufficiency; type 2 diabetes

Introduction

The development of microalbuminuria has been considered to be one of the first clinical signs of classic course of diabetic nephropathy, which leads to macroalbuminuria and then to progressive loss of glomerular filtration rate (GFR) and eventually end-stage renal disease. These steps were originally described in type 1 diabetes [1], whereas kidney disease in type 2 diabetes is more heterogeneous. Several reports have recently identified type 2 and type 1 diabetic patients with normoalbuminuria and low GFR [2–8]. The UK Prospective Diabetes Study even demonstrated that 51% of patients who progressed to chronic renal failure had no preceding albuminuria [9]. However, the proportions of patients with low GFR among type 2 diabetic patients with normoalbuminuria, microalbuminuria or macroalbuminuria remain uncertain, and few such data are available on Asian diabetic populations. Therefore, the clinical features of type 2 diabetic patients with normoalbuminuria and reduced GFR need to be clarified. Clinical factors associated with albuminuria and low GFR may be common but could be independent.

The estimated GFR (eGFR) using the abbreviated equation from the Modification of Diet in Renal Disease (MDRD) study has been suggested as the best validated means for transforming serum creatinine measurements into GFR in adults, using age, sex and ethnicity as surrogates for muscle mass [10–12]. Stages of chronic kidney disease (CKD) have been proposed by the Kidney Disease

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Outcomes Quality Initiative guidelines [13] according to the eGFR.

In this study with a large-scale population of Japanese type 2 diabetes, we investigated (1) the distribution of patients when stratified by albuminuria stages and CKD stages and (2) which clinical factors are common and independent for albuminuria and low eGFR.

Patients and methods

Study population

A multicentre study was conducted. It encompassed 17 medical clinics (i.e. general practitioners) or general/university-affiliated hospitals from different areas in Japan, using the same software to incorporate patient records, as a working study group, i.e. the Japan Diabetes Clinical Data Management (JDDM) Study Group [14,15]. The group consisted of medical doctors who volunteered to dedicate their daily standard clinical work to scientific analysis. The study was performed in primary care settings. Patients with type 2 diabetes aged between 20 and 70 years who visited each clinic/hospital from January 2004 to December 2005 and whose diabetes was diagnosed before 2003 were included in this study. The participants were not different from background patients ($n = 16\ 394$) of the JDDM study in terms of clinical characteristics described in a previous report [14], where a large-scale study of the daily management of diabetes at multiple clinics and hospitals in Japan was firstly demonstrated. Patients with type 1 diabetes were excluded. Treatment goals recommended by the Japan Diabetes Society (JDS) were glycosylated haemoglobin A1C (A1C) <6.5%, blood pressure (BP) <130/80 mmHg and serum concentrations of total cholesterol (TC) <5.17 mmol/L (200 mg/dL), triglycerides (TG) <1.68 mmol/L (150 mg/dL) and HDL cholesterol (HDL) >1.03 mmol/L (40 mg/dL) [16]. The JDDM study group has an independent ethical committee comprising a lawyer, a sociologist, patients with type 2 diabetes and a medical doctor not majoring in diabetes. The study protocol was approved by the ethical committees of the JDDM and each clinic. Data collection from the software was performed after subtracting patients' ID and name and replacing with a coded clinic-ID, and the database for the study was originated by an independent company. All patients gave written informed consent and the study was carried out in accordance with Helsinki Declaration II.

