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SPECIAL ARTICLE

A new classification of Diabetic Nephropathy 2014: a report from Joint Committee on Diabetic Nephropathy

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Abstract The Joint Committee on Diabetic Nephropathy has revised its Classification of Diabetic Nephropathy (Classification of Diabetic Nephropathy 2014) in line with the widespread use of key concepts such as the estimated glomerular filtration rate (eGFR) and chronic kidney disease. In revising the Classification, the Committee carefully evaluated, as relevant to current revision, the report of a study conducted by the Research Group of Diabetic Nephropathy, Ministry of Health, Labour and Welfare of Japan. Major revisions to the Classification are summarized as follows: (1) eGFR is substituted for GFR in the Classification; (2) the subdivisions A and B in stage 3 (overt nephropathy) have been reintegrated; (3) stage 4 (kidney failure) has been redefined as a GFR less than 30 mL/min/1.73 m^2, regardless of the extent of albuminuria; and (4) stress has been placed on the differential diagnosis of diabetic nephropathy versus non-diabetic kidney disease as being crucial in all stages of diabetic nephropathy.

Keywords Diabetic nephropathy · Chronic kidney disease (CKD) · Albuminuria · Proteinuria · Glomerular filtration rate (GFR)

Japan Diabetes Society, Japanese Society of Nephrology, Japanese Society for Dialysis Therapy, and Japan Society of Metabolism and Clinical Nutrition established the Joint Committee on Diabetic Nephropathy, which published the revised Classification of Diabetic Nephropathy 2014 in Japanese [1–4]. This is the English version of that revision.

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Introduction

Diabetic nephropathy became the leading cause of chronic dialysis in 1998. Since then, the incidence of this condition has increased with only a recent plateau. However, diabetic nephropathy continues to account for a large proportion of all cases of chronic kidney disease (CKD) and remains by far the most common underlying cause of chronic dialysis among all kidney diseases [5], consequently leading to the escalation of healthcare costs, thus representing a compelling medico-social issue of interest.

The Classification of Diabetic Nephropathy (hereafter "Classification") developed earlier by the Research Group

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of Diabetic Nephropathy at the Ministry of Health, Labour and Welfare (MHLW) [6] and later revised by the Joint Committee on Diabetic Nephropathy (hereafter "Committee") [7] is widely used in Japan. However, as the concept of CKD was proposed, followed by the classification of CKD stages [8], it became clear that there exists a subpopulation of patients with discrepant classifications of diabetic nephropathy and CKD. This is thought to be due to the fact that diabetic nephropathy is primarily classified according to the extent of albuminuria in addition to the glomerular filtration rate (GFR) (i.e., creatinine clearance [CCr]), whereas CKD is primarily classified based on the estimated GFR [estimated GFR (eGFR)]. Meanwhile, eGFR has become increasingly used to assess GFR, and a new classification of CKD was developed in 2012 [9]. Against this background, the Committee therefore discussed issues of interest in depth and sought to develop a revision of the Classification.

Development of the 2014 Classification (Revised Classification) (see Table 1)

Prior to revising the Classification, as part of a MHLW-subsidized project on kidney disease, entitled "Diabetic Nephropathy Research, from the Ministry of Health, Labour and Welfare of Japan", a "historical cohort study" was conducted by the Research Group of Diabetic Nephropathy, MHLW, involving a total of 4,355 subjects with type 2 diabetes from 10 participating healthcare facilities with the aim of evaluating renal events (i.e., a decrease in eGFR to half the baseline level and/or the need for dialysis), cardiovascular events and all-cause mortality [10, 11]. Summarized below are the major findings of this study (for detailed information, please access the MHLW website http://www.mhlw.go.jp/ or refer to the literature cited above).

1. Renal and cardiovascular events and all-cause mortality were significantly increased in the subjects with micro- or macroalbuminuria compared to that observed in the subjects with normoalbuminuria.
2. In those with renal impairment (defined as a GFR less than 60 mL/min/1.73 m^2):
   a. The risk of renal events increased in association with the onset of microalbuminuria and further increased with the onset of macroalbuminuria in the subjects;
   b. The risk of cardiovascular events was increased in those with micro-/macroalbuminuria; and
   c. All-cause mortality was increased in the subjects with macroalbuminuria as well as those with normoalbuminuria and microalbuminuria who exhibited a GFR of less than 30 mL/min/1.73 m^2.

While that study was not a true prospective study and involved only a limited number of facilities and patients from a population known to be less prone to cardiovascular

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events than those in Western countries, the findings provide important insight into the prognosis of diabetic nephropathy in Japanese patients. Therefore, in seeking to revise the Classification, the Committee gave due consideration to the above findings. At the same time, the following considerations were also taken into account.

1. The bulk of evidence for the classification of diabetic nephropathy comes from randomized controlled studies enrolling patients with diabetic nephropathy as defined based on the extent of albuminuria, and very little evidence is available for diabetic nephropathy as defined based on GFR.
2. The current "Medical Service Fee Schedule for Guidance on Preventing Diabetes-Associated Dialysis" was developed with the Classification in mind.
3. The "Guidelines for Clinical Efficacy Evaluation of Pharmacological Agents for Diabetic Nephropathy (Draft)" currently in use were developed with the Classification in mind.

Therefore, after giving due consideration to all of these issues during the course of several sessions, the Committee decided to leave the Classification essentially unchanged for now (Table 1), while showing how it may be aligned with the widespread CKD classification based on GFR (eGFR) ("see Appendix"). The former is not, however, presented as a heat map, due to the limitations of the study referred to above, which involved a small number of patients with diabetic nephropathy and included no dialysis patients, providing the basis for this revision. Again, as all kidney diseases affecting patients with diabetes are covered in the Classification, the Committee called for attention with notes included which were required, in order to highlight the importance of the differential diagnosis between diabetic nephropathy and non-diabetic kidney disease in all stages. The differential diagnosis calls for collaboration with nephrologists; such collaboration is not limited to cases requiring a renal biopsy. Furthermore, given that the disease may not always progress in some patients, numerous notes were included in the table in order to call attention to these cases. Additionally, in view of the potential need to use multiple anti-diabetic drugs over time, "Key Precautions in View of Drug Use" are included below the table. The major revisions to the Classification are summarized below:

1. eGFR is now substituted for GFR in the Classification.

Table 1 Classification of Diabetic Nephropathy 2014

Stage	Urinary albumin (mg/g Cr) or urinary protein (g/g Cr)	GFR (eGFR) (mL/min/1.73 m^2)
Stage 1 (pre-nephropathy)	Normoalbuminuria (< 30)	≥30[a]
Stage 2 (incipient nephropathy)	Microalbuminuria (30–299)[b]	≥30
Stage 3 (overt nephropathy)	Macroalbuminuria (≥ 300) or Persistent proteinuria (≥ 0.5)	≥30[c]
Stage 4 (kidney failure)	Any albuminuria/proteinuria status[d]	<30
Stage 5 (dialysis therapy)	Any status on continued dialysis therapy	

Diabetic nephropathy does not always progress from one stage to the next. The revised classification takes into account findings on the prognosis of type 2 diabetic patients from a "historical cohort study" conducted as part of the MHLW-subsidized Project on Kidney Disease, entitled "Diabetic Nephropathy Research, from the Ministry of Health, Labour and Welfare of Japan" [10, 11]

[a] While a GFR of less than 60 mL/min/1.73 m^2 is consistent with the diagnosis of CKD, underlying causes other than diabetic nephropathy may be involved in patients with a GFR below 60 mL/min/1.73 m^2 thus calling for the differential diagnosis between diabetic nephropathy and any other potential non-diabetic kidney diseases

