$r=0.256$, $p<0.01$). Furthermore, cystatin C was significantly correlated with CIMT in men and with BMI, SBP, and LDL-C in women. In all the participants, cystatin C was significantly correlated with age, WC, TG, HDL-C, UA, Cre, eGFR, and CAVI as well as CIMT according to the results of simple linear regression analysis (**Table 2**).

By multiple linear regression analysis adjusted for confounding factors associated with arteriosclerosis, cystatin C was found to be significantly correlated with CAVI in women, but not in men (**Table 3A**); however, cystatin C was not correlated with CIMT in any participants, unrelated to gender (**Table 3B**). In addition, we analyzed the association between eGFR, which is routinely used as a surrogate marker of kidney function, and CAVI or CIMT using multivariate analysis, but did not find any association between eGFR, and CAVI or CIMT in any participants (**Table 4A** and **4B**).

Table 2. Simple correlation analysis of CysC and other variables

	Men	Women	All participants
Age	0.374**	0.347**	0.343**
BMI	0.145	0.287**	0.239**
WC	0.212**	0.320**	0.291**
SBP	0.092	0.160**	0.134**
TG	0.226**	0.199**	0.209**
HDL-C	−0.190*	−0.208**	−0.222**
LDL-C	0.098	0.129*	0.085
UA	0.244**	0.312**	0.332**
HbA1c	0.042	0.106	0.076
U-Alb/Cre	−0.009	0.086	0.005
Cre	0.420**	0.426**	0.426**
eGFR	−0.516**	−0.513**	−0.495**
CIMT	0.228**	0.108	0.181**
CAVI	0.240**	0.247**	0.256**

*$p<0.05$ and **$p<0.01$

Discussion

In this study, we investigated the association between cystatin C and arteriosclerosis in adult Japanese subjects who underwent a physical examination, who were determined not to have CKD based on the absence of proteinuria and eGFR >60 mL/min. In consideration of the effects of age, BMI, diabetes mellitus, dyslipidemia, hypertension, and smoking, we found a significant correlation between cystatin C and CAVI in women.

The association between progressive impairment of kidney function and arteriosclerosis with CVD has been previously demonstrated[3, 4]; however, in people without CKD, the association between cystatin C and arteriosclerosis has been unclear. Although a few studies have investigated the association between arteriosclerosis and serum cystatin C, which is considered more sensitive in detecting early-stage renal impairment as compared to serum creatinine[31-33], their results have differed due to variations in the targets and indicators used for arteriosclerosis. Thus, in the present study, we simultaneously measured CAVI, CIMT, and serum cystatin C levels in a non-CKD population; to the best of our knowledge, this is the first report to demonstrate that cystatin C was associated with CAVI in female non-CKD subjects with no proteinuria and eGFR >60 mL/min.

These findings indicate that a slight decrease in kidney function even within the normal range may promote arteriosclerosis, similar to the report by Verhave *et al.* that arteriosclerotic risk factors, such as increasing diastolic blood pressure and serum triglycerides, were associated with a decrease in kidney function in the population who had normal kidney function[34]. On the other hand, our results also showed that very mild dysfunction caused by arteriosclerosis might be detected by cystatin C.

After adjustment for cofounding factors, we could not find a significant association between cystatin C and CIMT. A number of studies have investigated the association between cystatin C and CIMT as a marker of arteriosclerosis; these studies targeted a healthy Chinese population[20], middle-aged adults in the Seychelles[23], and cardiovascular disease-free people[22]; however, no relationship was observed between cystatin C and CIMT in these studies, as in our study. On the other hand, a study that targeted hypertensive patients reported a positive correlation between cystatin C and CIMT[24, 26]. One reason for this result might be the insufficient number of participants. Furthermore, our results can be explained by a report that CAVI could detect arterial stiffness prior to evident carotid arteriosclerosis and high CAVI might imply the progression of carotid arteriosclerosis[35]; that is, CAVI may be more sensitive than CIMT for detecting arteriosclerosis.

Furthermore, the difference between men and women in the smoking rate might explain why a significant association between cystatin C and CAVI was not observed in men. In our subjects, the smoking rates were 23.2% in men and 3.0% in women. Previously, it was reported that elevated cystatin C was independently associated with smoking[36]. Cystatin C is the most widespread and potent inhibitor of cathepsins B and L and it has been considered that a cathep-

Table 3A. Multiple linear regression analysis of CysC with relevant factors

	All		Men		Women	
	β	*p* value	β	*p* value	β	*p* value
Age	0.319	<0.001	0.404	<0.001	0.306	<0.001
UA	0.116	0.018	0.134	0.051	0.154	0.005
BMI	0.169	<0.001	0.136	0.042	0.194	<0.001
Diabetes mellitus	−0.006	0.886	0.012	0.847	0.016	0.748
Dyslipidemia	0.033	0.417	0.029	0.661	−0.029	0.573
Hypertension	−0.042	0.336	−0.031	0.635	−0.070	0.245
Smoking	0.052	0.205	0.202	0.002	−0.030	0.559
Cre	0.349	<0.001	0.397	<0.001	0.392	<0.001
CAVI	0.075	0.101	0.042	0.569	0.117	0.049

β: regression coefficient; CI: confidence interval.

Table 3B. Multiple linear regression analysis of CysC with relevant factors

	All		Men		Women	
	β	*p* value	β	*p* value	β	*p* value
Age	0.363	<0.001	0.394	<0.001	0.384	<0.001
UA	0.129	0.008	0.150	0.030	0.182	0.001
BMI	0.162	<0.001	0.145	0.029	0.164	0.003
Diabetes mellitus	−0.001	0.987	0.010	0.874	0.027	0.586
Dyslipidemia	0.038	0.341	0.027	0.675	−0.032	0.541
Hypertension	−0.032	0.456	−0.033	0.611	−0.039	0.510
Smoking	0.060	0.144	0.202	0.002	−0.003	0.961
Cre	0.353	<0.001	0.394	<0.001	0.395	<0.001
CIMT	0.015	0.736	0.089	0.206	−0.062	0.280

β: regression coefficient; CI: confidence interval.

sin-cystatin C imbalance causes tissue destruction; therefore, elevated cystatin C influences the state of lung tissue destruction, such as emphysema. We consider that cystatin C in smokers might be possibly elevated not only as a result of early renal dysfunction but also as a direct response to smoking. In our study, smoking might have influenced our results since cystatin C was significantly related to smoking in men. In addition, our subjects were comparatively older. It is well known that kidney function is correlated negatively with age. In fact, a strong correlation has been reported between cystatin C and age, regardless of the presence of impaired renal function[37-40]. Since the average age of our subjects was 67.0 years, there is a possibility that age influenced the serum cystatin C values. Moreover, it is known that women develop arteriosclerosis and cardiovascular disease typically after the menopause. As the mean age of women in our study was 67.4 years, ovarian hormone deprivation might also have affected our result that cystatin C was related to CAVI only in women.

In this study, we adopted cystatin C and eGFR as surrogate markers of renal function. Currently, eGFR is accepted as a surrogate marker of kidney function worldwide; however, Coll *et al.* reported that serum cystatin C levels began to increase beyond the normal limit when the GFR was 88 mL/min/1.73 m^2, whereas serum creatinine levels began to increase when the GFR was 75 mL/min/1.73 m^2 [41]. These data suggest that the measurement of serum cystatin C may be useful for estimating GFR, especially for detecting mild reductions in GFR, and may therefore be important in the detection of early renal insufficiency in a variety of renal diseases for which early treatment is critical.

In this study the subjects had eGFR >60 mL/min and relatively intact renal function; therefore, we considered that cystatin C was a more sensitive marker than eGFR for detecting slight decreases in GFR. We subsequently focused upon the correlations of cystatin

Table 4A. Multiple linear regression analysis of eGFR with relevant factors

	All		Men		Women	
	β	*p* value	β	*p* value	β	*p* value
Age	−0.010	0.841	−0.099	0.229	0.037	0.586
UA	−0.090	0.052	−0.199	0.003	−0.126	0.333
BMI	0.066	0.147	0.110	0.105	0.036	0.565
Diabetes mellitus	0.027	0.513	0.015	0.864	0.016	0.762
Dyslipidemia	−0.114	0.006	−0.136	0.037	−0.062	0.264
Hypertension	−0.049	0.278	−0.034	0.600	−0.066	0.301
Smoking	0.154	<0.001	0.203	0.002	−0.041	0.451
CysC	−0.462	<0.001	−0.444	<0.001	−0.462	<0.001
CAVI	−0.030	0.529	0.016	0.829	−0.060	0.343

β: regression coefficient; CI: confidence interval.