Measurements

Type 2 diabetes was diagnosed according to the JDS criteria, i.e. fasting blood glucose ≥6.99 mmol/L (126 mg/dL) or casual blood glucose ≥11.10 mmol/L (200 mg/dL), and mostly not treated with insulin in the first year after diagnosis [16]. Overweight was defined as BMI ≥25.0 kg/m^2. The presence of cardiovascular diseases (CVD) was diagnosed by the physician as a history of ischaemic stroke, coronary heart disease (CHD) and/or peripheral arterial disease (PAD). Stroke (ischaemic cerebrovascular disease) included only symptomatic brain infarction, and did not include silent brain infarction, transient ischaemic attack or brain haemorrhage. CHD included a previous history of myocardial infarction, angina pectoris, the presence of coronary interventions or the presence of ECG abnormalities suggestive of CHD, which was confirmed by a physician. PAD was diagnosed by an ankle-brachial pressure index of <0.9 and/or two absent foot pulses. Diabetic retinopathy was assessed by fundus photography after pupillary dilation and graded as none, simple or proliferative retinopathy. Smoking was defined as never/past/current. Neuropathy was diagnosed in patients with two or more of the following three components: presence of symptoms, absence of ankle tendon reflexes or abnormal scores of vibration perception threshold using a C128 tuning fork, where bilateral spontaneous pain, hypoesthesia or paraesthesias of the legs were considered as the neuropathic symptoms.

BP was measured with an appropriate-sized cuff in the sitting position after 5-min rest, and the average of three measurements on different days was recorded. The pulse pressure (PP) was defined as the difference between systolic and diastolic BP. Hypertension was defined by a systolic blood pressure (SBP) of >140 mmHg or a diastolic blood pressure (DBP) of >90 mmHg, or both, or patients already being treated with antihypertensive drugs. Non-fasting blood samples were obtained for measurements of A1C and serum concentrations of lipids. Each laboratory measured A1C by high-performance liquid chromatography. The normal range of A1C was from 4.3 to 5.8%. The method was standardized by the JDS and was calibrated using a control agent. Hyperlipidaemia was defined by serum concentrations of TC of >5.69 mmol/L or TG >1.68 mmol/L or HDL <1.03 mmol/L or patients already being treated by lipid lowering agents.

Serum and urinary concentrations of creatinine were measured by an enzymatic method. The inter-laboratory coefficient of variation for the creatinine value was <5%. Urinary albumin was measured in random urine samples using a turbidimetric immunoassay with the lowest detection limit of 0.5 μg/mL. The urinary albumin excretion rate (AER) was presented as the albumin-to-creatinine ratio (ACR; mg/g creatinine). The measurement of ACR was performed at 12 laboratories using the same method. Laboratory-to-laboratory variation was evaluated by measuring the same urine samples, and the coefficient of variation was 10.5% at a mean ACR of 28.6 mg/g creatinine, 22.9% at 47.0 mg/g creatinine and 10.9% at 306.5 mg/g creatinine as previously reported [15].

eGFR was calculated using the following equation, originated from the MDRD study group [9,10], and refitted for Japanese individuals as just recently recommended by the Japanese Society of Nephrology : eGFR (mL/min/1.73 m^2) = $194 \times \mathrm{Scr}^{-1.094} \times \mathrm{Age}^{-0.287} \times 0.739$ (if female) [17]. At first, patients were stratified by eGFR values (mL/min/1.73 m^2) into five CKD stages as per the National Kidney Foundation guidelines [13]: CKD 1, eGFR ≥90; CKD 2, eGFR 60–89; CKD 3, eGFR 30–59; CKD 4, eGFR 15–29; and CKD 5, <15 mL/min/1.73 m^2. Then we combined CKD stages 1 and 2 into a single category, since eGFR could be underestimated when the value is >60 as compared to the measured GFR [12]. Renal insufficiency, i.e. low eGFR, was defined as an eGFR <60. Nephropathy was staged as follows: normoalbuminuria, ACR <30;

microalbuminuria, ACR ≥30 and <300; macroalbuminuria, ACR ≥ 300, in at least two of three consecutive samples.

Statistical analysis

Results are given as mean ± SD unless otherwise stated. Statistical significance of the differences between the groups was determined by chi-squared tests for categorical variables and unpaired Student's *t*-test for continuous variables. Comparison of clinical variables among the groups was performed by one-way analysis of variance. Multiple logistic regression was used to describe the associations of variables with the presence of renal insufficiency and micro/macroalbuminuria controlling for potential confounders. The validity of the model was confirmed by conducting the likelihood-ratio test (Hosmer–Lemeshow test). The *P*-values under 5% (two-tailed) were considered to be significant. All analyses were performed with the statistical software package SPSS (Dr SPSS II version, SPSS Japan Inc., Tokyo, Japan).

