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アブストラクトテーブル

論文コード	対象	方法	結果
1) DCCT Research Group, 1998 RCT レベル⑥	米国．1型糖尿病(1,441人)	強化インスリン療法(711人) vs. 従来インスリン療法(730人)，6.5年間	Intensive therapyは，糖尿病性網膜症の6～12ヵ月以内の初期悪化が高頻度であったが，18ヵ月後には改善した
2) 高橋良当ほか, 1998 症例研究 レベル⑦	日本．1型または2型糖尿病(86人)	インスリンの開始・増量(67人)，経口剤の開始(18人)，食事療法の開始(1人)	HbA_{1c}の改善は14%→8.8%(平均2ヵ月)で，下肢・腰部痛が出現
3) DCCT Research Group, 1993 RCT レベル⑥	米国．1型糖尿病(1,441人)	強化インスリン療法(711人) vs. 従来インスリン療法(730人)[6.5年間]	強化インスリン療法は，1型糖尿病において糖尿病網膜症，腎症，神経障害の発症・進展の抑制に有効である
4) DCCT Research Group, 1998 RCT レベル⑥	米国．1型糖尿病(1,441人)	強化インスリン療法(711人) vs. 従来インスリン療法(730人)[9年間]	強化インスリン療法は，1型糖尿病において自律神経障害の進展を抑制する
5) Lawson ML et al, 1999 システマティックレビュー レベル⑥+	1型糖尿病(1,732人)	強化インスリン療法(861人) vs. 従来インスリン療法(870人)[2年以上]	強化インスリン療法は，1型糖尿病において早期の大血管症(狭心症，心筋梗塞，血管形成術，冠動脈バイパス術)，自律神経障害の進展を抑制する
6) DCCT/EDIC Study Research Group, 2005 RCT レベル⑥	米国．1型糖尿病(1,441人)	強化インスリン療法(711人) vs. 従来インスリン療法(730人)，17年間	Intensive therapyは，1型糖尿病において大血管症(非致死性心筋梗塞，脳卒中，心血管死)のリスクを軽減させた
7) Ohkubo Y et al, 1995 RCT レベル⑥	日本．2型糖尿病(110人)	強化インスリン療法(52人) vs. 従来インスリン療法(50人)[6年間]	強化インスリン療法は，2型糖尿病において空腹時血糖値，HbA_{1c}値，尿中アルブミンの改善が良好であり，細小血管合併症の発症・進展の抑制に有効である
8) UKPDS 33, 1998 RCT レベル⑥	英国．2型糖尿病(3,867人)	スルホニル尿素薬投与群(1,573人) vs. インスリン投与群(1,156人) vs. 食事療法群(1,138人)[6年間]	スルホニル尿素薬やインスリンよる厳格な血糖コントロールにより細小血管症のリスクは減少したが，大血管症は変わらなかった
9) Shichiri M et al, 2000 RCT レベル⑥	日本．2型糖尿病(110人)	強化インスリン療法(55人) vs. 従来インスリン療法(55人)[6年間]	強化インスリン療法は，2型糖尿病において空腹時血糖値，HbA_{1c}値，尿中アルブミンの改善が良好であり，細小血管合併症の発症・進展の抑制に有効である
10) UKPDS 24, 1998 RCT レベル⑥	英国．2型糖尿病(食事療法で血糖コントロール不良)(458人)	スルホニル尿素薬投与群(231人) vs. インスリン投与群(178人) vs. メトホルミン投与群(49人)[6年間]	インスリン投与群は低血糖の頻度が多く，体重増加率も大きいので経口血糖降下薬から薬物療法を開始したほうがよい