[b] Patients with microalbuminuria are to be diagnosed as incipient nephropathy after the differential diagnosis based on the criteria for an early diagnosis of diabetic nephropathy

[c] Precautions are required in patients with macroalbuminuria, in whom renal events (e.g., a decrease in eGFR to half its baseline value, the need for dialysis) have been shown to increase as the GFR decreases below 60 mL/min/1.73 m^2

[d] All patients with a GFR of less than 30 mL/min/1.73 m^2 are classified as exhibiting kidney failure, regardless of their urinary albumin/protein values. However, in those with normoalbuminuria and microalbuminuria, the differential diagnosis is required between diabetic nephropathy and any other potential non-diabetic kidney diseases

Key Precautions in View of Drug Use: This table is intended, first and foremost, as a classification of diabetic nephropathy and not as a guide to drug use. All drugs, including anti-diabetic drugs, particularly renally metabolized agents, are to be used in accordance with their prescribing information, with due consideration to relevant factors such as GFR in each patient

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2. The stages used in the Classification have been simplified to include normoalbuminuria, microalbuminuria, macroalbuminuria and kidney failure.
3. The division between A and B (early versus late macroalbuminuria) in stage 3 has been abandoned and A and B have been reintegrated, due to the paucity of evidence for proteinuria of 1 g/day as the threshold for dividing the stage.
4. Kidney failure has been redefined in all cases as a GFR less than 30 mL/min/1.73 m^2, which represents the threshold value for kidney failure obtained by quantifying the existing definition of kidney failure in the Classification based on the Classification of the Japanese Society of Nephrology (JSN) [12] with all other pre-kidney failure conditions redefined as a GFR of 30 mL/min/1.73 m^2 or greater.
5. Qualifying or illustrating phases in parentheses, such as "e.g., incipient nephropathy", have been retained throughout the Classification, as they have become common currency in the field, although their removal from the Classification was suggested during the process of revision.
6. Stress is now placed on the differential diagnosis of diabetic nephropathy versus non-diabetic kidney disease as being crucial in all stages of diabetic nephropathy.

Of note, the American Diabetes Association (ADA) proposed in its Clinical Practice Recommendations 2013 that all cases of albuminuria of 30 μg/mg Cr (=mg/g Cr) be defined as "increased urinary albumin excretion", thus abandoning the division between micro- and macroalbuminuria [13]. Again, while this concept was retained in the Clinical Practice Recommendations 2014, the ADA further proposed that microalbuminuria and macroalbuminuria be redefined as persistent albuminuria of 30–299 mg/24 h and ≥300 mg/24 h, respectively [14]. While this change may result in the terms micro- and macroalbuminuria ceasing to be common currency in the clinical setting in the US, to avoid confusion, the Committee has chosen not to follow suit and rather err on the side of caution, thereby retaining these terms in the Classification, given that they are less likely to no longer be used in scientific publications and are expected to remain common currency in Japan.

Last but not least, with a number of multicenter prospective studies currently underway, including the Japan Diabetes Complication and Prevention prospective (JDCP) study, JSN registries, Japan Diabetes Clinical Data Management (JDDM) studies and Japan Diabetes Optimal Integrated Treatment for 3 Major Risk Factors of Cardiovascular Diseases (J-DOIT3) randomized study, the Committee also plans to further revise the Classification in a timely fashion as required, as relevant evidence becomes available from these and other studies.

Conclusions

In order to resolve the discrepancy between the existing Classification of Diabetic Nephropathy and the current Classification of CKD stages, the Joint Committee on Diabetic Nephropathy revised its Classification of Diabetic Nephropathy. The new classification has already been uploaded onto the website of each member society represented on the Joint Committee as of January 10, 2014. Again, in view of further revisions in the years to come, the Joint Committee has termed the revised classification as the "Classification of Diabetic Nephropathy 2014."

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Conflict of interest Masakazu Haneda has received speaker honoraria from pharmaceutical companies Boehringer Ingelheim GmbH, Mitsubishi Tanabe Pharma Corporation, Novo Nordisk Pharma Ltd., Daiichi-Sankyo Co., Ltd., Taisho Pharmaceutical Co., Ltd., Sanofi K.K., Merck Sharp & Dohme, Astellas Pharma Inc., Kyowa Hakko Kirin Co., Ltd., Kowa Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Novartis Pharma K.K., scholarship grants from Astellas Pharma Inc., Daiichi-Sankyo Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Ltd., Novo Nordisk Pharma Ltd., Merck Sharp & Dohme, Boehringer Ingelheim GmbH, and Eli Lilly and Company; Daisuke Koya has received speaker honoraria from pharmaceutical companies Mitsubishi Tanabe Pharma Corporation, Boehringer Ingelheim GmbH, and Eli Lilly and Company, research grants from Mitsubishi Tanabe Pharma Corporation, Boehringer Ingelheim GmbH, Japan Tabacco Inc., Eli Lilly and Company, and Ono Pharmaceutical Co., Ltd.; Tetsuya Babazono has received speaker honoraria from pharmaceutical company Merck Sharp & Dohme; Tatsumi Moriya has received travel expenses from pharmaceutical companies Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Novo Nordisk Pharma Ltd., and Daiichi-Sankyo Co., Ltd.; Hirofumi Makino has received speaker honoraria from pharmaceutical companies Teijin Pharma Limited, Chugai Pharmaceutical Co., Ltd., AbbVie GK, Astellas Pharma Inc., Boehringer Ingelheim GmbH, Daiichi-Sankyo Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Merck Sharp & Dohme, Novartis Pharma K.K., Pfizer Japan Inc., Takeda Pharmaceutical Co., and Mitsubishi Tanabe Pharma Corporation, research grants from Project for accelerating Practice and Research on Community Medicine in Okayama Prefecture, scholarship grants from Astellas Pharma Inc., Daiichi-Sankyo Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Merck Sharp & Dohme, Takeda Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Novo Nordisk Pharma Ltd., and Mitsubishi Tanabe Pharma Corporation; Kenjiro Kimura has received research grants from pharmaceutical companies Otsuka Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Limited, Boehringer Ingelheim GmbH, Baxter International Inc., and Sekisui Medical Co., Ltd.; Takashi Wada has received speaker honoraria from pharmaceutical company Daiichi-Sankyo Co., Ltd., scholarship grants from Chugai pharmaceutical Co., Ltd.; Susumu Ogawa has received speaker honoraria from pharmaceutical companies Daiichi-Sankyo Co., Ltd., Eli Lilly and Company, and Novo Nordisk

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Human rights statement and Informed consent This article does not contain any studies with human or animal subjects performed by the any of the authors.

Appendix

Relationship between the 2014 categories for diabetic nephropathy stages and the CKD severity categories

	Albuminuria category	A1	A2	A3
	Quantitative urinary albumin estimation Urinary albumin/Cr ratio (mg/g Cr) (quantitative urinary protein estimation) (urinary protein/Cr ratio (g/g Cr)	Normoalbuminuria < 30	Microalbuminuria 30-299	Macroalbuminuria ≥300 (or increased proteinuria) (≥0.50)
GFR category (mL/min/1.73 m^2)	≥90 60-89 45-59 30-44	Stage 1 (pre-nephropathy)	Stage 2 (incipient nephropathy)	Stage 3 (overt nephropathy)
	15-29 < 15	Stage 4 (kidney failure)		
	(dialysis therapy)	Stage 5 (dialysis therapy)		

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研究・事例・症例報告

宅配治療食利用者の現状に関するアンケート調査

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The state of the users receiving the food delivery services