Results

Clinical characteristics of patients according the stages of nephropathy and CKD

The clinical and metabolic parameters of patients are shown according to the nephropathy stages (Table 1) and CKD stages (Table 2). The parameters that commonly aggravated albuminuria stages and CKD stages were age, duration of diabetes, levels of systemic BP and PP, serum concentrations of HDL and TG, use of insulin and proportion of hypertension, hyperlipidaemia, retinopathy, neuropathy and CVD. Proportions of men and smokers and A1C increased according to albuminuria stage, but decreased according to CKD stage. The attainment rate for treatment goals of A1C, BP and lipids decreased according to albuminuria stages and CKD stages, except that the attainment rate of A1C <6.5% did not change according to CKD stages.

Proportion of patients stratified by the stages of CKD and nephropathy

Cross-classification by CKD stages and albuminuria stages and the proportion of patients (95% CI) are demonstrated in Table 3. The proportion of subjects with an eGFR <60 was 15.3% (506/3297; 95% CI: 14.1–16.6%) in the study sample, while it was 11.4% (262/2298; 95% CI: 10.1–12.7%) among those with normoalbuminuria, 14.9% (105/705; 95% CI: 12.3–17.5%) among those with microalbuminuria and 47.3% (139/294; 95% CI: 41.6–53.0%) among those with macroalbuminuria.

Associated clinical factors for albuminuria and low eGFR (Table 4)

Clinical factors that were associated with both albuminuria (normo/micro/macroalbuminuria) and low eGFR

Table 1. Clinical characteristics of diabetic patients according to the nephropathy stages ($N = 3297$)

	Nephropathy stages			*P*-value
	Normoalbuminuria $N = 2298$	Microalbuminuria $N = 705$	Macroalbuminuria $N = 294$	
Age (years)	58 ± 8	59 ± 8	60 ± 8	0.0025
Male (%)	63.2	65.8	66.7	0.2860
BMI (kg/m^2)	24.4 ± 3.5	25.4 ± 3.8	26.1 ± 4.8	<0.0001
BMI ≥25 (%)	38.0	49.5	52.4	<0.0001
Duration of diabetes (years)	10 ± 8	12 ± 8	14 ± 8	<0.0001
Diet/tablet/insulin (%)	16/66/18	9/68/23	4/56/40	<0.0001
A1C (%)	7.0 ± 1.0	7.3 ± 1.2	7.4 ± 1.3	<0.0001
Serum creatinine (μmol/L)	65.4 ± 15.0	66.3 ± 18.6	122.9 ± 145.9	<0.0001
Hypertension (%)	42.0	58.1	77.8	<0.0001
SBP (mmHg)	127 ± 14	132 ± 14	135 ± 15	<0.0001
DBP (mmHg)	74 ± 9	76 ± 9	77 ± 9	<0.0001
PP (mmHg)	53 ± 11	56 ± 12	58 ± 13	<0.0001
Hyperlipidaemia (%)	60.8	63.4	75.3	<0.0001
TC (mmol/L)	5.12 ± 0.80	5.22 ± 0.91	5.28 ± 1.09	0.0006
HDL (mmol/L)	1.42 ± 0.41	1.42 ± 0.49	1.34 ± 0.41	0.0019
TG (mmol/L)[a]	1.32 (0.92–1.94)	1.42 (0.97–1.99)	1.69 (1.15–2.40)	<0.0001
Smoking current/past/never (%)	30/21/49	35/19/47	36/24/40	0.0070
CVD (%)	7.1	12.9	18.0	<0.0001
Retinopathy proliferative/simple/ no (%)	5/18/77	15/27/58	28/45/27	<0.0001
Neuropathy (%)	18.8	25.5	49.0	<0.0001
Attainment rate (%)				
A1C <6.5%	32.0	23.2	23.8	<0.0001
BP <130/80 mmHg	46.8	36.1	21.8	<0.0001
Lipids	34.4	32.4	24.4	0.0030
TC <5.17 and TG <1.68 and HDL≥1.03 mmol/L				

[a]Median and interquartile ranges are given.