Table 4B. Multiple linear regression analysis of eGFR with relevant factors

	All		Men		Women	
	β	*p* value	β	*p* value	β	*p* value
Age	−0.008	0.876	−0.067	0.398	0.032	0.635
UA	−0.097	0.036	−0.200	0.004	−0.133	0.025
BMI	0.066	0.145	0.116	0.087	0.038	0.531
Diabetes mellitus	0.026	0.523	0.019	0.766	0.013	0.813
Dyslipidemia	−0.117	0.005	−0.129	0.047	−0.065	0.238
Hypertension	−0.044	0.322	−0.029	0.658	−0.063	0.314
Smoking	0.157	<0.001	0.212	0.001	−0.043	0.432
CysC	−0.464	<0.001	−0.445	<0.001	−0.469	<0.001
CIMT	−0.035	0.456	−0.032	0.653	−0.059	0.330

β: regression coefficient; CI: confidence interval.

C with CAVI and CIMT, although it is unfortunate that our results only led to the conclusion that cystatin C is superior to eGFR with regard to the association with arteriosclerosis. In contrast, although the urinary albumin-to-creatinine ratio (UACR) is also known to be a sensitive marker of kidney injury, no significant association was observed between UACR and cystatin C or eGFR in our study. UACR mainly reflects glomerular injury or increased intra-glomerular pressure, but not GFR, while cystatin C is a sensitive marker that reflects GFR[42]. In other words, while cystatin C and UACR are both markers of kidney dysfunction, we consider that they reflect fundamentally different conditions. One such example is nephrosclerosis, which is an underlying disease of chronic kidney failure; even when proteinuria is not observed, this entity leads to decreased kidney function, wherein cystatin C or eGFR and UACR do not necessarily display identical changes. Therefore, although no correlation was observed between cystatin C and UACR, we consider that our result is helpful for subjects whose eGFR is >60 mL/min with no evident proteinuria.

Apart from renal function, classical risk factors for arteriosclerosis, such as hypertension, DM, dyslipidemia, and smoking, may also affect the level of CAVI or CIMT; this may have affected our results. The relationship of DM and LDL-C with kidney function and arteriosclerosis has been previously demonstrated[43, 44]; however, no association between DM and cystatin C was observed in our study and we believe that this was because the overall proportion of DM patients was only 6.7%. With regard to the association between cystatin C and dyslipidemia, although univariate analysis found no correlation between LDL-C and cystatin C, a significant negative correlation was observed between cystatin C and HDL-C. Low HDL-C is also defined as dyslipidemia and is believed to be a risk factor for arteriosclerosis[45]; therefore, we consider that our results are consistent with previous studies. In this study, the mean LDL-C (143

mg/dL) was relatively low, which may have influenced the lack of a significant association between cystatin C and LDL-C.

There were some limitations of our study. First, our subjects were selected within a confined geographical area. Thus, our results might have been affected by this selection bias. We therefore hope for future large-scale studies. Second, there is no standard assay system or cutoff value for cystatin C[46]. The possibility that the lack of such standards affected the results of not only our study but also previous research cannot be ruled out. It is therefore necessary to define a cutoff value for cystatin C and to establish a universal assay system for cystatin C.

In conclusion, we observed a significant correlation between cystatin C and CAVI in women in a non-CKD population with no proteinuria and eGFR >60 mL/min. This may imply that patients with a high level of cystatin C, even within the normal range, have the potential to develop CKD or CVD. Therefore, patients with high levels of cystatin C or CAVI in medical screening studies should be carefully monitored for kidney function and arteriosclerosis severity in order to prevent CKD or CVD.

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Conflicts of Interest

None.

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I. 血栓と腎の病態

4. 腎臓病と血管炎

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THROMBOSIS and Circulation

§論文のポイント

[1] 血管炎とは液性免疫・細胞性免疫の異常などによって血管壁に炎症が生じる病態であり，全身性の炎症性疾患である．

[2] 罹患する血管のサイズに基づいて分類する Chapel Hill 分類が用いられてきたが，2013 年に新分類である CHCC2012 が発表された．

[3] 炎症に伴う全身症状と多臓器の虚血や出血による多彩な症状を呈するが，特に腎臓は血管に富み血管炎の好発臓器である．

[4] 近年，小血管を主体とした壊死性血管炎である ANCA 関連血管炎が増加しているが，急速進行性糸球体腎炎を呈し，病理学的には半月体形成性の糸球体腎炎が認められることが多い．

[5] ANCA 関連血管炎については，日米欧での前向き試験などから診断基準や標準治療法が確立されつつある．

§キーワード

Chapel Hill 分類／CHCC2012／ANCA 関連血管炎／急速進行性糸球体腎炎／半月体形成性糸球体腎炎

血管炎とは

血管炎とは液性免疫・細胞性免疫の異常などによって血管壁に炎症が生じる病態であり，全身性の炎症性疾患である．

血管炎の分類は，罹患サイズに基づいて大血管炎・中血管炎・小血管炎の3つのカテゴリーに分類するChapel Hill 分類[1]が有名だが，2011年5月に North Carolina 大学 Chapel Hill 校で開かれた Consensus Conference にて，新しい分類と定義が討議され「CHCC2012」として2013年1月に発表された(図1)[2]．

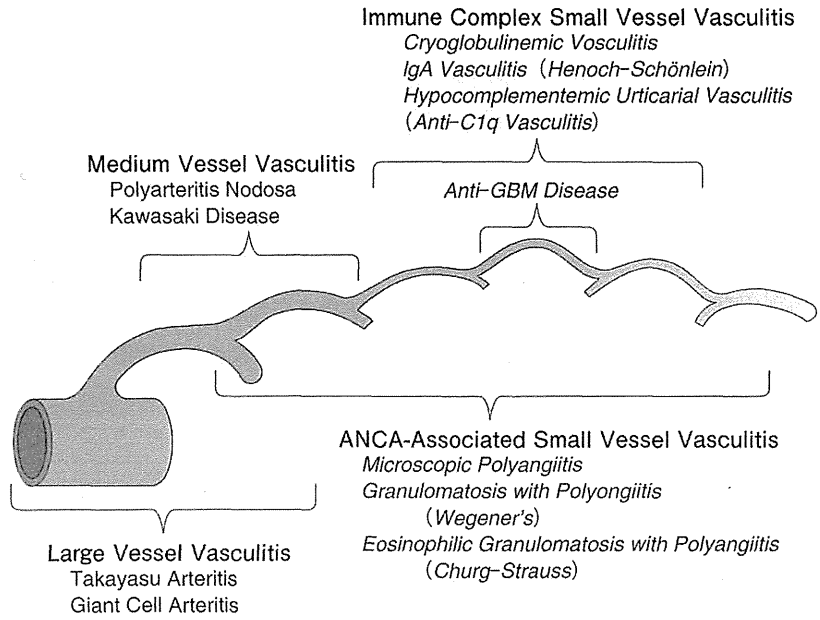

図1　CHCC2012

CHCC2012では上記の3つのカテゴリーに加え Variable vessel vasculitis：VVV (Behçet 病などのさまざまなタイプの血管を侵す血管炎)，Single organ vasculitis：SOV (皮膚白血球破砕性血管炎など単一臓器を侵す血管炎)，Vasculitis associated with systemic disease (SLE や関節リウマチなど全身疾患に関連した血管炎)，Vasculitis associated with probable etiology (肝炎ウイルスや薬剤など病因が判明している血管炎)の4つのカテゴリーが新たに加えられた．

また小型血管炎については ANCA 関連血管炎(ANCA-associated vasculitis：AAV)と Immune complex vasculitis (免疫複合体型血管炎)の2つに細分類された．

AAV には顕微鏡的多発血管炎(microscopic polyangiitis：MPA)・Wegener 肉芽腫症・Churg-Strauss 症候群が含まれるが，Wegener 肉芽腫症は多発血管炎性肉芽腫症(Granulomatosis with polyangiitis：GPA)に，Churg-Strauss 症候群は好酸球性多発血管炎性肉芽腫症(Eosinophilic granulomatosis with polyangiitis：EGPA)へと名称変更がなされた．