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要旨：宅配治療食利用者の現状を把握することを目的とし、エネルギー調整食・たんぱく質調整食の利用者を対象に、アンケート調査を実施した。396名の調査結果を集計・解析したところ、70歳以上の利用者が76.0%であり、家族と同居している者が65.4%であった。宅配治療食の利点としては、「適量が分かるようになった」等、「食事療法に役立った」と回答した者が上位を占めていた。栄養指導を受けた経験のある者は、57.0%であり、栄養指導を受けたことがない者と比べて、「減量できた」、「血糖値が改善した」等、健康状態が改善したと回答した者の割合が、高い結果であった。

利用者は糖尿病をはじめとし、糖尿病性腎症、慢性腎不全といったさまざまな病態を持つ者が、混在していることが明らかになった。利用者が病態に応じた食事を選択できているかどうか不明である。今後、栄養指導に関わる医師・管理栄養士等の医療従事者と、宅配治療食業者が患者の病態に関する情報を、個人情報に配慮しながら共有していく必要があると考えられた。

キーワード：宅配治療食、エネルギー調整食、たんぱく質調整食、栄養指導

I 緒　言

近年、食生活が多様化する中、糖尿病等の疾病を持つ患者を対象とし、食品の機能に着目したさまざまな特定保健用食品・栄養機能食品、宅配食品等が開発され、利用されるようになってきている。また、調理済みの治療食を家庭へ宅配する宅配治療食においても、「糖尿病者用宅配食品栄養指針」（平成6年・厚生省）、「食事療法用宅配食品栄養指針について」（平成7年・厚生省）に基づいた商品が次々と開発され、利用者は増加傾向にある。平成21年には、在宅療養を支援し、栄養管理がなされた食事を宅配で利用できる、宅配食品の適正利用を一層推進する観点から、「食事療法用宅配食品等栄養指針について」（厚生労働省）[1)]が通知され、今後、ますます利用者が増加していくことが推測される。

これまで宅配治療食を使用したことにより、栄養指導の効果が向上した等の報告はあるものの[2-4)]、宅配治療食利用者の実情を示したものは少ない。そこで、本研究では、宅配治療食利用者の現状を把握することを目的とし、アンケート調査を実施し、検討を行った。

受付日：平成26年5月16日、受理日：平成26年8月6日
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Ⅱ 方 法

平成22年7月、M社が提供しているエネルギー調整食・たんぱく質調整食の宅配治療食利用者1,000名（エネルギー調整食600名、たんぱく質調整食400名）を対象とし、無記名、記述式のアンケート調査を実施した。エネルギー調整食は、エネルギー1,400 kcal・1,600 kcal・1,800 kcal、3種類の3食コースと1,100 kcal、1種類の2食コースである。たんぱく質調整食は、たんぱく質40～50 g・エネルギー1,600～1,800 kcalで調整した4種類の3食コースと、たんぱく質27～33 g・エネルギー1,100～1,250 kcalで調整した4種類の2食コースである。価格は3食当たり2,800～3,100円である。対象は、東京都および東京都近郊に在住する利用者とした。

本調査の主旨については、対象者に対して、配送員が個別に説明を行い、同意が得られた者のみに調査を依頼した。調査表の配布・回収は、宅配治療食の配送時に配送員が行った。アンケートの調査項目は、利用者の年齢、性別、身長、体重、家族構成、利用理由、利用期間、宅配治療食の摂取量、健康状態、栄養指導を受けた経験の有無、通院の有無、宅配治療食の利点等とした。なお、本調査で使用した宅配治療食は、調理済みの食事を冷蔵保存した状態で配送し、利用者が電子レンジで温めて喫食するタイプのものとした。

アンケートの回収・集計が可能であった、エネルギー調整食利用者およびたんぱく質調整食利用者の回答内容より、初めに利用者全体の集計・解析を行い、次にエネルギー調整食利用者と、たんぱく質調整食利用者の比較・解析を行った。統計解析はIBM SPSS Statistics Ver.19.0を使用し、有意水準は5%未満で判定した。

Ⅲ 結 果

1．宅配治療食利用者全体の集計結果

(1) 研究協力者の臨床像

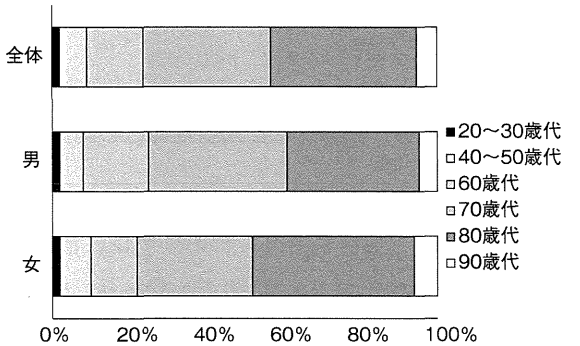
実施したアンケートの回収ができたのは425名であり（回収率は42.5%）、そのうち、年齢・性別の記載がなかった者24名、BMI 15.0 kg/m^{2}未満あるいは34.8 kg/m^{2}以上の者5名を除いた396名の回答内容を集計・解析した。その内訳は、エネルギー調整食利用者252名、たんぱく質調整食利用者144名であった。利用者全体の身体的特徴（**表1**）は、平均身長158.2 cm、平均体重55.8 kg、平均BMI 22.2 kg/m^{2}であった。男性と女性とでは、身長、体重に有意差が認められた。BMIは、（一社）日本肥満学会の判定基準により分類すると、普通体重（18.5以上～25.0未満）に該当する者が67.2%、低体重（18.5未満）が13.9%、肥満Ⅰ度（25.0以上～30.0未満）が14.4%、肥満Ⅱ度（30.0以上～35.0未満）が4.5%であった。

●表1● 利用者全体の身体的特徴（n=396）

	全 体	男	女
対象者数	396	213	183
年 齢	75 ±11	75 ±11	76 ±12
身長（cm）	158.2± 9.2	164.3± 6.3	151.1± 6.6*
体重（kg）	55.8±11.5	60.8±10.4	49.9±10.0*
BMI（kg/m^2）	22.2± 3.5	21.6± 1.2	22.0± 3.7

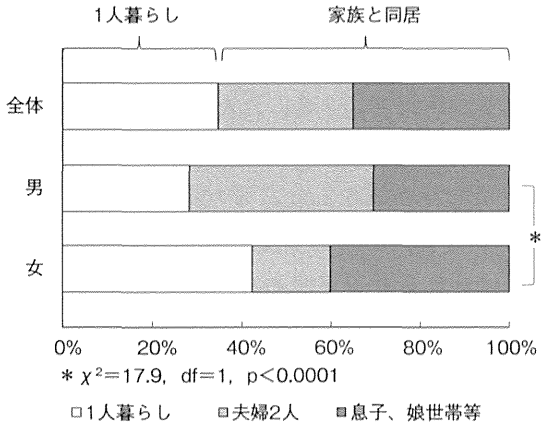
平均値±標準偏差
*男性と比較して有意差あり $p<0.001$

利用者の年齢構成（**図1**）は、20歳代から90歳代と、幅広い年齢層で利用されており、20～30歳代が2%、40～50歳代が7%、60歳代が15%、70歳代が33%、80歳代が38%、90歳代が5%であった。70歳以上の利用者が、76.0%を占めていた。



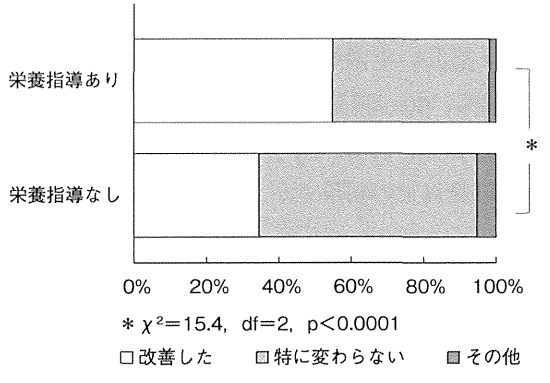
●図1● 年齢構成

家族構成（**図2**）は、1人暮らしが34.6%、夫婦2人が30.3%、息子、娘夫婦等と同居等が35.1%であった。男女別に家族構成を見ると、男性の1人暮らしが28.2%であるのに対し、女性は42.1%で