BMI: body mass index, A1C: glycosylated haemoglobin A1C, SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, TC: total cholesterol, HDL: HDL-cholesterol, TG: triglycerides, CVD: cardiovascular disease.

Table 2. Clinical characteristics of diabetic patients according to the CKD stages ($N = 3297$)

	CKD stages				*P*-value
	eGFR ≥60	eGFR 30–59	eGFR 15–29	eGFR <15	
	CKD 1–2 $N = 2791$	CKD 3 $N = 459$	CKD 4 $N = 31$	CKD 5 $N = 16$	
Age (years)	58 ± 8	63 ± 6	61 ± 5	58 ± 6	<0.0001
Male (%)	65.1	58.4	64.5	50.0	0.0280
BMI (kg/m^2)	24.7 ± 3.7	25.0 ± 3.9	26.1 ± 4.2	24.6 ± 4.0	0.0564
BMI ≥25 (%)	41.5	42.7	58.1	25.0	0.1400
Duration of diabetes (years)	11 ± 7	13 ± 8	18 ± 10	17 ± 7	<0.0001
Diet/tablet/insulin (%)	14/67/19	12/59/29	3/52/45	0/31/69	<0.0001
A1C (%)	7.1 ± 1.1	6.9 ± 1.0	6.7 ± 1.0	7.1 ± 1.4	0.0153
Serum creatinine (μmol/L)	62.1 ± 12.5	93.1 ± 18.9	204.2 ± 51.3	632.9 ± 282.0	<0.0001
Hypertension (%)	45.1	65.7	96.8	87.5	<0.0001
SBP (mmHg)	128 ± 14	131 ± 15	142 ± 19	141 ± 24	<0.0001
DBP (mmHg)	75 ± 9	75 ± 10	78 ± 11	80 ± 13	0.0484
PP (mmHg)	53 ± 11	56 ± 13	65 ± 13	62 ± 14	<0.0001
Hyperlipidaemia (%)	60.7	72.1	90.0	75.0	<0.0001
TC (mmol/L)	5.15 ± 0.85	5.17 ± 0.85	5.28 ± 1.19	5.09 ± 0.98	0.6055
HDL (mmol/L)	1.42 ± 0.44	1.37 ± 0.41	1.22 ± 0.39	1.22 ± 0.41	0.0003
TG (mmol/L)[a]	1.34 (0.92–1.94)	1.52 (1.12–2.20)	1.83 (1.18–2.42)	1.71 (1.25–2.62)	<0.0001
Smoking current/past/ never (%)	32/21/47	25/21/54	32/29/39	31/13/56	0.0490
CVD (%)	7.6	17.9	32.3	12.5	<0.0001
Retinopathy proliferative/simple/no (%)	8/21/71	12/31/57	55/32/13	62/38/0	<0.0001
Neuropathy (%)	20.8	31.2	58.1	81.3	<0.0001
Attainment rate (%)					
A1C <6.5%	28.9	30.3	48.4	43.8	0.0590
BP <130/80 mmHg	43.6	37.7	6.5	12.5	<0.0001
Lipids	34.0	29.2	13.3	18.8	0.0120
TC <5.17 and TG <1.68 and HDL≥1.03 mmol/L					

[a]Median and interquartile ranges are given.

BMI: body mass index, A1C: glycosylated haemoglobin A1C, SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, TC: total cholesterol, HDL: HDL-cholesterol, TG: triglycerides, CVD: cardiovascular disease.