免疫複合体型血管炎には Henoch-Schönlein 紫斑病(IgA vasculitis に名称変更)，本態性クリオグロブリン血症(cryoglobulinemic vasculitis に名称変更)，低補体性蕁麻疹様血管炎と抗 GBM 病が含まれる．本邦では抗 GBM 抗体による急速進行性糸球体腎炎は，免疫複合体によるものと分けて分類されており，治療指針も異なる[3]．

AAV のうち人名のついた病名が変更された一方で，高安動脈炎や川崎病など，本邦の医学者の名を冠した疾患名はそのまま残された．

わが国で多い血管炎は，MPA，Buerger 病，悪性関節リウマチ(malignant rheumatoid arthritis：MRA)，高安動脈炎である(Buerger 病は CHCC2012 には含まれていない)．MPA＋結節性多発動脈炎(polyarteritis nodosa：PAN)は年々増加の一途をたどり，2010年度には Buerger 病を抜き1位となった(図2)[4]．

血管炎では，炎症に伴う発熱や体重減少などの全身症状とともに，多臓器の虚血や出血による多彩な症状を呈する．検査所見としては，高度の炎症性病変を反映して白血球(好中球・好酸球)や C 反応性蛋白が増加し，小血管炎においては抗好中球細胞質抗体(anti-neutrophil cytoplasmic antibody：ANCA)などの疾患特異的な免疫異常を認めることがある．大・中型血管炎では血管造影や MR angiography (MRA) の他，18F-FDG-PET/CT などの画像検査が有用である．病理学的には，血管

壁への炎症細胞浸潤による壊死性変化・肉芽腫性変化が認められる．

腎臓は血管に富み血管炎の好発臓器である．腎臓においては中型血管である腎動脈と葉間動脈・弓状動脈などの小型血管が共存しており，血管炎の種類により多様な臨症所見を呈する．大型血管炎である高安動脈炎では腎動脈狭窄による高血圧に起因する腎障害や虚血による腎機能低下がみられ，血尿は通常陰性である．中型～小型血管炎であるPANでは腎血管狭窄による高血圧性病変や腎梗塞および動脈瘤破綻による出血がみられる．小型血管炎であるAAVでは急速進行性糸球体腎炎を呈し，病理学的には半月体形成性の糸球体腎炎が認められる．その他免疫複合体による血管炎や新分類で加えられたSLEやRAなど全身疾患に関連した血管炎でも腎障害は認められ，その病態は極めて多様である．CHCC2012では含まれる疾患の数が10から26に増えたが，紙面の都合上，本稿ではAAVについて概説する．

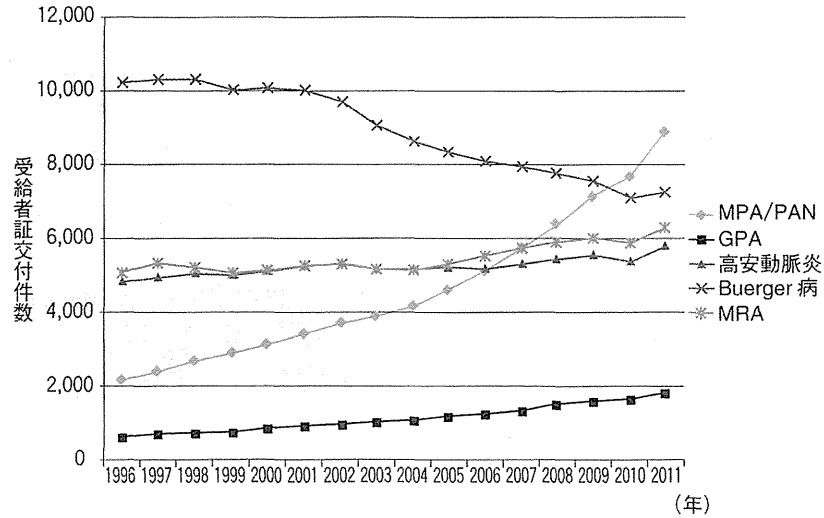

図2　血管炎患者数の推移
（文献4より受給者証交付件数を入手して作成）

ANCA関連血管炎

1994年にChapel Hillで開かれた国際会議において，血管壁への免疫複合体沈着がほとんどみられず，ANCA陽性率が高い，小血管（毛細血管，細小動静脈）を主体とした壊死性血管炎が，ANCA関連血管炎と定義された[1]．CHCC2012でもMPA，GPA，EGPAの3疾患が含まれ，MPAのうち腎のみに臓器障害を認める場合には，腎限局型血管炎と呼ばれる（本邦では間質性肺炎など肺のみに障害を認める場合に肺限局型血管炎と呼ぶこともある）．

ANCAについては，プロテイナーゼ3を対応抗原とするPR3-ANCAとミエロペルオキシダーゼを対応抗原とするMPO-ANCAが知られており，PR3-ANCAは主にGPAの，MPO-ANCAはその他のAAVの疾患標識抗体となる．

MPAはAAVのうち肉芽腫性病変のみられないものと定義される．男女比はほぼ1：1で，高齢者に多い．わが国ではMPAが最も多くGPAがこれに次ぐが，欧米ではGPAが圧倒的に多く，疫学的な相違が存在する．発熱，体重減少，易疲労などの全身症状とともに組織の出血や虚血・梗塞による徴候が出現する．組織学的には壊死性糸球体腎炎が最も高頻度であり，急速進行性糸球体腎炎を呈する．その他，皮疹（palpable purpuraなど），多発性単神経炎，関節痛・筋痛などが高頻度にみられる．肺毛細管炎による間質性肺炎や肺胞出血など肺病変の頻度も高く，間質性肺炎（UIPなど）・肺線維症が多いのがわが国のMPA患者の特徴である[5]．確定診断には組織の生検，特に腎生検が必要である．半月体形成や糸球体のフィブリノイド壊死を伴う壊死性糸球体腎炎で免疫グロブリンや補体の沈着がないか乏しいことを確認する（pauci-immune）（図3）．腎生検が困難な場合は，病変のある皮膚，腓腹神経などが生検対象となる．

GPAは病理組織学的に全身の壊死性・肉芽腫性血管炎を呈し，上気道と肺を好んで侵す．本邦では欧米と比較して患者数が少なく2011年度の医療受給者証交付件数は1,834件である．発熱，体重減少などの全身症状とともに，❶上気道の症状：膿性鼻漏，鼻出血，鞍鼻，中耳炎など，❷肺症状：血痰，呼吸困難など，❸急速進行性腎炎，❹その他：紫斑，多発関節痛，多発神経炎などがあり，通常❶→❷→❸の順序で起こる．元来生命予後の極めて悪い疾患であ

るが，発症早期に免疫抑制療法を開始すると，高率に寛解を導入できる疾患であることがわかってきた[4]．

EGPAは先行症状として気管支炎喘息やアレルギー性鼻炎がみられ，末梢血好酸球増多を伴う，血管周囲の好中球と著明な好酸球浸潤を認める細小血管の肉芽腫性壊死性血管炎である．男：女＝4：6でやや女性に多い．主要臨床症状は，先行する気管支喘息あるいはアレルギー性鼻炎と，血管炎によるもので，末梢神経炎(多発性単神経炎)が多い．多発性単神経炎は，急性症状が改善してからも遷延することがある[4]．

AAVの分類には米国リウマチ学会分類基準およびChapel Hill分類が適用されてきたが，分類の混乱や分類不能の症例が少なからず存在することが指摘されていた．2007年にWattsらは疫学研究への適用を目的として，新しい分類アルゴリズムを提唱した[6]．米国リウマチ学会分類基準・Chapel Hill分類に加え，臓器障害の臨床指標(代用マーカー)，ANCA所見を用いて単一疾患に分類できる方法である．その後，欧米のリウマチ学会を中心に，国際的に統一された基準が必要であるとの考えの下，2008年から原発性全身性血管炎の分類・診断基準作成のための多施設国際共同研究(Diagnostic and Classification Criteria for Primary Systemic Vasculitis：DCVAS)が進行中であり，日本からも専門家らが参加し世界統一の診断基準作成が行われている．