論文コード	対象	方法	結果
11) Feinglos MN et al, 1998 RCT **クロスオーバー試験** レベル②⁻	米国．2型糖尿病(インスリン治療中)(37人)	プラセボ併用とスルホニル尿素薬併用[前後比較，3ヵ月間]	スルホニル尿素薬併用で比較的早期に空腹時血糖値が改善，24時間の平均血糖値の改善が良好であった
12) UKPDS 57, 2002 RCT レベル②	英国．2型糖尿病(新規診断)(826人)	食事療法単独群(242人) vs. インスリン単独群(245人) vs. スルホニル尿素薬＋インスリン併用群(339人)[6年間]	スルホニル尿素薬最大量投与に早期にインスリンを加えるのは低血糖や体重増加させることなく血糖コントロールを改善した
13) Avilés-Santa L et al, 1999 RCT レベル②⁻	米国．2型糖尿病(インスリン治療中)(43人)	プラセボ併用群(21人) vs. メトホルミン併用群(22人)[24週間]	メトホルミン投与群で HbA_{1c} 値の改善が良好，インスリン必要量が減少し，体重増加が少ない
14) Relimpio F et al, 1998 RCT レベル②⁻	スペイン．2型糖尿病(インスリン治療中)(48人)	インスリンのみの投与群(24人) vs. メトホルミン併用群(24人)[4ヵ月間]	メトホルミン併用群で HbA_{1c} 値，総コレステロール値，LDLコレステロール値の改善が良好であり体重増加が少ない
15) Yki-Järvinen H et al, 1999 RCT レベル②	フィンランド．2型糖尿病(スルホニル尿素薬で血糖コントロール不良)(88人)	眠前の中間型インスリンに加え，朝のインスリンを追加した群(24人) vs. スルホニル尿素薬を併用した群(22人) vs. メトホルミンを併用した群(19人) vs. スルホニル尿素薬およびメトホルミンを併用した群(23人)[1年間]	眠前のインスリンにメトホルミンを併用した群で体重増加が少なく，低血糖のリスクが減少，HbA_{1c} 値の改善が良好であった
16) Ponssen HH et al, 2000 RCT **クロスオーバー試験** レベル②⁻	オランダ．2型糖尿病(31人)	インスリンのみの投与群 vs. メトホルミン併用群[4ヵ月間]	メトホルミン併用群で血糖コントロールは改善し，インスリンの必要量も減少した
17) Kelley DE et al, 1998 RCT レベル②	米国．2型糖尿病(食事療法およびインスリンで血糖コントロール不良)(145人)	プラセボ投与群(73人) vs. アカルボース投与群(72人)[26週間]	アカルボース投与群で HbA_{1c} 値，食後血糖値，食後中性脂肪値が低下した
18) Juntti-Berggren L et al, 2000 RCT **クロスオーバー試験** レベル②⁻	デンマーク．1型糖尿病(10人)	プラセボ併用群 vs. アカルボース併用[10±3日間]	アカルボース併用でインスリンの必要量が減少した
19) Buse JB et al, 1998 RCT レベル②	米国．2型糖尿病(222人)	プラセボ併用群(71人) vs. トログリタゾン併用群[200 mg(75人)，400 mg(76人)][26週間]	トログリタゾン併用群でインスリン必要量の減少が得られ，HbA_{1c} 値の改善が良好であった
20) Schwartz S et al, 1998 RCT レベル②	米国．2型糖尿病(インスリンで血糖コントロール不良)(350人)	プラセボ併用群(118人) vs. トログリタゾン併用群[200 mg(116人)，600 mg(116人)][26週間]	トログリタゾン併用群で HbA_{1c} 値，空腹時血糖値の改善が良好でインスリン必要量の減少が見込まれる
21) 小坂樹徳ほか，1996 RCT レベル②	日本．1型，2型糖尿病(インスリン治療中)(232人)	プラセボ併用群(118人) vs. トログリタゾン併用群(114人)[16週間]	トログリタゾン併用群で HbA_{1c} 値の改善が良好であった
22) Raskin P et al, 2001 RCT レベル②	米国．2型糖尿病(インスリン治療中)(319人)	プラセボ併用群（107人) vs. ロシグリタゾン併用群(212人)[26週間]	ロシグリタゾン併用群で HbA_{1c} 値の低下を認め，インスリン投与量が減少した

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論文コード	対象	方法	結果
23) Riddle MC et al, 1998 RCT レベル❷	米国．2型糖尿病(スルホニル尿素薬二次無効例)(132人)	中間型インスリン単独使用開始群(62人) vs. 中間型インスリンとグリメピリドの併用開始群(70人)[24週間]	グリメピリド併用開始群のほうが血糖値の改善が早く，インスリン必要量も少なかった
24) Shank ML et al, 1995 RCT レベル❷⁻	米国．2型糖尿病(スルホニル尿素薬二次無効例)(30人)	スルホニル尿素薬のみの投与群(10人) vs. 眠前の中間型インスリンのみの投与群(10人) vs. 両者併用群(10人)[1年間]	主として肝での糖新生の基礎値が抑制されることにより，両者併用群のほうが良好な血糖コントロールが得られる
25) Trischitta V et al, 1998 クロスオーバー試験 レベル❷⁻	イタリア．2型糖尿病(スルホニル尿素薬二次無効例)(50人)	眠前の中間型インスリン併用群，メトホルミン併用群 [前後比較，8週間]	併用した場合 HbA_{1c} 値の改善が良好，インスリン併用では空腹時血糖値の改善が良好，メトホルミン併用では，食後血糖値の改善が良好，体重増加はインスリン併用で大きかった
26) Home PD et al, 2000 RCT レベル❶	ヨーロッパ．1型糖尿病(1,070人)	速効型インスリン使用群 vs. 超速効型(アスパルト)インスリン使用群 [6ヵ月間]	超速効型インスリン使用で HbA_{1c} 値の軽度低下を認め，夜間の低血糖は減少した
27) Gale EAM et al, 2000 RCT クロスオーバー試験 レベル❷	英国．1型糖尿病(93人)	速効型インスリン使用群 vs. 超速効型(リスプロ)インスリン使用群 [12週間]	超速効型インスリン使用で HbA_{1c} 値は変化を認めなかったが，夜間の低血糖は減少した
28) 葛谷 健ほか，2000 RCT レベル❷⁻	日本．1型・2型糖尿病(426人)	速効型インスリン使用群(213人) vs. 超速効型(リスプロ)インスリン使用群(213人) [24週間]	超速効型インスリン使用群で食後2時間血糖値は低下したが，HbA_{1c} 値は差はなし．超速効型インスリンの安全性が確認された
29) 岩本安彦ほか，2001 RCT レベル❷⁻	日本．1型糖尿病(205人)	速効型インスリン使用群(62人) vs. 超速効型(リスプロ)インスリン使用群(143人) [24週間]	超速効型インスリン使用群で食後90分血糖値は低下したが，HbA_{1c} 値は差はなし．超速効型インスリンは食直前投与により有用
30) Raskin P et al, 2001 RCT クロスオーバー試験 レベル❷	米国．1型糖尿病(58人)	CSIIで速効型インスリン使用群 vs. 超速効型(リスプロ)インスリン使用群 [12週間]	CSIIで速効型インスリンに比べ超速効型インスリンを使用してほうが良好な血糖コントロールが得られた
31) Bode BW et al, 2001 オープンラベル試験 レベル❷⁻	米国．1型糖尿病(29人)	CSIIで速効型インスリン使用群(10人) vs. 超速効型インスリン使用群(19人)[7週間]	CSIIに超速効型インスリンと速効型インスリンを使用して両群とも血糖コントロールは良好にされた
32) Roach P et al, 1999 オープンラベル試験 クロスオーバー試験 レベル❷⁻	ヨーロッパ．1型または2型糖尿病(100人)	速効型混合インスリン使用群(朝食前50/50夕食前30/70) vs. 超速攻型混合インスリン使用群(朝食直前Mix50夕食直前Mix25)，6ヵ月間	朝食後，夕食後ともに血糖変動平均値は超速攻型混合製剤のほうが有意に低く，夜間の低血糖も少なかった