Table 3. Number (proportion and its 95% CI) of patients with type 2 diabetes classified by CKD stages and albuminuria stages in the JDDM study ($N = 3297$)

	Normoalbuminuria $N = 2298$ (69.7, 68.1–71.3)	Microalbuminuria $N = 705$ (21.4, 20.0–22.8)	Macroalbuminuria $N = 294$ (8.9, 7.9–9.9)
CKD 1–2 $N = 2791$ (84.7, 83.4–85.9)	$N = 2036$ (61.8, 60.1–63.4)	$N = 600$ (18.2, 16.9–19.5)	$N = 155$ (4.7, 4.0–5.4)
CKD 3 $N = 459$ (13.9, 12.7–15.1)	$N = 259$ (7.9, 6.9–8.8)	$N = 105$ (3.2, 2.6–3.8)	$N = 95$ (2.9, 2.3–3.5)
CKD 4 $N = 31$ (0.9, 0.6–1.3)	$N = 3$ (0.1, 0.0–0.2)	$N = 0$	$N = 28$ (0.8, 0.5–1.2)
CKD 5 $N = 16$ (0.5, 0.2–0.7)	$N = 0$	$N = 0$	$N = 16$ (0.5, 0.2–0.7)

CKD, chronic kidney disease.

(≥60/<60) were duration of diabetes, PP, hypertension, CVD, retinopathy and neuropathy. Age, low A1C and non-smoking were only associated with low eGFR. A1C, SBP, DBP, TG and smoking were only associated with albuminuria.

Factors associated with the presence of renal insufficiency and albuminuria were explored by multiple logistic regression analysis (Table 5). Age, sex, BMI, duration of diabetes, A1C, hypertension, hyperlipidaemia, smoking, CVD, retinopathy, neuropathy and renal insufficiency (or albuminuria) were entered as independent variables in the model after adjustment for an effect of different clinics/hospitals. Factors commonly associated with renal insufficiency and albuminuria were hypertension, CVD and proliferative retinopathy. Factors independently associated with renal insufficiency were age, duration of diabetes, A1C (negative), hyperlipidaemia, smoking (negative) and macroalbuminuria, whereas factors independently associated with albuminuria were male sex, BMI, A1C, simple retinopathy, neuropathy and eGFR <60.

Clinical profile of patients with normoalbuminuria and low eGFR (Table 4)

Among the 262 patients with normoalbuminuria and with low eGFR, 198 (75.6%, 95% CI: 70.4–80.8%) had no diabetic retinopathy, and 166 (63.4%, 95% CI: 57.5–69.2%) had no diabetic neuropathy in addition. As compared with those with normoalbuminuria and preserved eGFR, those with normoalbuminuria and low eGFR were older and more

Table 4. Clinical profiles in patients by status of albuminuria and renal insufficiency