AAVの治療については，2000年代に入って欧米でランダム化比較対照試験の成績が相次いで報告された．

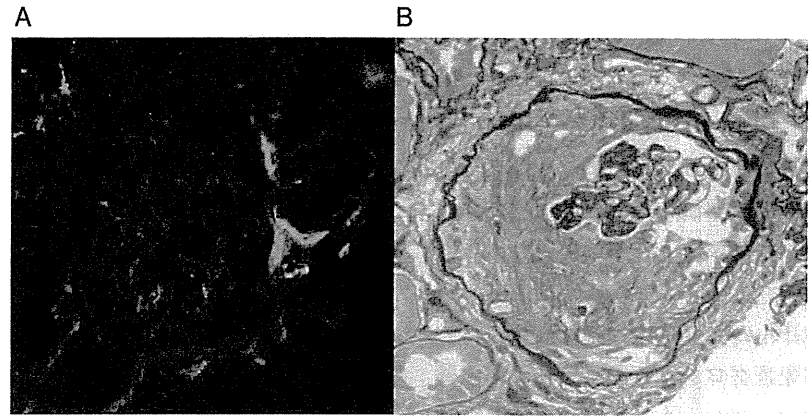

図3　MPA患者の腎組織像
A：蛍光抗体法，B：PAM染色

しかし本邦と欧米には疫学的な相違があり，そのままわが国で適用するには問題があった．そこで2004年，難治性血管炎に関する調査研究班(主任研究者 尾崎承一教授)において，MPO-ANCA関連血管炎に対する標準的治療プロトコルが作成され，その検証のための前向き臨床試験が開始された．この臨床試験は2008年3月に終了し，その研究成果[7]に欧州の2つのガイドライン(BSR and BHPR guidelines[8]とEULAR recommendations[9])を取り入れて，2010年にANCA関連血管炎のわが国における治療法の確立のための多施設共同前向き臨床研究班(主任研究者 尾崎承一教授)，難治性血管炎に関する調査研究班(主任研究者 槇野博史)，進行性腎障害に関する調査研究班(主任研究者 松尾清一教授)の三班合同によるANCA関連血管炎の診療ガイドラインが策定された[10]．

全身型の血管炎では，ステロイド(PSL換算で1 mg/kg/日)に加えてシクロフォスファミド(cyclophosphamide：CY)(経口2 mg/kg/日またはintravenous CY (IVCY) 15 mg/kgを2～3週毎)の併用が推奨されている．CYの投与量については，年齢や腎機能による減量が必要である．最近の報告では，IVCYは経口CYと比較して同等の寛解導入率でありながら，感染症や白血球減少の発生が少ないとされている[11]．

EULAR recommendationsで寛解導入療法としてCYを3～6ヵ月投与後，寛解が得られた場合にはCYを中止し，寛解維持療法に切り替えるとされている．少量ステロイドにAZAやMTXを併用し，12～18ヵ月継続することが推奨されている[9]．

免疫抑制剤併用時のステロイドの減量法として，上記のBSR and BHPR guidelines[8]では，PSL15 mg/日までは1～2週毎に減量するプロトコルを推奨している．一方EULAR recommendations[9]では最初の1ヵ月は初期高用量を維持し，3ヵ月以内に15 mg/日未満にすべきではないとしている．当科でのレトロスペクティブな検討では，毎週PSLを減量した9例とEULAR recom-

mendationsに従った15例を比較したところ，両者の再燃率に差は認められず，前者で感染症や耐糖能異常の合併が少なかった[12]．

また難治例に対しては免疫グロブリン静注療法やリツキシマブ，インフリキシマブ，MMFが用いられることがある．2010年1月にはEGPAの治療抵抗性神経障害に対して免疫グロブリン静注療法の保険適用が，2013年1月にはGPAとMPAに対してリツキシマブの公知申請が認められた．

本邦のMPAとGPAの治療の実態としては，2006年から2008年までに厚労省のデータベースに登録された938例(MPA 697例，GPA 241例)の解析から，CYの併用率はMPAで22.2%，GPAで58.5%であった．腎機能低下例ではCY併用が行われない傾向にあり，血漿交換が行われるケースがあった(MPAの5.2%，GPAの4.1%で血漿交換が併用されていた)[13]．

現在，難治性血管炎調査研究班において前向き観察コホート研究「ANCA関連血管炎の寛解導入治療の現状とその有効性と安全性に関する観察研究(RemIT-JAV)」，「ANCA関連血管炎・急速進行性糸球体腎炎の寛解導入治療の現状とその有効性と安全性に関する観察研究(RemIT-JAV-RPGN)」，「顕微鏡的多発血管炎の寛解維持に関する観察研究(Co-RemIT-JAV)」が行われており，本邦のAAV患者の特徴や適切な治療の選択，投与量設定やステロイドの減量方法が明らかになることが期待される．

おわりに

血管炎の発症機序については不明な点が多いが，全身の種々の臓器に出血や梗塞を起こしうる疾患であり，診断が遅れれば致命的になる場合がある．血管炎の中でもANCA関連血管炎は本邦で急増しているが，高齢者に発症することが多く，その大半が腎症候を有し，腎病変の程度は腎予後だけでなく，生命予後にも大きく影響することが知られている．原因不明の発熱患者をみた場合，紫斑・血尿・腎機能低下・間質性肺炎など一見脈絡のない多彩な全身症状を認めれば，血管炎を疑い，組織診断を含めた適切な検査で，早期治療につなげることが必要である．

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特集 ◆慢性腎臓病～CKD

慢性腎臓病(CKD)
新たな疾患概念の歴史とその意義

前島 洋平[1)] 槇野 博史[2)]

はじめに

慢性腎臓病(以下，CKD)は，2002年米国腎臓財団(NKF)によって，多くの腎疾患を包含する疾患概念として提唱され，蛋白尿など腎障害を示唆する所見あるいは腎機能の低下が，3か月以上持続する状態と定義されている[1](表)．わが国でも日本腎臓学会を中心にCKD対策・CKD啓発活動が盛んに行われ，近年その重要性が広く認識されるようになった．CKDは，急増する末期腎不全(以下，ESKD)患者の予備軍であること，心血管疾患(以下，CVD)を併発し国民の健康に重大な影響を及ぼすこと，そしてその頻度が予想以上に高いことから，現在CKDへの対策が緊急の課題となっている．

CKDは早期に発見し適切な治療介入を行うことで，ESKDへの移行を阻止し，CVDの発症を予防することが可能である．CKDの概念の導入により，腎臓病に対する認識が非腎臓専門医/かかりつけ医，保健師，栄養士，看護師，薬剤師等の医療従事者，さらには一般住民の間でも深まり，新たな国民病として社会をあげてその対策に取り組むことが，CKD患者の予後改善のために重要である．

表 CKDの定義(日本腎臓学会編：CKD診療ガイド2012より引用，改変)

1. 尿異常，画像診断，血液，病理で腎障害の存在が明らか，特に0.15 g/gCr以上の蛋白尿(30 mg/gCr以上のアルブミン尿)の存在が重要
2. GFR(糸球体濾過量)＜60 ml/min/1.73 m^2

1，2のいずれか，または両方が3か月以上持続する

[日本人のGFR推算式] (eGFR：推算GER)
eGFR(ml/min/1.73 m^2) = 194 × Cr$^{-1.094}$ × Age$^{-0.287}$
(女性は×0.739)

CKDの疾患概念提唱の背景

1. 世界と日本の透析患者数

ESKDにより透析導入・腎移植が必要となる患者数は，世界中で年々増加している．1990～2000年までの10年間で，世界中のESKD患者は43万人から106.5万人に増加した．2008年には，少なくとも165万人程度に増加している．一方，日本透析医学会の統計によると，2011年末の本邦の透析患者数は304,592人となっている(**図1**)[2]．国民の420人に1人が透析療法を受けている計算になり，わが国は世界で有数の透析大国となっている．人口100万人あたりの透析患者数は2,126名であり，台湾に次いで世界第2位である．透析導入に至る原疾患としては，慢性糸球体腎炎から，糖尿病性腎症や高血圧，動脈硬化を原因とする腎硬化症へとシフトしつつあり，