論文コード	対象	方法	結果
33）Boehm BO et al, 2002 オープンラベル試験 レベル❷⁻	ヨーロッパ．1型または2型糖尿病(294人)	超速効型混合製剤(30MIX)使用群(143人) vs. 速効型混合製剤(30R)使用群(151人)，12週間	超速効型混合製剤で朝食後，昼食前，夕食後，眠前の血糖値は低くかったが，低血糖に差はなかった
34）岩本安彦ほか, 2002 前後比較試験 レベル❷	日本．1型または2型糖尿病(248人)	ヒトインスリン混合製剤からリスプロ混合製剤への切り替え試験 30/70 → Mix25，50/50 → Mix50，12週間	リスプロ混合製剤で食後2時間血糖値，HbA_{1c}値の改善が得られた
35）岩本安彦ほか, 2003 オープンラベル試験 レベル❷⁻	日本．2型糖尿病(428人)	二相性インスリンアスパルト-30使用群(321人) vs. ヒトインスリン混合製剤(30R)使用群(107人)，48週間	二相性インスリンアスパルト-30使用群で朝食後90分血糖値の低下を認め，HbA_{1c}値や低血糖の頻度に差は認めなかった
36）Ratner RE et al, 2000 オープンラベル試験 レベル❷⁻	米国．1型糖尿病(534人)	中間型インスリン使用群(270人) vs. 持効型(グラルギン)インスリン使用群(264人)[28週間]	持効型インスリン使用群で空腹時血糖値は低下し，低血糖は減少した
37）Rossetti P et al, 2003 オープンラベル試験 レベル❷⁻	イタリア．1型糖尿病(51人)	眠前の中間型インスリン使用群(17人) vs. 夕食前の持効型(グラルギン)インスリン使用群(17人) vs. 眠前の持効型(グラルギン)インスリン使用(17人)[3ヵ月間]	持効型インスリン使用群でHbA_{1c}値の低下と低血糖の頻度は減少した．眠前の中間型インスリン使用に対し，夕食時の持効型インスリンでも血糖コントロールを増悪させなかった
38）Yki-Järvinen H et al, 2000 オープンラベル試験 レベル❷⁻	フィンランド．2型糖尿病(426人)	経口血糖降下薬に眠前の中間型インスリン追加群(208人) vs. 持効型(グラルギン)インスリン追加群(214人)[1年間]	持効型インスリン使用群で夕食後血糖値は低下し，夜間低血糖は減少した
39）Riddle MC et al, 2003 オープンラベル試験 レベル❷⁻	米国．2型糖尿病(756人)	経口血糖降下薬に眠前の中間型インスリン追加群(389人) vs. 持効型(グラルギン)インスリン追加群(367人)[24週間]	持効型インスリン使用群で夜間低血糖は減少した