●図２● 家族構成

あり、女性の１人暮らしの割合の方が、多い結果であった。また、全体では65％以上の者が、家族と同居しており、２人以上の世帯であることが明らかになった。栄養指導を受けた経験のある者は、57.0％であり、栄養指導を受けたことがない者と比べて、「減量できた」、「血糖値が改善した」等、健康状態が改善したと回答したものの割合が高い結果（$p<0.0001$）であった（図３）。



●図３● 健康状態と栄養指導との関係

(2) 宅配治療食利用の状況

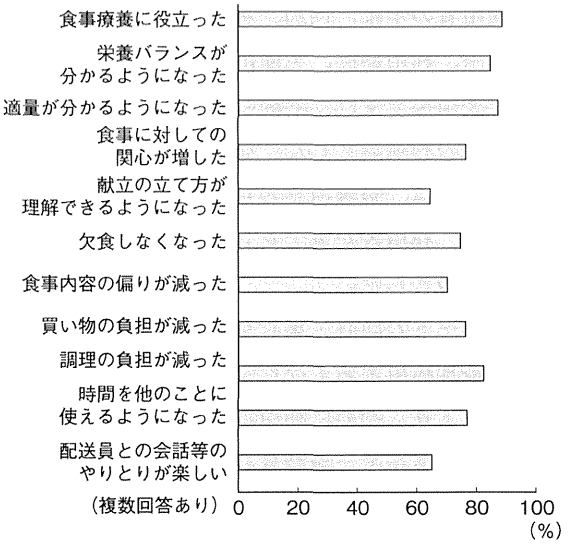
利用理由（複数回答あり）においては、治療を目的として通院している者が89.6％であり、「病院・福祉施設で勧められた」という回答が57.7％と最も多い結果であった。次いで「家族・友人に勧められた」者が29.7％であった。また、具体的に健康管理のために利用している者の中には、血糖値改善を目的としている者が44.1％と最も多く、次いで腎機能改善が34.6％、体重管理が20.2％であった。治療目的に使用している者が多い一方で、料理が面倒なために利用している者も18.6％であった。

宅配治療食を利用している期間は、５年以上の長期利用者が23.3％と最も多い結果であった。次いで、２年以上３年未満の者が19.7％、１年以上２年未満の者が18.9％であった。

(3) 宅配治療食についての意識

宅配治療食の量については、「ちょうどよい」と回答した者が84.5％であり、「多い」、「少ない」と回答した者は、おのおの7.8％、7.7％と少数であった。宅配治療食の摂取量については、「完食する」が51.3％、「ほぼ完食する」が38.0％であり、両者で89.3％を占めていた。

宅配治療食の利点（図４）としては、「適量が分かるようになった」87.2％、「栄養のバランスが分かるようになった」84.7％と「食事療法に役立った」と回答した者が上位を占めていた。一方で、「調理の負担が減った」82.4％、「時間を他のことに使えるようになった」77.0％、「配送員との会話等のやりとりが楽しい」65.2％といった回答もあった。



●図４● 宅配治療食の利点

２．エネルギー調整食利用者とたんぱく質調整食利用者との比較

(1) 研究協力者の臨床像

方法に示した通り実施した、アンケートの回収・集計が可能であった、エネルギー調整食利用者252名およびたんぱく質調整食利用者144名の集計結果より、各利用者の現状を比較した。

●表２● 調整食別 利用者の身体的特徴（n＝396）

	全 体	エネルギー調整食		たんぱく質調整食	
		男	女	男	女
対象者数	396	124	128	59	85
年 齢	75 ±11	74 ±12	76 ±12	76 ± 9	76 ±11
身長（cm）	158.2± 9.2	164.5± 6.3	158.2± 9.0	163.9± 6.3	149.9± 7.0
体重（kg）	55.8±11.5	61.1±10.5	55.8±11.5	60.3±10.4	49.1±10.0
BMI（kg/m^2）	22.2± 3.5	22.5± 3.3	22.2± 3.4	22.4± 3.4	21.8± 4.0

平均値±標準偏差

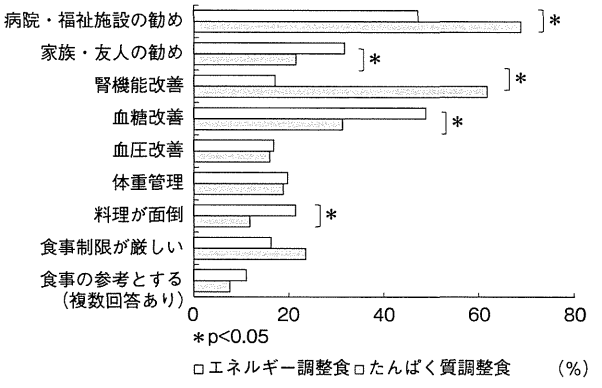
調整食別の利用者の身体的特徴（**表2**）は、身長、体重には男女差があるが、BMIは男女共に普通体重とされる22.0 kg/m^{2}に近い値であった。BMIは、（一社）日本肥満学会の判定基準より分類すると、エネルギー調整食は、普通体重に該当する者が68.7％、低体重が13.1％、肥満Ⅰ度が14.3％、肥満Ⅱ度が4.0％であった。たんぱく質調整食は、普通体重に該当する者が64.6％、低体重が15.3％、肥満Ⅰ度が14.6％、肥満Ⅱ度が5.6％であった。

利用者の年齢構成は、エネルギー調整食とたんぱく質調整食との両者間での差は、ほとんどなかった。栄養指導を受けた経験のある者の割合は、エネルギー調整食52.3％に比べ、たんぱく質調整食で65.4％（p＝0.014）と有意に高い結果であった。

(2) 宅配治療食利用の状況

利用理由（**図5**）については、病院や福祉施設で勧められて利用している者は、たんぱく質調整食で68.8％と多く、友人の勧めで利用している者は、エネルギー調整食で31.7％と多い結果であった（p＜0.05）。また、健康管理のために利用している者の中には、腎機能改善のために利用している者が、たんぱく質調整食61.8％、エネルギー調整食17.1％であった（p＜0.05）。血糖値改善のために利用している者はエネルギー調整食48.8％、たんぱく質調整食31.3％であった（p＜0.05）。治療目的に使用している者が多い一方で、料理が面倒なために利用している者は、エネルギー調整食で21.4％と多い結果（p＜0.05）であった。

利用期間は、5年以上の長期利用者は、エネルギー調整食で24.3％と多い傾向であった。



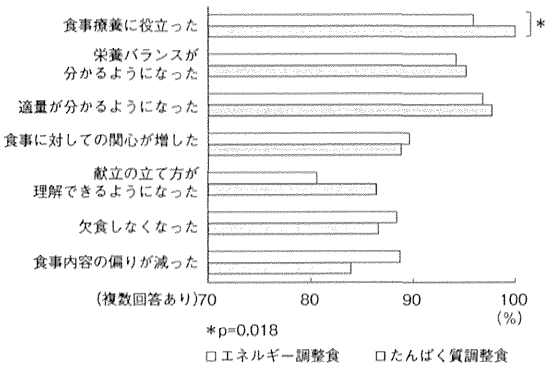
●図５● 利用理由

(3) 宅配治療食についての意識

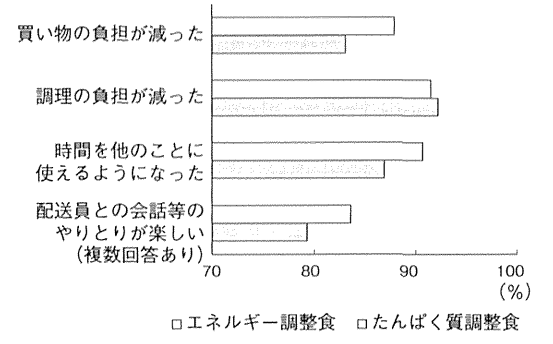
宅配治療食の摂取量については、エネルギー調整食では「完食する」、「ほぼ完食する」と回答した者が91.2％、たんぱく質調整食では85.8％であった。健康状態は、「改善した」と回答した者が、エネルギー調整食46.0％、たんぱく質調整食46.3％であった。「特に変わらない」と回答した者がエネルギー調整食51.1％。たんぱく質調整食50.0％と、ほぼ同様の比率であった。