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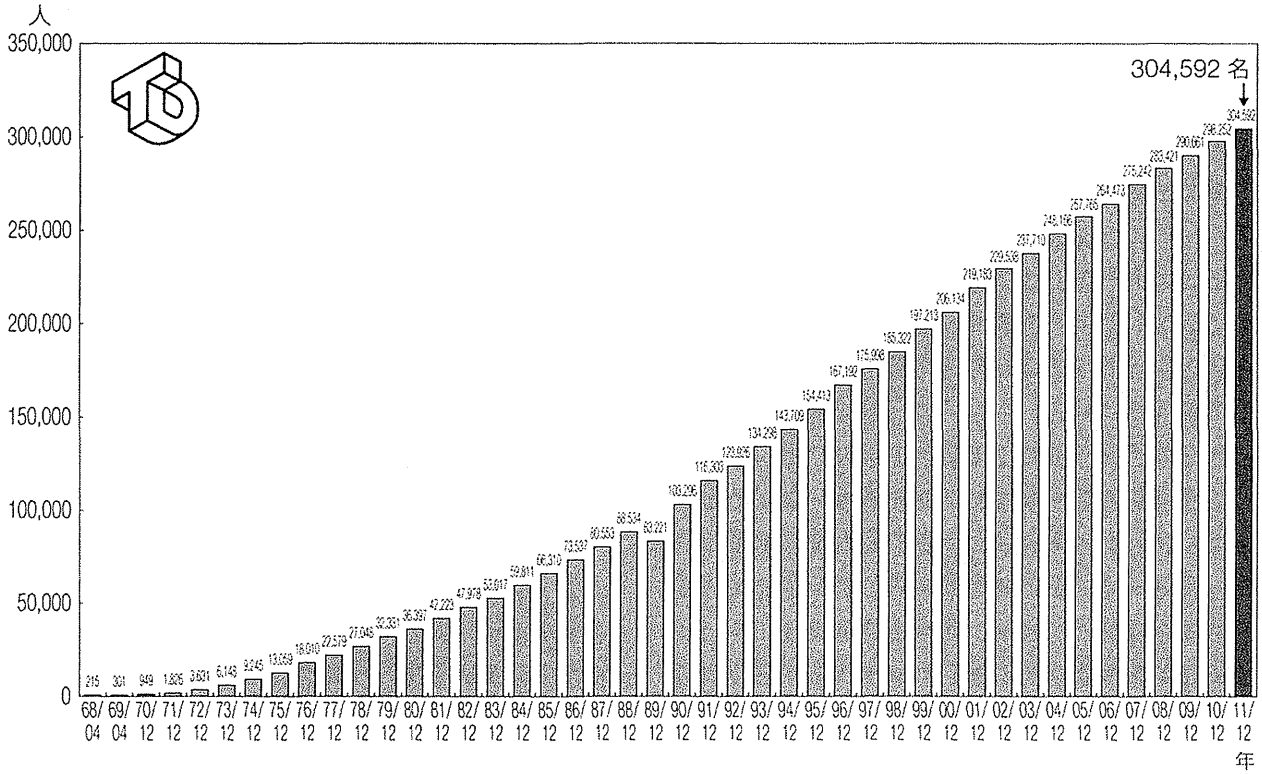

図1　わが国の慢性透析患者数の推移(日本透析医学会統計調査委員会：図説　わが国の慢性透析療法の現況［2011年12月31日現在］を一部改変)

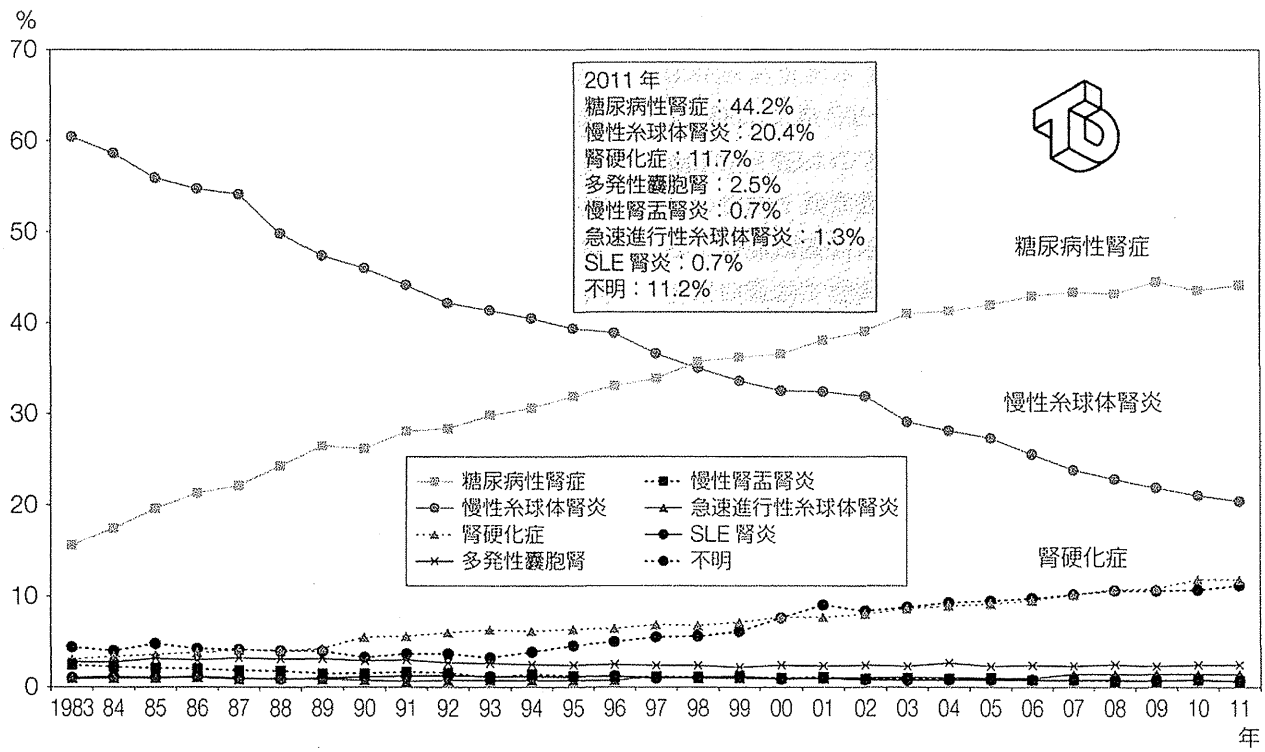

図2　年別透析導入患者の主要原疾患の推移(日本透析医学会統計調査委員会：図説　わが国の慢性透析療法の現況［2011年12月31日現在］を一部改変)

2011年では新規透析導入38,893人のうち，糖尿病性腎症が44.2%，腎硬化症が11.7%と，両者で約56%を占めている(**図2**)[2]．これらの患者では透析導入後も生命予後が不良であり，今後生活習慣病対策がCKDの観点からも重要と考えられる．

2. わが国のCKD患者数

CKDは世界中で増加し続けるESKDの予備軍である．米国の2000年のCKD患者数は成人人口の約13%に該当する2,561万人と推計されている．日本腎臓学会は2005年に全国11か所で行われた約57万人の健診データを用い，わが国のCKD患者数を推定した．この際腎機能の評価には，日本人のGFR(糸球体濾過量)推算式が用いられている．その結果，わが国の成人人口におけるCKD患者数は約1,330万人(12.9%)，実に成人の8人に1人がCKDと推計された[3]．以上より，CKDはcommon diseaseであることが明らかとなった．

3. ESKDへの進展リスクとしてのCKD

進行した腎機能低下はESKDのリスク因子である．GFR 60～69 ml/min/1.73 m^{2}群を基準とし2倍以上の速度でGFRが低下する場合をESKDの危険因子と定義すると，40～69歳でGFR 50 ml/min/1.73 m^{2}以下，70～79歳ではGFR 40 ml/min/1.73 m^{2}以下の場合に，腎機能低下進行のリスクが高かった[4]．一方，蛋白尿は腎機能低下の進行と強い相関があり，CKD診療では蛋白尿の抑制も重要である．わが国のCKD患者のうち，これらESKDへの進展が危惧されるハイリスク患者［eGFR(推算GFR)50 ml/min/1.73 m^{2}未満または蛋白尿陽性のいずれかまたは両方を満たす患者］は，約591万人(成人人口の5.7%)と推計されている．

4. CVDのリスクとしてのCKD

透析患者においては心不全や冠動脈疾患，脳卒中等の発症が多いことが知られていたが，軽度の腎機能低下や蛋白尿もCVDの危険因子であることが明らかとなり，心腎連関・脳腎連関という概念が提唱されている．欧米のCKD患者では，透析導入される患者数よりもCVDにより死亡する患者数の方が多い．わが国でもCVDに関するいくつかの疫学研究結果が報告され，CKDは今や糖尿病と同等のリスク因子と認識されるようになった．