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Original Article

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

Table 5. Determinants of low eGFR (<60 versus ≥60; left panel) and albuminuria (micro/macroalbuminuria versus normoalbuminuria; right panel) by multiple logistic regression analysis

	eGFR <60 versus ≥60 (reference)			Micro/macroalbuminuria versus normoalbuminuria (reference)		
	Wald χ^2 score	OR (95% CI)	*P*-value	Wald χ^2 score	OR (95% CI)	*P*-value
Age (per years)	76.3	1.08 (1.06–1.10)	0.000	1.9	1.01 (1.00–1.02)	0.170
Male	0.8	0.89 (0.68–1.17)	0.386	8.3	1.31 (1.09–1.57)	0.004
BMI (per kg/m^2)	3.1	1.03 (0.99–1.06)	0.078	22.6	1.06 (1.03–1.08)	0.000
Duration of diabetes (per years)	4.4	1.02 (1.00–1.03)	0.037	0.45	1.00 (0.99–1.02)	0.504
A1C (per %)	15.3	0.79 (0.70–0.89)	0.000	29.8	1.26 (1.16–1.36)	0.000
Hypertension	10.0	1.46 (1.16–1.86)	0.002	68.7	2.12 (1.77–2.53)	0.000
Hyperlipidaemia	9.7	1.47 (1.15–1.86)	0.002	0.9	1.09 (0.91–1.31)	0.338
Smoking versus never	5.1	0.77 (0.62–0.97)	0.030	2.0	1.16 (0.95–1.42)	0.158
CVD	15.7	1.87 (1.37–2.55)	0.000	14.5	1.69 (1.29–2.29)	0.000
Retinopathy versus none						
simple	7.4	1.47 (1.11–1.91)	0.151	52.1	2.10 (1.72–2.56)	0.000
proliferative	15.9	2.11 (1.46–3.05)	0.000	80.0	3.72 (2.79–4.96)	0.000
Neuropathy (%)	1.9	1.17 (0.92–1.56)	0.174	12.3	1.45 (1.18–1.79)	0.000
Nephropathy versus normoalbuminuria				N.A.	N.A.	N.A.
Microalbuminuria	0.4	1.01 (0.83–1.45)	0.506			
Macroalbuminuria	102.1	5.56 (4.00–7.76)	0.000			
eGFR <60 versus ≥60	N.A.	N.A.	N.A.	31.1	1.91 (1.52–2.40)	0.000

Both analyses were obtained after adjustment for an effect of different clinics/hospitals.
N.A., not applicable.

type 2 diabetes can commonly progress to a significant degree of renal insufficiency while remaining normoalbuminuric [3,9]. Furthermore, we found that more than 60% of patients with normoalbuminuria and low eGFR had neither diabetic retinopathy nor neuropathy. The finding strongly suggests that non-diabetic renal disease is not uncommon in type 2 diabetic patients [2].

Clinical features of patients with normoalbuminuria and renal insufficiency

Few reports have analysed the clinical characteristics of type 2 diabetic patients with normoalbuminuria and renal insufficiency. One report compared them with those with micro/macroalbuminuria and with renal insufficiency [3]. It showed that normoalbuminuric renal insufficiency patients were characterized by female predominance, lower SBP and higher HDL, which is in accordance with our findings. Similar findings were demonstrated in type 1 diabetes [5]. We have extended their findings by demonstrating lower prevalences of smokers, CVD, retinopathy and neuropathy. Another report compared them with those with normoalbuminuria and an eGFR ≥60, where the finding was similar to ours in terms of more women, older age and higher concentrations of TC and TG [4]. Our study provides further information such as higher levels of systemic BP and PP in those with renal insufficiency and with normoalbuminuria.

Proportion of patients with normoalbuminuria and with renal insufficiency

First, we should acknowledge that the proportion of patients with renal insufficiency is subject to the equation for eGFR. The proportion of 11.4% (low eGFR among those with normoalbuminuria) shown in this paper was 16.6% when the equation in the previous studies [12,15] was employed (data not shown). Secondly, one should be cautious about selection bias when calculating prevalences. The proportion of normoalbuminuria seems higher than in other cross-sectional large-scale-population-based prevalence studies [15,18], and it is possible that the included subjects had a lower prevalence of complications compared to the entire population of type 2 diabetic patients since inpatients and those who were treated solely by cardiologists/neurologists did not participate. The prevalence of renal insufficiency among those with normoalbuminuria was 12.7% (84/660) in a report from Brazil [4], which seems compatible with our finding of 11.4%. The prevalence of normoalbuminuria among those with renal insufficiency was 23.2% (20/86) in a report from Australia [3], but 42.7% (182/426) in our study: both studies performed adjustment for possible effects of the RAS inhibitor. The prevalence of 23.2% [3] was calculated at a tertiary referral clinic and the number was small. The above findings suggest that a significant proportion of type 2 diabetic patients have non-albuminuric renal insufficiency.