宅配治療食の利点としては、「食事療養に役立った」と回答した者が、たんぱく質調整食100.0％、エネルギー調整食95.9％と最も高値（p＝0.018）であった。また、「栄養バランスが分かるようになった」、「適量が分かるようになった」等、食事面全般において、利点を感じている利用者がほとんどであった（**図6-1**）。

食事面以外では、「調理の負担が減った」と回答した者が、たんぱく質調整食で92.2％、エネルギー調整食で91.5％と、両者ともに最も高値であった。また、「配送員との会話等のやりとりが楽しい」



●図 6-1● 宅配治療食の利点－食事面－



●図 6-2● 宅配治療食の利点－食事面以外－

と回答した者は、エネルギー調整食で83.6%、たんぱく質調整食で79.3%おり、宅配治療食を通して、配送員とのコミュニケーションが広がるといった利点もあることが、明らかになった（図6-2）。

Ⅳ 考 察

近年は、ライフスタイルや食生活が多様化する中、人びとが食に求める目的も多岐にわたってきている。生命維持のための栄養補給にとどまらず、健康増進、疾病予防、疾病治療、食べる喜び、休息の場、コミュニケーションの場、ファッション等、さまざまな目的で、食が位置付けられている。

また、わが国における食環境は、生産・流通機構の発達により、食事の場は内食から、中食、外食へと広がりを見せてきた。中食には、宅配食の開発が大きく寄与しているものと考えられる。宅配治療食においては、疾病予防や治療の観点からエネルギー・栄養素を調整したもの、介護予防の観点から咀しゃくをサポートするために、料理の軟らかさを調整したもの等、利用者のニーズに応じた、さまざまな食品が次々と開発されており、現在も進化し続けている。

上記の要素が相まって、個人の食環境は多様化、個別化、簡易化し、これらが相互に関連し、それぞれが情報化の影響を受けている[5]。そのため、患者自身が、正しい情報を選択し、食事療法に活用することが難しくなってきている。

わが国の住環境においては、高齢化が進むにつれ、65歳以上の者の単独世帯、夫婦のみの世帯が年々増加している。平成23年国民生活基礎調査（厚生労働省）によると、単独世帯は16.8%、夫婦のみの世帯は37.2%であった。単独世帯においては、女性の占める割合が72.2%と、高い傾向にあることが報告されている[6]。今回調査対象とした宅配治療食の利用者においても、65歳以上の高齢者が84.6%と多い結果であった。また、1人暮らしが36.4%であり、そのうち女性の1人暮らしが59.8%を占めていた。夫婦2人が30.8%、息子や娘夫婦と同居等が32.8%であり、63.6%が家族と同居していた。

一方、近年は、糖尿病や慢性腎臓病の患者数が増加傾向にあり[7, 8]、これらの生活習慣病の発症率は高齢になるほど高まることが報告されている[9]。糖尿病や慢性腎臓病等においては、毎日の食事療法が重要であることはいうまでもない。しかし、毎日の食事作りは、準備から片付けまでの一連の作業が、高齢者にとって負担となることが、容易に想像できる。治療のための食事療法を実践し、継続していくことは、さらに大きな負担となるものと考えられる。前述した通り、宅配治療食利用者は、家族と同居している者が多いことより、食事作りや治療のための食事療法の負担は、同居している家族がいても、カバーすることが難しいということが推察される。

このようなわが国における食環境や住環境等を踏まえ、生活習慣病を持つ患者の食事療法を実践に導き、QOL（Quality of Life）を高めていくには、どのような方法が有効なのであろうか。

食習慣等の習慣変容を促すには、「知識」、「技術」、「意欲」の3つの条件が必要であることが示されている[10]。先行研究においても、栄養教育とヘルシーメニューの提供等の食環境介入により、行動

変容のステージが前進したとの報告がある[11]。

習慣変容を促すため、患者が疾病や食事療法に関する知識を得る機会としては、病院等における栄養指導がある。本調査において、栄養指導を受けた経験のある者は、栄養指導を受けたことがない者に比べて、「減量できた」、「血糖値が改善した」等と回答した者が多く、主観的な健康感が向上した結果であった。また、利用者は宅配治療食を利用したことにより、「栄養バランスが分かるようになった」、「適量が分かるようになった」と回答した者が多く、宅配治療食を喫食したことにより、料理・食品の質的・量的な把握が、できるようになったものと考えられた。このことから、宅配治療食は、有効な指導媒体となる可能性があることが示唆された。

習慣変容を促す2つ目の条件である「技術」を学ぶ機会としては、前述した栄養指導において、料理・食品の選択方法や調理方法等の技術を学ぶことが考えられる。しかしながら、栄養指導の指示通りに家庭で調理を行うことが簡単ではないことも、容易に想像できる。そこで、上記の技術が不十分であっても、それを補完してくれるものが、宅配治療食であるとも考えられる。また、本調査の結果では、宅配治療食を利用したことにより、「調理の負担が減った」、「時間を他のことに使えるようになった」という回答が約80%であった。

習慣変容を促す3つ目の条件である「意欲」を促すものとしては、医師・管理栄養士等からの指導により、患者が食事療養の必要性を実感したことや、宅配治療食であれば食事療法の実現が可能であると感じたこと等が、動機付けになったものと考えられる。本調査では、利用理由に「病院・福祉施設で勧められた」と回答した者が多い結果であった。また、宅配治療食を利用したことにより、「減量できた」、「血糖値が改善した」等と具体的に記載した利用者においては、自己効力感を得られたことが強化因子となり、モチベーションアップにつながったものと考えられる。利用者には、5年以上の長期利用者が多かったことから、これらの3つの条件が相互に作用したことにより、食事療法を継続しているものと推察された。

さらに、生活習慣病における食事療法は、モチベーションを維持しながら、長期間継続していくことが大切である。先行研究では、宅配治療食と栄養指導を併用して行う場合、栄養指導の介入早期に宅配治療食を導入する方が、費用対効果も優れていた[2]。宅配治療食のみで食事療法を実施した場合、栄養指導を受けた場合に比べ、食行動の改善を維持できた者（行動変容ステージの継続期・維持期）の割合が少ない傾向になったとの報告がある[3]。長期にわたって食事療法を継続していくに当たり、栄養指導と宅配治療食の導入のタイミングを計り、いかに効果的に行っていくかは、今後の課題であると考えられた。

本研究の限界は、情報源が利用者本人のみであり、また調査票の配布・回収は、宅配治療食の配送時に配送員が行ったため、血液検査等の臨床情報が不正確な点である。また、宅配治療食を利用した際の効果について、利点を中心に問う形式の設問であったため、価格、味付け、嗜好（しこう）等の利用者が感じることが想定されるデメリット等に関する回答が、充分に得られていない点である。