2002年のK/DOQI(Kidney Disease Outcome Quality Initiative)によるCKDの定義では，重症度に関してはGFRのみで区分されていた．2009年のCKDの定義と重症度分類に関するKDIGO(Kidney Disease : Improving Global Outcome)のコントラバシー会議にて，世界中の約156万人のコホートの解析が行われ，eGFRに加えてアルブミン尿が独立した全死亡，心血管死亡の危険因子となることが確認された[5]．その結果，①CKDの原疾患の記載，②ステージ3をeGFR 45 ml/分/1.73 m^{2}にて細分化，③すべてのCKDステージにて尿蛋白の程度を参考とする，というコンセンサスが得られ，新たなCKD重症度分類(KDIGO2009)が提唱された．『CKD診療ガイド2012』[6]においても，上記分類に基づいたCKD重症度分類が新たに示されている．

5. CKDの普及啓発と戦略研究「FROM-J」

CKDは無症状のうちに徐々に進展するため，一般住民における認知度は未だに低いのが現状である．CKD普及啓発の目的で，毎年3月の第二木曜日を世界腎臓デー(World Kidney Day)と制定し，CKD対策のキャンペーンが世界各国で実施されている．

日本慢性腎臓病対策協議会(J-CKDI)はCKD対策の重要性を広く啓発し，その対策を推進する目的で2006年6月に設立された．J-CKDIではCKD啓発イベント講演会を2007年から世界腎臓デーに合わせて開催し，全国各地での世界腎臓デー啓発キャンペーンをサポートしている．2012年には，23都道府県にて世界腎臓デー啓発イベントが開催された．厚生労働省も慢性腎臓病特別対策事業として都道府県単位での地域のCKD対策を支援している．また，厚生労働省科学研究「CKDの普及啓発のあり方に関する研究(秋澤班)」にて，CKD啓発ツール，CKD病診連携マ

ニュアルが作成され，J-CKDI ホームページ上に掲載され，活用されている．

日本腎臓学会は，2007 年および 2009 年に非腎臓専門医/かかりつけ医での CKD 診療レベルの向上を目的に『CKD 診療ガイド』を刊行した．CKD 診療ガイドには CKD の定義，病期分類，診断，治療，フォローアップ等に関して記述されている．2012 年 6 月に改訂版の『CKD 診療ガイド 2012』[6]が刊行されたが，CKD 重症度分類の追加などが行われている．

厚生労働省は戦略研究のテーマとして CKD を採択し，2007 年度より「腎臓病重症化予防のための戦略研究（Frontier of Renal Outcome Modification in Japan : FROM-J）」が開始された．本研究の課題名は「かかりつけ医/非腎臓専門医と腎臓専門医の連携を促進する慢性腎臓病患者の重症化予防のための診療システムの有用性を検討する研究」と定められている．また，成果目標は「慢性腎臓病診療指針の遵守率，達成目標の達成度を上げることにより，5 年後の透析導入患者数を 5 年後に予測される導入数の 15% 減少した値とする」と定められている．筑波大学の山縣邦弘教授を研究リーダーとし，研究が進行している．FROM-J 研究は，2012 年 4 月からは，厚生労働科学研究，そして日本腎臓学会のコホート研究として現在も継続されている．本研究成果に基づく CKD 重症化予防に有用な診療連携システムの構築が期待される．

6. CKD の予防と治療戦略

CKD は，ESKD，CVD 合併ならびに全死亡のリスクを増加させ，医療経済的にも大きな社会的負担となる．一般住民において検診にて CKD ハイリスク群を早期からスクリーニングし，CKD の初期段階でリスク因子に対する適切な治療介入を行うことで，腎機能低下の進行を抑制し，腎不全を予防することが可能になるものと考えられる．また，CKD 診療では心血管イベント発症予防についても留意して管理することが必要である．

岡山市では，国民健康保険（岡山市国保）加入者における透析医療費・透析患者数の増加の背景から，「腎機能低下の予防」を新たな視点に盛り込んだ健診フォローアップ事業「岡山市国保特定健診フォローアップ（CKD 対策）事業」を平成 23（2011）年度より開始している．同事業では，血清 Cr ならびに尿酸値が必須検査項目に追加され，メタボリック症候群非該当の CKD ハイリスク者を含む生活習慣を改善する必要性の高い健診受診者に対し，保健師による保健指導または医療機関の受診勧奨を実施している．

わが国の CKD 患者数は 1,330 万人に上ると推計されるが，腎専門医数は全国で約 3,600 名に留まり，CKD 診療において腎専門医とかかりつけ医との病診連携が必要不可欠と考えられる．上述の，CKD 病診連携マニュアルや，CKD 診療ガイドに基づく，かかりつけ医における CKD 診療水準の向上，腎臓専門医への紹介基準に達した患者さんの紹介システムの普及，病診連携の推進が必要である．岡山市においても，CKD 病診連携の推進と重症化予防を目的に，2007 年に岡山市 CKD 病診連携ネットワーク（OCKD-NET）が設立された．現在岡山大学，岡山市内腎専門医施設，120 以上のかかりつけ医施設が参加している．

CKD の多くは加齢による動脈硬化や高血圧，糖尿病，肥満などの生活習慣病と密接に関連する．このため，まずは食事療法や運動療法を中心とした生活習慣の改善に取り組み，降圧治療，糖尿病や脂質異常症を治療することにより，予後を改善することが重要である．

おわりに

わが国の CKD 対策は日本腎臓学会が中心となり，疫学調査研究，診療システムの構築，社会への働きかけ，国際協調・貢献を 4 つの柱に，総合的に行われてきた．その成果として，日本人に適した GFR 推算式が作成され，膨大な数の CKD 患者の存在が明らかとなった．また，『CKD 診療ガイド』の刊行により，腎専門医・かかりつけ医との病診連携が可能となった．

腎臓病は自覚症状が乏しいため，尿異常や軽度

特集

の腎機能低下があっても放置されやすいが，治療法の進歩により早期に治療介入を行うことで，腎臓病の治療が可能となっている．今後CKDの概念の普及・啓発により，潜在する多くのCKD患者の早期発見，早期治療が可能となり，ひいては透析患者数の減少，CVDの発症抑制に繋がる有用なCKD診療システムの構築と実践が期待される．

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Hypertension Research (2013), 1–7

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ORIGINAL ARTICLE

Significance of estimated salt excretion as a possible predictor of the efficacy of concomitant angiotensin receptor blocker (ARB) and low-dose thiazide in patients with ARB resistance

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The purpose of this study was to assess the factors affecting the efficacy of combination therapy with losartan and thiazide, with a focus on the significance of salt excretion, via a multicenter observational study. Adult patients with essential hypertension showing therapy resistance to angiotensin receptor blocker (ARB) as a monotherapy or in combination with Ca channel blockers (CCB) were enrolled, and their previously administered ARBs were replaced with the combination tablet containing losartan (50 mg per day) and hydrochlorothiazide (12.5 mg per day). Blood pressure and biochemical parameters were monitored for a year. The baseline blood pressure (153.4 ± 14.8/86.4 ± 11.3 mm Hg) was significantly lowered at the 3rd month (137.3 ± 17.4/78.2 ± 11.1 mm Hg, $n=93$) and was maintained at this lower level until the 12th month (135.3 ± 14.0/76.4 ± 11.1 mm Hg, $n=74$). The baseline value of estimated salt excretion (eSE), calculated using Tanaka's formula, differed significantly between the high and low treatment response groups, which were defined by the average change in mean blood pressure (MBP-C, −11.3 mm Hg; eSE = 10.8 ± 2.9 g per day in high responders *vs.* 9.2 ± 2.3 g per day in low responders, $P=0.004$). Univariate and multivariate analyses showed a significant correlation between eSE and MBP-C ($R=-0.288$, $P=0.007$) and indicated the clinical effectiveness of eSE as a possible predictor for MBP-C ($P=0.021$). In addition, the urine Na-to-Cr ratio (NCR) demonstrated significant correlations with eSE ($R=0.848$, $P<0.001$) and MBP-C ($R=-0.344$, $P<0.001$). These results suggest that eSE or NCR could, to a certain extent, predict the efficacy of combination therapy with losartan and low-dose thiazide in patients demonstrating ARB resistance. Combination therapy with losartan and thiazide might thus be suitable for patients with a large amount of salt excretion.
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Keywords: angiotensin receptor blocker; salt excretion; salt sensitivity; thiazide