Factors associated for albuminuria and low eGFR

The clinical factors associated with albuminuria and low eGFR were comparable with those found in other longitudinal [5,9] and cross-sectional [3,4,6,19] studies. The UK Prospective Diabetes Study revealed that over a median of 15 years' follow-up, risk factors for development of albuminuria were male sex, TG, LDL-C, A1C, smoking and retinopathy, and those for renal insufficiency were female sex, age and neuropathy [9]. A female predilection for normoalbuminuria and renal insufficiency has been noted by other cross-sectional [3,4,6] and follow-up [5] studies, but to date the reason for this association is unknown. Lower A1C values were observed in those with low eGFR than

in those with preserved eGFR in our study, particularly in those with micro/macroalbuminuria. This could be due to a reduced erythropoietin production caused by reduced renal function [20], although our study did not collect data for haemoglobin concentrations. A decreased haemoglobin concentration has been shown to be an independent factor associated with renal dysfunction in diabetic patients [21]. Smoking is associated with albuminuria, suggesting that smoking may be an important correlate of albuminuria in the presence or absence of low eGFR. Subjects who had never smoked were more prevalent in those with low eGFR than in those with preserved eGFR among those with normo- and microalbuminuria. The same result was seen in another report [19]; however, the reason remains uncertain from these cross-sectional studies. Taken together, distinct factors associated with albuminuria and low eGFR are indicated. Indeed, no significant associations between renal insufficiency and microalbuminuria were found in multivariate analysis. These findings support the concept that albuminuria and low eGFR are not necessarily linked in type 2 diabetes [9].

Reason of low eGFR in type 2 diabetic patients

The mechanism for low eGFR in normoalbuminuric type 2 diabetic patients is still unknown, despite the involvement of non-diabetic renal disease being indicated. Among normoalbuminuric patients, greater age, longer duration of diabetes and higher prevalences of hypertension, hyperlipidaemia, diabetic neuropathy and CVD were found in those with low eGFR than in those with preserved eGFR. A lower concentration of HDL was observed in macroalbuminuric patients with renal insufficiency. These findings indicate that low eGFR could be due to age-associated senescence and interstitial fibrosis, and renal ischaemia due to intrarenal arteriosclerosis and cholesterol emboli involvements [2,22]. Lipid abnormalities by high TG and low HDL were indicated in association with progression of renal dysfunction [23]. Our finding that the prevalence of CVD was persistently twofold higher in patients with low eGFR than in those with preserved eGFR regardless of the degree of albuminuria indicates that the low eGFR is substantially associated with atherosclerotic vascular disease.

Limitation of the study

The study design was cross-sectional; therefore it cannot explore causal relationships. A single measurement of serum creatinine for calculating eGFR could mislead the classification of CKD stages. Since age and female sex both reduce the MDRD equation, it cannot be denied that the association of these factors with low eGFR was generated in part by the equation. Direct measurement of GFR should be a standard clinical procedure, although it is time consuming and not feasible for screening and large-scale studies. The usefulness of eGFR has been demonstrated by several follow-up studies [24,25], and a recent validation study indicated that the difference between eGFR by MDRD and measured GFR was slight and not significant even in cross-sectional analysis of normoalbuminuric and albuminuric diabetic patients [5]. On the other hand, the strengths of this study include the large-scale population with type 2 diabetes, a nation-wide multicentre-based design and multiple measurements of ACR and blood pressure. Finally, since the subjects included in this study were recruited from practice and seemed less complicated, we cannot evaluate the prevalence of severe renal failure from this study although it is likely to be higher than we have found.

Attainment of treatment goals

The low attainment rate of treatment goals for A1C, BP and lipids may indicate that those with increasing albuminuria stages and CKD stages are refractory to standard therapy despite aggressive use of insulin, antihypertensive and lipid-lowering agents. This finding is in line with other studies [26], indicating the need for aggressive treatment of these modifiable risk factors. In diabetic patients even without albuminuria, it may be reasonable to encourage screening for low eGFR. The potential benefit of achieving current treatment goals in patients with micro/macroalbuminuria and/or low eGFR offers hope for the future reduction of CVD and end-stage renal disease if a more focused and multifactorial approach is applied.

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Conflict of interest statement. None declared.

A3

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ORIGINAL

Association between Body Mass Index and Core Components of Metabolic Syndrome in 1486 Patients with Type 1 Diabetes Mellitus in Japan (JDDM 13)

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Abstract. There is no recent study on the prevalence of overweight and obesity in patients with type 1 diabetes mellitus (T1DM) in Japan. Being overweight has a significant effect on the metabolic condition and glycemic control of such patients. In the present cross-sectional study, we investigated the effects of body mass index (BMI) on lipid profile, blood pressure, and glycemic control in patients with T1DM. In total, 1486 patients with T1DM (including 401 patients with early onset T1DM who were <20 years of age at diagnosis) were included. Patients were divided into four groups according to their BMI, and glycosylated hemoglobin (HbA1c), daily insulin dose per kg body weight, lipid profile, and blood pressure were compared between groups. We found that 15.7% of all patients were overweight (BMI ≥25.0 kg/m^2) and 2.0% were obese (BMI ≥30.0 kg/m^2), compared with 17.5% and 2.0%, respectively, in the early onset T1DM subgroup. Significant changes in lipid profiles and blood pressure were found with increasing BMI in both the entire population and the early onset T1DM subgroup. In the entire study population HbA1c and the body weight-adjusted daily insulin dose were significantly higher in patients with a BMI ≥23 kg/m^2 compared with those with a BMI <23 kg/m^2; however, this was not the case in the early onset T1DM subgroup. This difference may be due to the relatively small number of patients in that subgroup. In conclusion, the prevalence of overweight and obesity in patients with T1DM was less than that in the normal Japanese population. For patients with T1DM, being overweight was associated with higher blood pressure and dyslipidemia. Furthermore, we cannot exclude an association between being overweight and the need for higher daily doses of insulin.