		Normoalbuminuria	Microalbuminuria	Macroalbuminuria	*P*-value among groups with normo/micro/ macroalbuminuria
		eGFR <60; $N = 262$ eGFR ≥60; $N = 2036$	eGFR <60; $N = 105$ eGFR ≥60; $N = 600$	eGFR <60; $N = 139$ eGFR ≥60; $N = 155$	
Age (years)	eGFR <60	62 ± 6****	64 ± 5****	61 ± 6****	0.0090
	eGFR ≥60	57 ± 9	58 ± 8	58 ± 8	0.4209
Male (%)	eGFR <60	52.7***	64.8	64.7	0.0220
	eGFR ≥60	64.6	66.0	68.4	0.5530
BMI (kg/m^2)	eGFR <60	24.8 ± 3.7	25.0 ± 3.8	25.6 ± 4.4*	0.1910
	eGFR ≥60	24.3 ± 3.5	25.4 ± 3.8	26.7 ± 5.0	<0.0001
BMI ≥25 (%)	eGFR <60	40.5	43.8	47.5	0.3950
	eGFR ≥60	37.7	50.5	56.2	<0.0001
Duration of diabetes (years)	eGFR <60	11 ± 8***	14 ± 9**	17 ± 9****	<0.0001
	eGFR ≥60	10 ± 7	12 ± 7	12 ± 8	<0.0001
A1C (%)	eGFR <60	6.8 ± 0.9	7.0 ± 0.9*	7.1 ± 1.2****	0.0077
	eGFR ≥60	7.0 ± 1.0	7.3 ± 1.2	7.7 ± 1.3	<0.0001
SBP (mmHg)	eGFR <60	130 ± 16*****	133 ± 15	137 ± 16	<0.0001
	eGFR ≥60	127 ± 14	131 ± 14	134 ± 15	<0.0001
DBP (mmHg)	eGFR <60	75 ± 10	74 ± 10**	77 ± 10	0.0284
	eGFR ≥60	74 ± 9	76 ± 9	77 ± 9	<0.0001
PP (mmHg)	eGFR <60	55 ± 13***	59 ± 14***	60 ± 13	0.0002
	eGFR ≥60	53 ± 11	55 ± 11	56 ± 12	<0.0001
Hypertension (%)	eGFR <60	58.2****	69.5*	86.3**	<0.0001
	eGFR ≥60	39.9	56.1	69.7	<0.0001
Hyperlipidaemia (%)	eGFR <60	71.6****	68.9	79.7	0.1180
	eGFR ≥60	59.4	62.4	71.2	0.0090
TC (mmol/L)	eGFR <60	5.19 ± 0.78**	5.12 ± 0.85	5.42 ± 1.37	0.7562
	eGFR ≥60	5.09 ± 0.83	5.22 ± 0.93	5.33 ± 1.09	<0.0001
HDL (mmol/L)	eGFR <60	1.37 ± 0.36	1.40 ± 0.51	1.27 ± 0.41**	0.0119
	eGFR ≥60	1.42 ± 0.41	1.42 ± 0.49	1.40 ± 0.39	0.5120
TG (mmol/L)[a]	eGFR <60	1.46 (1.12–2.18)****	1.48 (1.09–2.04)	1.76 (1.18–2.36)	0.0242
	eGFR ≥60	1.30 (0.90–1.89)	1.41 (0.96–1.98)	1.62 (1.10–2.53)	<0.0001
Smoking current/past/ never (%)	eGFR<60	23/18/59**	23/23/54*	34/25/41	0.0100
	eGFR ≥60	30/22/48	37/18/45	37/24/39	0.0150
CVD (%)	eGFR <60	12.6***	22.9**	26.6***	0.0010
	eGFR ≥60	6.4	11.2	10.3	<0.0001
Retinopathy proliferative/ simple/no (%)	eGFR <60	4/19/77	18/35/47 d)	37/50/12****	<0.0001
	eGFR ≥60	5/18/77	14/26/60	19/40/41	<0.0001
Neuropathy (%)	eGFR <60	20.0	38.5**	58.7**	<0.0001
	eGFR ≥60	18.6	23.3	40.1	<0.0001

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$,****$P < 0.0001$ versus patients with an eGFR ≥60.

[a] Median and interquartile ranges are given.

BMI: body mass index, A1C: glycosylated haemoglobin A1C, SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, TC: total cholesterol, HDL: HDL-cholesterol, TG: triglycerides, CVD: cardiovascular disease.

often women, had higher prevalences of hypertension, hyperlipidaemia and CVD, had higher levels of SBP, PP, TC and TG and included fewer smokers. As compared with those with micro/macroalbuminuria and low eGFR, normoalbuminuric patients with low eGFR were characterized by a significantly higher proportion of women, lower prevalences of hypertension, smoking, CVD, retinopathy and neuropathy, and lower values of diabetes duration, systemic BP and PP. The prevalence of normoalbuminuria among those with low eGFR was 262/506 (51.8%, 95% CI: 47.4–56.1%). It was then calculated after excluding 80 of 262 patients whose normoalbuminuric status was possibly altered by the use of the renin–angiotensin system (RAS) inhibitor. After this adjustment the prevalence of normoalbuminuria among those with low eGFR was 182 of 426 (42.7%, 95% CI: 38.0–47.4%).

Discussion

This study, in a large-scale population of Japanese type 2 diabetes, indicated that the proportion of subjects with low eGFR was 11.4% among those with normoalbuminuria, 14.9% among those with microalbuminuria and 47.3% among those with macroalbuminuria. The prevalence of normoalbuminuria among patients with low eGFR was as high as 42.7% even after adjustment for the RAS inhibitor effect. This finding supports the concept that patients with