今回の結果より、利用者は糖尿病をはじめとし、糖尿病性腎症、慢性腎不全といった、さまざまな病態を持つ者が混在していることが明らかになった。利用者の中には、栄養指導を受けた経験のない者もいたため、利用者が病態に応じた食事が、選択できているかどうか不明である。特に管理栄養士が常勤していない診療所に通院している患者が、多い可能性もあるために、何らかの形で栄養指導を指示する医師と、治療食業者が患者の病態に関する情報を、共有する必要があると思われた。また、病院の管理栄養士等が利用者に対して、栄養指導を行う機会を増やしていくことによって、利用者自身が、自分の病態に応じた指示栄養量を理解した上で、宅配治療食や多様な食品・料理を、選択できるようになることが望ましい。それによって、利用者が毎日の食生活を充実させ、疾患を管理しながら、より一層日常生活のQOLを高めていくことに、貢献できるのではないかと考えられた。

また、利用者は宅配治療食を配送員から受け取るときに、「配送員との会話等のやりとりが楽しい」と感じている者が過半数を占めており、宅配治療食

を通して生まれるコミュニケーションの広がりは、高齢者を孤立させない社会づくりの一助にもなるものと考えられた。

V 結 語

本研究では、宅配治療食利用者の現状を把握することを目的とし、アンケート調査を行った。65歳以上の利用者が84.6%であり、そのうち、家族と同居している者が半数以上であった。宅配治療食の利点としては、「適量が分かるようになった」、「食事療法に役立った」と回答したものが上位を占めていた。栄養指導を受けたことがある者は、栄養指導を受けたことがない者と比べて、主観的な健康感が向上していた。利用者は、糖尿病をはじめとし、糖尿病性腎症、慢性腎不全といった、さまざまな病態を持つものが混在していることが明らかになった。

今後、栄養指導に関わる医師・管理栄養士等の医療従事者と宅配治療食業者が、患者の病態に関する情報を共有していく必要があると考えられた。

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Abstract : The purpose of this study was to investigate the status of the users who usually receive the food delivery services. The food delivery services are energy controlled meals or protein controlled meals. A total of 396 persons answered the questionnaire on the delivery. The users are 76.0% of elder people aged over 70years, and 65.4% of people who live with family. These results suggested that food delivery services were useful “to learn how much to eat.”, not just providing meals for solitary life. 57.0% of users had an experience of dietary education, they felt improvement with their health condition (body weight reducing, blood sugar level improving) than the users who did not have an experience of nutrition education.

The users have various diseases, such as diabetes or diabetic nephropathy, chronic renal failure, etc. However, it remained unclear whether the users have chosen the proper food based on their conditions. It is necessary that medical staffs (doctors or registered dietitians) and food delivery services’ dealers to share the information of the users.

Key words : food delivery services, energy controlled meals, protein controlled meals, nutrition education

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Original Paper

Renin-Angiotensin System Inhibitors Reduce Serum Asymmetric Dimethylarginine Levels and Oxidative Stress in Normotensive Patients with Chronic Kidney Disease

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Key Words
Chronic kidney disease · Renin-angiotensin system inhibitor · Asymmetric dimethylarginine · Oxidative stress

Abstract
Background/Aims: The purpose of our study was to elucidate the relationship between asymmetric dimethylarginine (ADMA) and intrarenal lesions and to determine the effect of renin-angiotensin system inhibitors (RAS-Is) on serum ADMA levels, nitric oxide (NO) synthesis and oxidative stress in normotensive patients with chronic kidney disease (CKD). ***Methods:*** This study included 23 normotensive patients with chronic glomerulonephritis and normal or mildly impaired renal function who underwent renal biopsy. We evaluated the relationship between serum ADMA levels and intrarenal lesions, and examined renal function, urinary protein excretion, ADMA levels, NO synthesis, oxidative stress and blood pressure (BP) before and 3 months after starting the treatment with RAS-Is. ***Results:*** Serum ADMA levels were correlated only with arterial intimal fibroplastic thickness. Despite comparable renal function and BP, serum ADMA levels and excretion of urinary protein excretion significantly decreased, and urinary NO metabolite excretion significantly increased after starting the treatment with RAS-Is. Oxidative stress markers also tended to be reduced by the treatment. ***Conclusion:*** These findings suggest that RAS-Is improve the NO system and decrease oxidative stress in normotensive patients with CKD. In addition, ADMA may be associated with intrarenal lesions and can be a useful marker for the effects of treatment in the early stages of CKD.

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Introduction

It is well known that chronic kidney disease (CKD) is a very important risk factor associated with cardiovascular events and mortality [1]. Therefore, its management is essential for improving patients' prognoses. Renin-angiotensin system inhibitors (RAS-Is) including angiotensin-converting enzyme inhibitor and angiotensin receptor blocker (ARB) can not only reduce urinary protein excretion and slow the decline of renal function but also prevent the progression of cardiovascular disease (CVD) in patients with CKD [2, 3]. Furthermore, basic and clinical reports have demonstrated that RAS-Is can suppress the activity of glomerular nephropathy. For example, an in vivo study showed that RAS-Is increase the permeability and size-selective functions of the glomerulus [4]. Furthermore, a clinical study of patients with IgA nephropathy demonstrated that RAS-Is significantly improve renal survival in proteinuric patients with normal or moderately reduced renal function [5]. Another study has reported that RAS-Is effectively reduce proteinuria and improve serum albumin in patients with lupus nephritis [6]. To summarize, RAS-Is are effective for the treatment of various types of CKD.

Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide (NO) synthase, has been suggested to be a marker of endothelial dysfunction and atherosclerosis [7]. ADMA is also associated with the production of oxidative stress [8]. A previous study has reported that serum ADMA levels are increased in patients with CKD and are associated with renal function and proteinuria [9]. In addition, both experimental and clinical studies have demonstrated that RAS-Is decrease serum ADMA levels and improve endothelial dysfunction [10].

Although many studies have demonstrated the effect of RAS-Is in patients with CKD and hypertension, to the best of our knowledge, detailed data in normotensive patients with CKD are lacking. In the present study, we examined the effects of RAS-I treatment on oxidative stress and the NO system in normotensive patients with CKD.

Subjects and Methods

Study Population

Thirty-one normotensive patients with chronic glomerulonephritis who were hospitalized in our institution between January 2008 and December 2009 were enrolled in the present study. All patients met the criteria for normotensive subjects according to the guidelines of the Japanese Society of Hypertension. Patients who were taking RAS-Is or an immunosuppressant or who had a history of smoking, hypertension, diabetes mellitus, hyperlipidemia, overt infection, malignancy, inflammatory disease or CVD were excluded. Of the 31 patients, 8 were excluded from this study because of the discontinuation of prescribed medication, transfer to another facility or insufficient clinical data. For the 23 remaining patients, renal biopsies were performed after enrolment, and RAS-Is were administered for at least 3 months (losartan, n = 11; olmesartan, n = 6; valsartan, n = 5, and enalapril, n = 1). The patients did not take any other antihypertensive or renoprotective drugs, and there was no change in the medication dose during the study period. To compare the histological findings, 5 subjects with mild proteinuria whose renal histological findings showed only minor glomerular abnormalities were evaluated as controls. In addition, as for serum ADMA levels, 20 young healthy volunteers were evaluated. For the study patients, we prospectively performed blood and urinary examinations, renal histological analyses and blood pressure (BP) measurement before and 3 months after starting treatment with RAS-Is. The experimental protocols were approved by the appropriate institutional review committee and performed in accordance with the Helsinki Declaration of 1975, as revised in 2000.