Key words: type 1 diabetes mellitus (T1DM), body mass index (BMI), insulin resistance, metabolic syndrome

CLASSICALLY, diabetes mellitus has been categorized into types 1 and 2. Type 1 diabetes mellitus (T1DM) was considered an autoimmune disorder of childhood, characterized by acute onset, ketoacidosis, and insulin dependency. Conversely, type 2 diabetes mellitus (T2DM), typically diagnosed in middle-aged patients, was considered a metabolic disorder with a slow onset, for which insulin treatment was not always required. However, in recent years, the characteristics of T1DM and T2DM seem to have changed. Now, more than half the patients with T1DM present in adulthood (i.e. slow onset) and many do not develop acidosis or require insulin treatment until much later [1, 2]. At the same time, T2DM is being diagnosed more frequently in teenagers [3]. These patients

sometimes become ketoacidotic [4, 5] and insulin dependency often ensues. The accelerator hypothesis, proposed in 2001, states that T1DM and T2DM are, in most respects, the same and can be distinguished only by the rate of β-cell loss and the accelerator responsible [6]. Furthermore, some patients may present with disease processes of both T1DM and T2DM, or develop them sequentially over time, which has been termed 'double diabetes' [7, 8].

The prevalence of overweight and obesity has increased in the US and Europe, as well as in Asian countries, such as Japan. Metabolic syndrome occurs in both nondiabetic subjects and patients with T2DM. It is a cluster of metabolically related cardiovascular risk factors, the core components of which comprise central obesity, insulin resistance, dyslipidemia, and hypertension [9–11]. There are multiple definitions of metabolic syndrome [12–14], with the most recent one being provided in the consensus statement issued by the International Diabetes Federation [15]. The presence of increased insulin resistance appears to be central to the development of metabolic syndrome. Insulin resistance is common in obesity [16], and hyperglycemia resulting from insulin resistance induces β-cell insufficiency [6]. Excessive weight gain or obesity in infancy may be associated with a higher risk of T1DM in children [17]. Although obesity is not generally considered a typical feature of T1DM, it has a similar prevalence in individuals with T1DM to that of the general population.

Furthermore, the intensive insulin therapy required to obtain good glycemic control and to reduce diabetic complications is itself associated with weight gain, unless it is complemented by appropriate diet therapy [18, 19]. This raises the question of how to balance the need for increasing insulin doses to maintain good glycemic control against possible weight gain, because central obesity is associated not only with insulin resistance, but also with dyslipidemia and hypertension, both of which are core components of metabolic syndrome. Thus, the aim of the present study was to investigate whether body mass index (BMI) has any effect on the core components of metabolic syndrome, including lipid profile, blood pressure, and glycemic control, in patients with T1DM in Japan.

Materials and Methods

Research design and methods

The present cross-sectional study used data obtained in 2005 from 1486 patients (645 men and 841 women) with T1DM, aged between 16 and 90 years. T1DM was diagnosed on the basis of permanent insulinopenia and being either prone to the development of ketosis (idiopathic T1DM) or positive for markers of autoimmune destruction, such as glutamic acid decarboxylase (immune-mediated T1DM). This definition of T1DM is in accordance with that of the Committee of the Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus [20], with the diagnosis criteria almost identical to those proposed by the World Health Organization (WHO) [21]. In the present study, data from 401 patients who were <20 years of age at the time of diagnosis of presumed T1DM were analyzed separately, as the early onset subgroup. Any patients with a primary or subsequent diagnosis of T2DM were excluded from the study. Patients were recruited at clinics and hospitals that belonged to the Japan Diabetes Clinical Data Management Study Group (JDDM; see Appendix I). Clinical data were standardized and saved using CoDiC software, as described previously [22]. Data were collected at the central analytical facility, where the information was treated anonymously and subsequently analyzed using JMP software (SAS Institute, Cary, NC, USA) [23]. The JDDM operates as an intermediate organization under the supervision of the central analytical facility and an ethics committee.

Informed consent was obtained from all patients at each institute prior to their participation in the study, in accordance with the Guidelines for Epidemiological Studies in Japan.

BMI and patient groups

Weight and height were measured using standardized techniques and equipment, with BMI calculated as weight (kg) divided by height squared (m^2). Overweight and obesity were defined as BMI ≥25.0 and ≥30.0 kg/m^2, respectively. These definitions are consistent with those of the WHO [24]. Patients were subdivided into four groups on the basis of their BMI as follows: (i) group 1, BMI <23.0 kg/m^2; (ii) group 2, 23.0 kg/m^2≤BMI<25.0 kg/m^2; (iii) group 3, 25 kg/m^2≤BMI<27.0 kg/m^2; and (iv) group 4, BMI ≥27.0 kg/m^2. Because of the small number of patients in the present study defined as obese, we did not include a separate group with BMI ≥30.0 kg/m^2 for analysis.