INTRODUCTION

It has been well established that salt intake is highly related to blood pressure. In general, changes in the body's salt balance should affect the maintenance of blood pressure,[1] and salt load always induces an increase in blood pressure, even in normal subjects.[2] The central role of salt balance or intake on the blood pressure is supported by the observation that a majority of the genetic abnormalities that cause hypertension are closely related to the functional abnormalities involved in the excretion of salt from the kidneys.[3] The role of impaired salt balance in blood pressure elevation is particularly important for Japanese people because the Japanese diet includes large amounts of salt. The recent annual report from the National Institute of Health and Nutrition of Japan showed that the average salt intake in Japanese men and women is 12.0 and 10.3 g per day, respectively, which are near the highest levels among the developed countries.[4] Excess salt intake results in salt accumulation in the body, leading to an increase in the extracellular fluid (ECF) volume and resultant intravascular volume overload.[5] Salt intake or accumulation also generates vascular resistance through cellular atrophy and increased nitric oxide production in the vascular smooth muscle.[6,7] Furthermore, a high salt intake induces pressure natriuresis to accelerate renal salt excretion.[8] All of those factors and mechanisms lead to an elevation of blood pressure. Excessive salt intake is also involved in the activation of the renin–angiotensin system in the blood vessels, brain and kidney,[9] the development of obesity[10] and insulin resistance,[11,12] and the activation of TGF-β[13] or NFκB.[14,15]

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All of those factors also contribute to the elevation of blood pressure. In addition, excess salt intake is known to directly induce blood pressure elevation by increasing the salt concentration in the hypothalamus, which leads to the angiotensin-related activation of the sympathetic nervous system.[16,17] Thiazide, a diuretic agent that mainly demonstrates salt elimination, could decrease the elevated blood pressure by reducing ECF volume and triggering the additional mechanisms indicated above. Indeed, recent large-scale clinical trials have shown that thiazide is clinically effective for the treatment of hypertension.[18]

Angiotensin receptor blockers (ARBs) are now recommended as first-line antihypertensive agents in a variety of guidelines for hypertension therapy in various countries, including in the latest Japanese guidelines (JSH-2009), because ARBs have superior effects on blood pressure and various organ-protective benefits.[19–21] However, ARB monotherapy sometimes fails to achieve a sufficient decrease in blood pressure. Some patients who show resistance to ARB monotherapy might exhibit over-consumption or over-accumulation of salt, which would overcome or cancel the effect of ARBs. Such a pathological setting might be particularly prominent among patients with enhanced salt sensitivity. It is known that resistance to ARB monotherapy is frequently observed in patients with obesity, metabolic syndrome, chronic kidney disease (CKD) or diabetes, and in patients with a high salt intake, all of whom are likely to show enhanced salt sensitivity.[19,20] Consequently, the coadministration of thiazide to patients who exhibit resistance to ARB monotherapy is a suitable strategy to consider. Indeed, ARB and thiazide combination therapy is recommended in a variety of guidelines for hypertension therapy.[19,20] The clinical effectiveness of ARB and thiazide combination therapy would be expected to indicate a correlation between this therapeutic modality and the amount of salt in the body or the amount of salt intake. However, this issue has not been sufficiently analyzed at the clinical level. The present study was designed to study the factors that contribute to decreasing blood pressure by focusing on the correlation between treatment response and salt excretion (or intake) in cases resistant to either ARB monotherapy or combination therapy with an ARB and a Ca channel blocker (CCB) in a multicenter cohort study in Saitama Prefecture in Japan (Saitama Anti-hypertension Losartan-hydrochlorothiazide Trial: the SALT study group). It is hoped that the results will expand our treatment options for patients with ARB-resistant hypertension.

METHODS

Study subjects

This study was conducted at 16 centers participating in the SALT study group (Appendix). The study was performed in accordance with the principles of the Declaration of Helsinki, and the investigational protocol was approved by the Ethics Committee for Human Studies at the Saitama Medical University. Patients who visited one of the participating centers between May 2008 and April 2010, were diagnosed with essential hypertension, and were prescribed an ARB with or without concomitant CCBs for >1 month were considered for screening. Among those patients, adult cases who did not achieve the target blood pressure for anti-hypertension therapy described in the 2004 Japanese Society of Hypertension Guidelines for the Management of Hypertension (≤130/85 mm Hg for young and middle-aged adults and ≤140/90 mm Hg for adults older than 75 years)[22] were considered potential candidates for entry into the trial. All of the enrolled patients provided their informed consent. Patients were excluded from the study if they were taking any type of diuretic or thiazolidinedione and if they exhibited renal insufficiency (serum creatinine >2.00 mg dl^{-1} or estimated glomerular filtration rate (eGFR) <30 ml min^{-1}), heart failure (New York Heart Association functional class III or IV for dyspnea at exertion) or severe liver dysfunction.

Study protocol

After screening, 104 patients were enrolled in the study. Their blood and first morning urine were sampled for baseline biochemical laboratory data, and their ARB regimens were switched to a regimen of concomitant losartan (50 mg per day) and hydrochlorothiazide (HCTZ, 12.5 mg per day) by use of combination tablet. After the medication switch, the enrolled patients were followed up monthly at the individual centers for a 12-month period. The follow-up visits included blood pressure measurement and medical interviews to confirm the absence of adverse effects from the medications. At the 3rd- and 12th-month visits, each patient again provided blood and urine samples for the same measurements that were taken at baseline. During the first 3 months of follow-up, 11 cases were excluded from this study because the patients were not compliant with the medication regimen (4 cases) or because of loss to follow-up due to a move or other causes (7 cases). Consequently, 93 participants (38–95 years old) finished the initial 3-month observation. The baseline characteristics of the 93 participants who were eligible for analysis are provided in Table 1, along with the number and average doses of previously prescribed ARBs. During the next 9 months of follow-up, another 19 patients were excluded from the study because they discontinued the medications (9 cases), were lost to follow-up (9 cases) or withdrew consent (1 case); thus the final group consisted of the 74 participants who were successfully followed up for 12 months. Estimated salt excretion (eSE, g per day) was converted from the value of estimated 24-h Na excretion (24HUNaV), which was determined using the following equation, proposed by Tanaka *et al*:[23]

predicted value of 24-h urine Cr (PRCr, mg per day)
$= -2.04 \times \text{age} + 14.89 \times \text{body weight (kg)} + 16.14 \times \text{height (cm)} - 2244.45$
$24\text{HUNaV (mEq per day)} = (21.98 \times (\text{uNa/uCr}) \times \text{PRCr})^{0.392}$
$\text{eSE (g per day)} = (58.5 \times 24\text{HUNaV})/1000$

Statistical analysis

All biochemical parameters except brain natriuretic peptide (BNP) and the urine albumin-to-creatinine ratio (ACR) are expressed as the means ± s.d. As the BNP and ACR values did not show normal (parametric) distribution, they were expressed as median, first and third quartile values. The significance of the difference for continuous variables with parametric distribution was

Table 1 Baseline characteristics and drug usage in patients over a 3-month observation period

n		93
Age (years)		67.7 ± 12.6
Male (*n*)		55 (59.1%)
BMI (kg m^{-2})		24.6 ± 3.6
Obesity (*n* (%))		32 (34.4%)
Diabetes (*n* (%))		20 (21.5%)
Chronic kidney disease (*n* (%))		21 (22.6%)
Dyslipidemia (*n* (%))		41 (44.1%)
Cerebrovascular diseases (*n* (%))		15 (16.1%)
Acute coronary syndrome (*n* (%))		4 (4.3%)
Pre-prescribed ARB	n *(%)*	*Average doses (mg per day)*
Olmesartan	25 (26.9)	20.0
Losartan	22 (23.7)	50.0
Valsartan	18 (19.4)	92.5
Telmisartan	14 (15.1)	38.7
Candesartan	11 (11.8)	7.6
Irbesartan	3 (3.2)	100.0
Total	93 (100)	—

Abbreviations: ARB, angiotensin receptor blocker; BMI, body mass index.

determined with a paired *t*-test if the analysis of variance (ANOVA) demonstrated equal distribution, and it was determined with Welch's *t*-test if the ANOVA demonstrated non-equal distribution. Analysis of the mean values of unpaired variables with parametric distribution was made using a *t*-test followed by ANOVA. The significance of paired and unpaired variables with non-parametric distribution was evaluated using Wilcoxon's signed-rank test and Mann–Whitney's *U*-test, respectively. For all of the statistical analyses, we used a microcomputer-assisted program with SPSS (Version 10.0) for Windows Xp (SPSS, Chicago, IL, USA), and *P*-values <0.05 were considered significant.