Table 1. Patients' baseline characteristics (n = 23)

Age, years	48±4
Males/females	15/8
Systolic BP, mm Hg	115.6±3.1
Diastolic BP, mm Hg	67.6±2.3
Cr, mg/dl	0.99±0.07
eGFR, ml/min/1.73 m^2	65.6±4.1
BUN, mg/dl	15.2±1.0
TP, g/dl	6.74±0.20
Albumin, g/dl	3.73±0.12
ADMA, nmol/ml	0.46±0.01
U-8-OHdG, ng/mg•Cr	99.1±14.4
U-NOx/U-Cr	1.29±0.16
U-protein, g/g•Cr	1.22±0.32

Cr = Creatinine; eGFR = estimated glomerular filtration rate; BUN = blood urea nitrogen; TP = total protein; U-8-OHdG = urinary 8-OHdG; U-Cr = urinary creatinine; U-protein = urinary protein.

Table 2. Renal histological findings

	Control (n = 5)	CKD (n = 17)	p value
Global sclerosis, %	0	12.3±3.4	0.038
Interstitial fibrosis, %	0	13.4±3.7	0.042
Hyalinosis, %	0	5.3±4.0	0.439
Arterial intimal fibroplastic thickness, %	7.6±0.3	22.0±3.4	0.036
8-OHdG-positive cell score	42.1±6.7	84.3±3.8	0.032

Renal Histological Analysis

Of the 23 study patients, renal biopsy specimens of 17 patients were available for histological analysis. We evaluated the extent of glomerulosclerosis, interstitial fibrosis, arteriolar hyalinosis and intimal fibroplastic thickness of interlobular arteries in a blinded manner. The number of globally sclerotic glomeruli was counted to determine the extent of global sclerosis. Furthermore, formation of 8-hydroxydeoxyguanosine (8-OHdG) was assessed with anti-8-OHdG monoclonal antibodies raised in humans (NOF Corp., Tokyo, Japan). 8-OHdG-positive cells in all glomeruli were counted, and the average was used as the 8-OHdG-positive cell score. The following formulae were used to calculate global sclerosis, interstitial fibrosis, arteriolar hyalinosis and arterial intimal fibroplastic thickness, respectively:

global sclerosis (%) = 100 × (number of globally sclerotic glomeruli/total number of glomeruli),

interstitial fibrosis (%) = 100 × (area of fibrosis/total area of the specimens),

arteriolar hyalinosis (%) = 100 × (number of arterioles with hyalinization/total number of arterioles), and

arterial intimal fibroplastic thickness (%) = 100 × (a + b)/od, where a and b = intimal thickness of interlobular arteries and od = outer diameter.

Serum and Urine Measurements

Before and 3 months after starting treatment with RAS-Is, venous blood was collected from study patients in the morning following overnight fasting. Urinary NO metabolites (U-NOx) and 8-OHdG excretion were determined using ELISA kits (NOx: Dojindo Laboratories, Kumamoto, Japan; 8-OHdG: Japan Institute for Control of Aging, Shizuoka, Japan). Serum ADMA

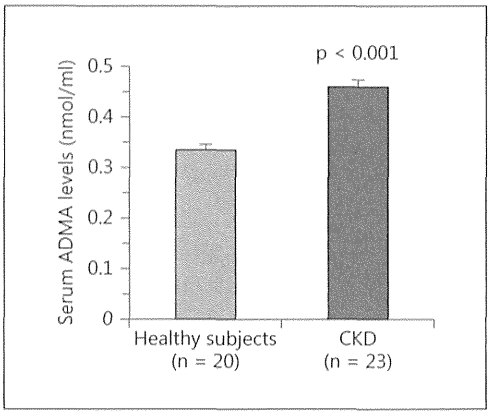

Fig. 1. Comparison of serum ADMA levels between healthy subjects and patients with CKD.

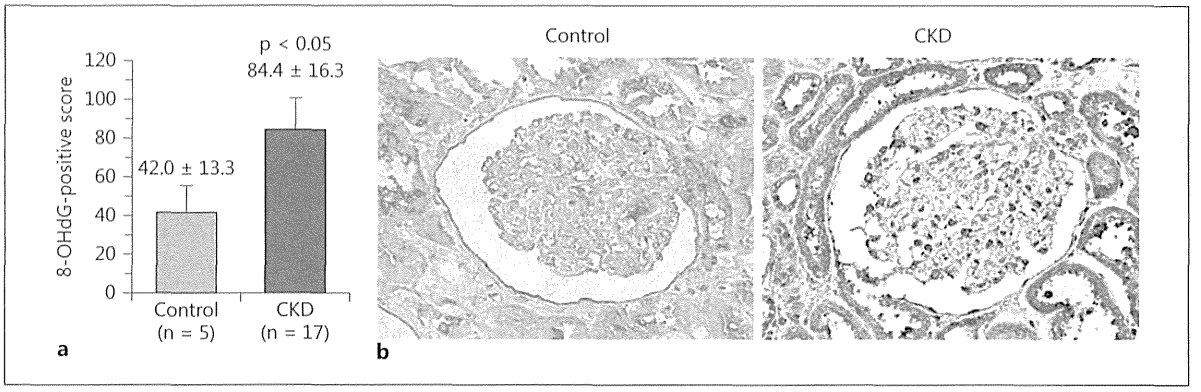

Fig. 2. Histological examination of the kidney sections for 8-OHdG. **a** 8-OHdG-positive cell scores were significantly higher in the patients with CKD than in the control subjects. **b** Immunostaining for 8-OHdG is indicated by brown reaction products.

levels were determined using a novel high-performance liquid chromatography method. Other laboratory tests were conducted using standardized clinical laboratory methods.

Statistical Analysis

We used the computer software application StatView 5.0 (SAS Institute, Cary, N.C., USA) for all statistical analyses. Values are presented as mean ± SEM. For continuous variables, the Mann-Whitney U test was used to analyze the significance of the differences between the 2 groups. Pearson's correlation coefficient was used to analyze the relationship between the variables. $p < 0.05$ was considered to be statistically significant.

Results

Patients' Characteristics and Renal Histology

The baseline characteristics of the study patients are shown in table 1. Serum ADMA levels in the study patients were higher than those in the healthy subjects (fig. 1). Renal histological analysis revealed more severe lesions in the study patients compared with the control subjects (table 2). Furthermore, the 8-OHdG-positive cell score was significantly higher in the patients with CKD than in the control subjects (fig. 2).

Table 3. Relationship between serum ADMA levels and clinical characteristics

	r	p value
Age	0.362	0.117
Sex	0.298	0.203
Systolic BP	0.013	0.933
Diastolic BP	0.165	0.272
Cr	0.274	0.065
eGFR	−0.336	0.024
BUN	0.375	0.010
TP	0.050	0.833
Albumin	0.015	0.950
U-8-OHdG	0.219	0.163
U-NOx/U-Cr	−0.160	0.313
U-protein	0.275	0.064

Cr = Creatinine; eGFR = estimated glomerular filtration rate; BUN = blood urea nitrogen; TP = total protein; U-8-OHdG = urinary 8-OHdG; U-Cr = urinary creatinine; U-protein = urinary protein.

Table 4. Relationship between serum ADMA levels and renal histological findings

	r	p value
Global sclerosis	0.205	0.415
Interstitial fibrosis	0.309	0.212
Hyalinosis	0.092	0.910
Arterial intimal fibroplastic thickness	0.573	0.013

Correlation of ADMA with Clinical Characteristics and Renal Histology

We evaluated the correlation of serum ADMA levels with the patients' clinical characteristics (table 3) and renal histological findings (table 4). Serum ADMA levels were significantly correlated with estimated glomerular filtration rate and tended to be correlated with the degree of urinary protein excretion. Among the renal histological findings, we found that only arterial intimal fibroplastic thickness was significantly related to serum ADMA levels.