Measurement and standardization of data

The daily dose of insulin was normalized against body weight (U/kg body weight). Blood pressure was measured using standard techniques. Glycosylated hemoglobin (HbA1c) was measured by high-performance liquid chromatography, with the normal range defined as 4.3%–5.8%. Serum concentrations of cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol were determined using standard techniques. The measurement of all parameters assessed in the present study was standardized across all institutions.

Statistical analysis

Statistical analyses were performed using JMP software. Triglyceride concentrations were converted to natural logarithms for analysis and are expressed as the median with interquartile ranges. Differences between groups were assessed by analysis of variance (ANOVA), followed by the Tukey-Kramer honestly significant different test for multiple comparisons with a total significance level of 5%. To assess the strength and independence of associations between either HbA1c or BMI as objective variables and other parameters as explanatory variables, multiple regression analysis was performed and standard regression coefficients with P values were calculated. All data, other than triglyceride concentrations, are expressed as the mean ± SD. $P < 0.05$ was considered significant.

Results

Prevalence of overweight and obese individuals

In the present study, 15.7% of all individuals (15.7% of men and 15.5% of women) were overweight (including those who were obese); 2.0% of individuals (1.7% of men and 2.0% of women) were obese. In the early onset subgroup of patients with T1DM, 17.5% of patients (20.8% of men and 15.5% of women) were overweight and 2.0% of patients (2.7% of men and 1.6% of women) were obese.

Association between BMI or HbA1c and daily insulin dose, lipid profile, and blood pressure in the study cohort

Table 1a summarizes the clinical characteristics of patients in each of the four BMI groups. Mean HbA1c was significantly higher in group 2 compared with that in group 1 (7.96 ± 1.58% vs. 7.68 ± 1.57%, respectively). Mean daily insulin doses, total cholesterol, systolic blood pressure (SBP), and triglyceride levels (median natural log) were significantly higher in groups 2–4 compared with group 1. Mean HDL cholesterol

concentrations were significantly lower, whereas diastolic blood pressure (DBP) was significantly higher, in groups 3 and 4 compared with group 1. There were no significant differences in casual plasma glucose concentrations between the four groups.

Table 1b summarizes the results of multiple linear regression analysis. A positive correlation was found between BMI and natural log triglyceride concentrations, SBP, total cholesterol concentrations, and HbA1c. However, BMI was found to be negatively correlated with age and HDL cholesterol concentrations. Positive correlations were found between HbA1c and casual plasma glucose, total cholesterol, daily insulin doses, and natural log triglyceride concentrations, whereas female sex was negatively correlated with HbA1c.

Association between BMI or HbA1c and daily insulin dose, lipid profile, and blood pressure in patients with early onset T1DM

Table 2a summarizes the clinical characteristics of the subgroup of patients with early onset T1DM according to BMI. The median natural log triglyceride concentration was significantly higher in group 4 than in groups 1–3. Mean total cholesterol concentrations and mean SBP were significantly higher in groups 3 and 4 compared with group 1. The mean HDL cholesterol concentration was significantly lower, whereas mean DBP was significantly higher, in group 4 compared with group 1. There were no significant differences in mean HbA1c, daily insulin doses, or casual plasma glucose concentrations between the four groups.

Results of multiple linear regression analysis are summarized in Table 2b. A positive correlation was found between BMI and SBP and total cholesterol concentrations. However, a negative correlation was found between BMI and HDL cholesterol concentrations. There was a positive correlation between HbA1c and total cholesterol, casual plasma glucose, daily insulin doses, and female sex.

Discussion

In Japan, the trend over the past 25 years has been for a consistent increase in the prevalence of overweight men; however, there has been, instead, a decrease in the number of overweight women in the 20–39 years age group [25]. The National Nutrition Survey of Japan, conducted in 2001 [25], revealed that 25.1% of men were overweight and 2.9% were obese, compared with 18.2% and 3.4% of women, respectively. In the US, in 2000, 64.5% of individuals (both men and women) were overweight and 30.5% were obese [26]. In European Union countries, recent estimates indicate that 17.0% of men and 18.8% of women are obese, compared with 16.5% of men and 30.8% of women in Eastern European countries [27]. Thus, the prevalence of obesity in the general population in the US and Europe is higher than in Japan.

Obesity is not generally considered a typical feature of T1DM, but the world-wide trend towards increased body weight is apparent in these patients. The negative association between BMI and age in the present study may reflect this trend. In the US, up to 25.0% of children with T1DM are overweight [28]. In the UK, the prevalence of obesity is similar in diabetic and nondiabetic children [29]. The prevalence of obesity in patients with T1DM in Italy is approximately 6.0% [30]. In the present study, the prevalence of overweight and obesity in patients with T1DM was 15.7% and 2.0%, respectively, for men and 15.5% and 2.0%, respectively, for women. These rates are less than those for the general population in Japan [25], as well as less than those reported for patients with T1DM in the US and Europe.