Changes of ADMA, NO and 8-OHdG by RAS-Is

Although BP and renal function did not differ significantly during the study period, the degree of urinary protein excretion was significantly reduced 3 months after starting treatment with RAS-Is (fig. 3). In addition, serum ADMA levels and U-NOx and urinary 8-OHdG excretion were improved 3 months after starting treatment with RAS-Is compared with the respective values at baseline (fig. 4).

Discussion

Our study demonstrated that serum ADMA levels were significantly higher in the normotensive patients with CKD than in the control subjects, that arterial intimal fibroplastic thickness was significantly correlated with serum ADMA levels and that RAS-Is lowered the elevated serum ADMA levels and oxidative stress and increased NO production.

The mechanisms underlying abnormalities in CKD are complicated, and several factors contribute to their pathogenesis. Of these factors, oxidative stress is considered to play a key

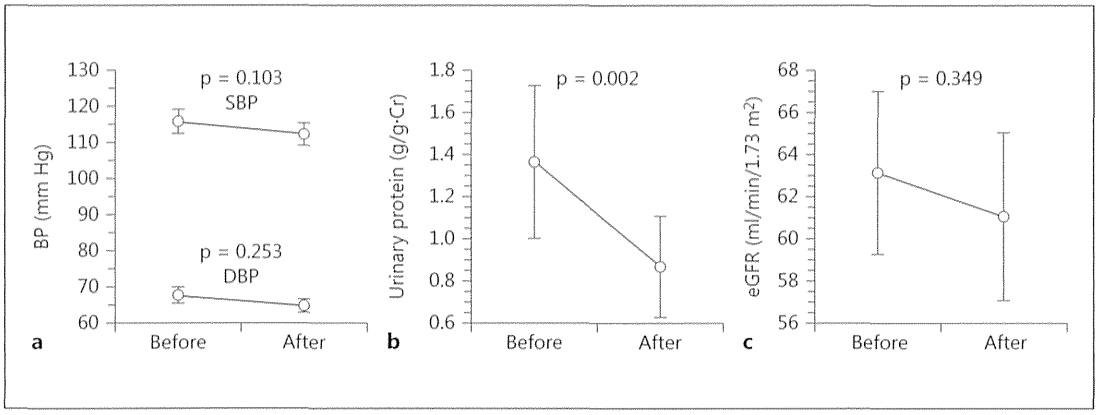

Fig. 3. Changes in systolic (SBP) and diastolic BP (DBP) (**a**), urinary protein excretion (**b**) and renal function after starting treatment with RAS-Is (**c**). eGFR = Estimated glomerular filtration rate; before = before treatment; after = after treatment.

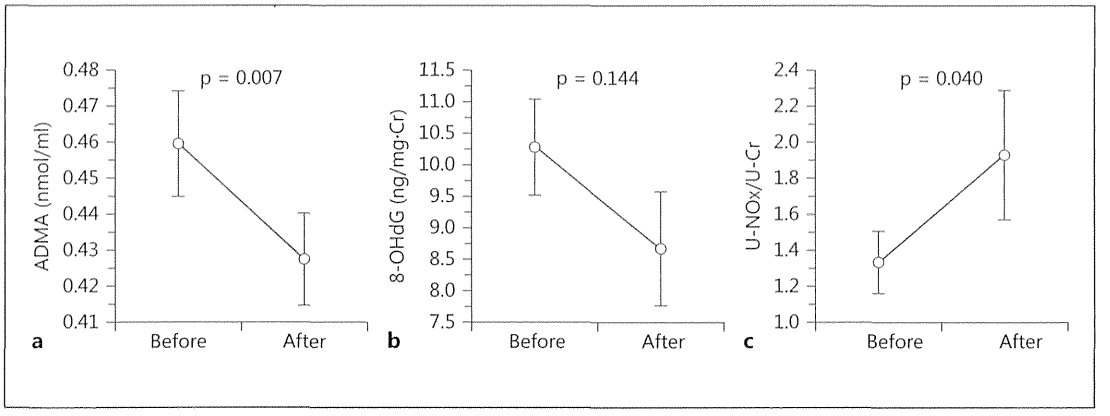

Fig. 4. Changes in ADMA (**a**), U-NOx (**b**) and oxidative stress (**c**) after starting treatment with RAS-Is. U-Cr = Urinary concentration of creatinine.

role in the progression of CKD [11, 12]. In the present study, compared with healthy subjects, systemic and intrarenal oxidative stress increased in normotensive patients with CKD. These findings suggested a relationship between oxidative stress and the progression of CKD in such patients.

ADMA is an endogenous competitive inhibitor of NO synthase, and NO is a potent anti-atherosclerotic molecule [7]. Therefore, increased ADMA levels lead to a decrease in NO synthesis and progressive damage due to impaired vascular function in the kidneys, heart and other systemic organs. Elevated ADMA levels are associated not only with endothelial dysfunction [8, 13, 14] but also with increased oxidative stress [15, 16], thereby linking vascular function and redox mechanisms in CKD and CVD. In addition, serum ADMA levels have been reported to be markers of endothelial dysfunction and/or atherosclerosis [17] and to be associated not only with renal function but also with proteinuria in CKD [8, 18]. The results of our study demonstrated that serum ADMA levels were significantly correlated with the intrarenal vascular lesions even in normotensive patients with CKD. With regard to the clinical data, serum ADMA levels were correlated with renal function and proteinuria. Taking

these results into account, the increase of serum ADMA levels is believed to be the first step in the process of the progression of CKD. Therefore, these findings suggested that serum ADMA levels reflect the severity of CKD and could be used as a surrogate marker for the progression of CKD.

Many reports have shown the efficacy of RAS-Is in renal diseases. Angiotensin-converting enzyme inhibitor and ARB have been shown to reduce urinary protein excretion and slow the progression of renal dysfunction [2, 3]. However, only few studies have demonstrated the efficacy of RAS-Is in normotensive patients with CKD in clinical settings. Makino et al. [19] reported that ARB reduces the transition to overt nephropathy in normotensive diabetic patients, suggesting that ARB has favorable BP-independent effects on CKD. Web et al. [20, 21] demonstrated that RAS-Is effectively reduced proteinuria in normotensive children with CKD.

Angiotensin II, which acts on angiotensin II type 1 receptors, increases oxidative stress, in part by activating nicotinamide adenine dinucleotide phosphate oxidase and ADMA, which in turn activates the local renin-angiotensin system [15, 22, 23]. Therefore, RAS-Is can lower oxidative stress, which has been suggested to be associated with a reduction in serum ADMA levels independently of lowering the BP. In patients with CKD, RAS-Is has been reported to reduce ADMA, proteinuria levels and oxidative stress [24, 25]. However, no study has actually demonstrated that RAS-Is can reduce ADMA levels in normotensive patients with CKD.

The main limitation of our study was the small number of study patients. However, our patients were carefully and appropriately treated and we closely observed them prospectively and longitudinally. Although only few prospective and longitudinal studies have elucidated the detailed mechanisms of the progression of CKD on this topic in the early stages of CKD, we performed both a biochemical analysis and histological evaluations. Therefore, we consider the results of the present study to be valuable for understanding the mechanisms and effects of RAS-Is on the progression of CKD. Another limitation was that the present study included a group of patients with heterogeneous renal etiologies. However, all study patients were normotensive and relatively young. Other patient characteristics were very similar. In the near future, we plan to conduct a randomized controlled trial with a large number of study patients to clarify these details.

Our data suggest that RAS-Is prevent the progression of chronic glomerulonephritis by reducing serum ADMA levels and oxidative stress in normotensive patients with CKD. In addition, the findings suggest that ADMA may be associated with intrarenal lesions and can be used as a useful surrogate marker for the effects of treatment in the early stages of CKD.

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Disclosure Statement

None of the authors have any conflict of interest to report.

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