Of the components of metabolic syndrome investigated in the present study, even though an association was found for both lipid profile and blood pressure with BMI, only lipid profile was associated with increasing HbA1c. Although an association has been

demonstrated between HbA1c levels and both dyslipidemia and hypertension in patients with T2DM [22]. It has been suggested that metabolic syndrome impacts on advanced diabetic nephropathy in T1DM [31] and that it is associated with an increase in cardiovascular risk in T2DM [32]. Further studies are necessary to determine whether there is an association between dyslipidemia and micro- or macrovascular complications in patients with T1DM.

On the basis of results of multiple linear regression analysis, in the present study HbA1c appears to be associated with casual plasma glucose, the daily insulin dose per kg body weight, total cholesterol concentration, and female sex in both the entire group and the early onset subgroup. Multiple linear regression analysis did not indicate a significant association between BMI and any of these variables, except for total cholesterol, in either the entire cohort or the early onset subgroup (Table 1b, Table 2b). However, when all patients with T1DM were stratified according to BMI, it was found that the daily dose of insulin per kg body weight was greater in patients with BMI $\geq$23 kg/m^2 (Table 1a). The results suggest that patients with T1DM may develop insulin resistance that is dependent on increases in body weight.

The requirement for exogenous insulin in T1DM depends on the insulin sensitivity in target tissues, regardless of any residual β-cell function. Adolescent girls tend to be less sensitive to insulin than boys [33]. The finding in the present study that female sex was significantly correlated with deteriorations in HbA1c levels is consistent with that previous report (Table 1b,Table 2b). Insulin resistance is a prominent clinical feature of obesity in children and adults [16], as well as in patients with T2DM. In the present study, for the entire group, a higher BMI (even within the normal range) was associated with higher insulin doses and deteriorating HbA1c levels (Table 1a). Nevertheless, the possibility cannot be excluded that the small number of subjects in the early onset subgroup may have prevented some differences from reaching significance (Table 2a). Another factor in the development of insulin resistance may be hyperglycemia itself. In patients with T1DM, the action of insulin is reduced following a 24-hour period of hyperglycemia compared with that following a 24-hour period of euglycemia, suggesting that the antecedent hyperglycemia results in insulin resistance [34].

Eventually, not only hyperglycemia, but also insulin resistance may promote the development of micro- and macrovascular complications in T1DM [35–37]. In the present study, increased doses of insulin used to improve glycemic control may have caused slight weight gain in patients with T1DM (Table 1a). Increasing doses of insulin, when needed, to improve glycemic control may prevent the development of micro- and macrovascular complications of hyperglycemia. Further studies are needed to determine whether increasing insulin doses to improve glycemic control will result in excessive weight gain in patients with T1DM over a prolonged period.

In conclusion, in the present study of Japanese patients with T1DM, 15% were found to be overweight and 2% were found to be obese. These rates are less than those for the normal population in Japan, as well as less than those reported for patients with T1DM in the US and Europe. In our study population, being overweight was associated with higher blood pressure and dyslipidemia. In patients with T1DM, such metabolic changes may begin to develop even in those patients with a normal BMI. The possibility of a positive association between overweight and increased insulin doses cannot be excluded.

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Appendix I. Members of the Japan Diabetes Clinical Data Management Study Group (JDDM) who participated in the present study (listed alphabetically).

Nobuyuki Abe, Yasuko Chiba, Kazumasa Chikamori, Fumihiko Dake, Kunihiro Doi, Hiroshi Fujiya, Yoshihide Fukumoto, Atsushi Hasegawa, Yoshiyuki Hattori, Hiroshi Hayashi, Kotaro Iemitsu, Hiroshi Ishizu, Masaaki Ito, Koichi Iwasaki, Yoshio Kaku, Akira Kanamori, Azuma Kanazuka, Munemasa Kasayama, Masakazu Kato, Sumio Kato, Koichi Kawai, Kei Kawara, Katsutoshi Komori, Mikihiko Kudo, Shogo Kurebayashi, Shinichi Kuribayashi, Yoshio Kurihara, Gendai Lee, Hajime Maeda, Hideo Manaka, Naoki Manda, Kiyokazu Matoba, Masae Minami, Kazuhiro Miyazawa, Hiroshi Ninomiya, Yoko Notoya, Hisako Ogawara, Mariko Oishi, Akira Okada, Takeshi Osonoi, Sachiko Ota, Miyoko Saito, Hideo Sasaki, Hidekatsu Sugimoto, Hiromichi Sugiyama, Madoka Taguchi, Masato Takagi, Chieko Takahashi, Masahiko Takai, Hiroshi Takamura, Hiroshi Takeda, Kokichi Tanaka, Shinji Taneda, Osamu Tomonaga, Akira Tsuruoka, Takako Wada, Noriharu Yagi, Ritsuko Yamamoto, Morifumi Yanagisawa, Yoshifumi Yokomizo, Atsuyoshi Yuhara.

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