RESULTS

Figure 1 shows the changes in the average systolic blood pressure (SBP) and diastolic blood pressure (DBP) values in the patients who completed the 12-month observation (Figure 1a), and the average changes in blood pressure from the baseline values are also depicted (Figure 1b). In the 3rd month, both SBP and DBP showed a significant decrease from baseline ($153.4 \pm 14.8/86.4 \pm 11.3$ mm Hg at baseline, $137.3 \pm 17.4/78.2 \pm 11.1$ mm Hg in the 3rd month). However, the blood pressures did not change further over the subsequent 9 months ($135.3 \pm 14.0/76.4 \pm 11.1$ mm Hg in the 12th month), indicating that the significant decrease in blood pressures achieved by the losartan and thiazide combination therapy occurred within the initial 3 months. The blood pressure changes in the 3rd month were -16.1 ± 13.6 mm Hg for SBP and -7.9 ± 12.1 mm Hg for DBP, as shown in Figure 1b.

Table 1 shows the baseline characteristics of the enrolled patients who completed the first 3 months of observation (93 cases). The criteria for obesity, diabetes and dyslipidemia were as follows: obesity, body mass index (BMI) $\geqslant 25.0$; diabetes, the use of anti-hyperglycemic medications or fasting blood glucose >125 mg dl^{-1}; dyslipidemia, the use of lipid-lowering medications or total cholesterol $\geqslant 220$ mg dl^{-1} and/or high-density lipoprotein-cholesterol $\leqslant 40$ mg dl^{-1} and/or triglyceride $\geqslant 150$ mg dl^{-1}. The ARBs that the subjects were taking upon enrollment in this study are also listed in Table 1, along with their average doses. Thirty-five patients were concomitantly taking a CCB upon their enrollment in this study; the CCBs used included amlodipine (20 cases, 5.6 mg per day in average), long-acting nifedipine (6 cases, 23.3 mg per day), azelnidipine (5 cases, 12.8 mg per day), benidipine (2 cases, 6.0 mg per day), cilnidipine (1 case, 10.0 mg per day) and nicardipine (1 case, 5.0 mg).

The time-differential changes in the biochemical parameters of the blood and urine tests are summarized in Table 2. The majority of parameters, including serum K, serum uric acid, blood sugar and hemoglobin A1c, did not show significant differences during the observation period. The eGFR based on a Japanese population[24] showed a significant decrease at the 3rd month, although there was no significant difference in eGFR between the 3rd and 12th months. The BNP level and ACR also showed significant decreases in the 3rd month compared with their baseline values, and the ACR showed a further significant decrease in the 12th month compared with its value in the 3rd month.

Mean blood pressure (MBP, shown by $((SBP + DBP) \times 2)/3$) decreased from 109.6 ± 10.7 mm Hg at baseline to 98.2 ± 11.1 mm Hg in the 3rd month, and the average MBP-change was -11.3 ± 11.7 mm Hg. Based on this value, the enrolled patients were divided into two groups, a high treatment response group (MBP-change $\leqslant -11$ mm Hg) and a low treatment response group (MBP-change > -11 mm Hg), to assess possible contributory factors to the reduction in blood pressure, as shown in Table 3. With the exception of DBP and eSE, none of the parameters were significantly different between the two groups. The eSE value in the low-response group was significantly lower than that in the high-response group, indicating that eSE and baseline DBP might be the only parameters that show a significant difference related to the blood pressure-change induced by combination therapy. Subsequently, the correlation between eSE and the change in MBP was assessed using univariate analysis. The results showed that aside from DBP and MBP, eSE was the only parameter to show a significant correlation with MBP change, as Table 4 shows. The baseline eSE also demonstrated a significant correlation with SBP and DBP change in the 3rd month, as demonstrated in Figures 2a and b. To confirm the significance of eSE as a predictive factor for the efficacy of this combination therapy, multivariate analysis was also applied. Parameters that showed a high probability in the univariate analysis or were presumed to be clinically important were examined for their significance as predictor variables. The analysis showed that eSE was the only factor that significantly predicted a change in MBP, with the exception of baseline DBP (Table 4). Additionally, the difference in parameters between the groups with high and low salt excretion was also studied using the enrolled patients' mean eSE value (9.95 ± 2.70 g per day). In the high eSE group, the MBP-change (-14.2 ± 10.6 *vs.* -8.4 ± 11.3 mm Hg, $P=0.013$) and ACR

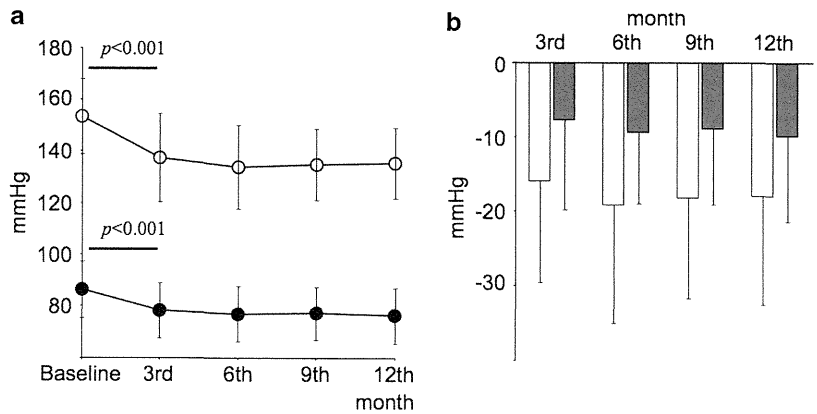

Figure 1 Changes in blood pressure over a 12-month observation period. (**a**) Changes in the average SBP (open circle) and DBP (closed circle), and (**b**) changes in SBP (open bar) and DBP (closed bar) from the baseline values in patients who underwent 12 months of observation ($n=74$) are depicted. The results are expressed as the means ± s.d. DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 2 Changes in biochemical parameters

	0 M (n = 93)	*3 M (n = 93)*	*12 M (n = 74)*
Blood test			
Albumin ($g\,dl^{-1}$)	4.33 ± 0.39	4.28 ± 0.31	4.25 ± 0.40
eGFR ($ml\,min^{-1}$)	78.8 ± 19.8	71.8 ± 19.3**	71.3 ± 0.20.2**
Urea nitrogen ($mg\,dl^{-1}$)	15.5 ± 4.3	17.1 ± 5.0**	16.3 ± 4.3
Uric acid ($mg\,dl^{-1}$)	5.73 ± 1.70	5.63 ± 1.62	5.89 ± 1.73
Na ($mEq\,l^{-1}$)	141.2 ± 1.6	140.1 ± 2.1	140.6 ± 2.4
K ($mEq\,l^{-1}$)	4.27 ± 0.57	4.27 ± 0.60	4.16 ± 0.59
Cl ($mEq\,l^{-1}$)	103.7 ± 2.7	101.9 ± 3.1	102.0 ± 2.5
BNP ($pg\,ml^{-1}$)	22.9 (10.9, 37.7)	16.0 (6.7, 33.6)**	14.4 (5.4, 41.0)**
FBS ($mg\,dl^{-1}$)	119.4 ± 51.8	110.7 ± 33.0	117.6 ± 39.0
A1c (%)	5.4 ± 1.1	5.5 ± 1.0	5.6 ± 1.1
Urine test			
Creatinine ($g\,l^{-1}$)	0.84 ± 0.54	0.80 ± 0.22	0.91 ± 0.59
Na (mEq per g of Cr)	120.8 ± 51.9	130.8 ± 66.5	121.1 ± 57.0
K ($mEq\,l^{-1}$)	35.9 ± 26.9	40.9 ± 30.4	34.4 ± 23.4
ACR (μg per mg of Cr)	11.2 (5.8, 46.3)	8.7 (4.6, 16.5)**	4.6 (2.8, 14.9)**,##

Abbreviations: ACR, albumin-to-creatinine ratio; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; M, months.
Note: Values of BNP and ACR are expressed as the median (1st quartile, 3rd quartile).
*$P<0.05$ *vs.* 0 M, **$P<0.01$ *vs.* 0 M.
#$P<0.05$ *vs.* 3 M, ##$P<0.01$ *vs.* 3 M.

Table 3 Comparative analysis of baseline parameters between high and low responders

	High responders (MBP-change ⩾ −11 mm Hg, n = 46)	*Low responders (MBP-change < −11 mm Hg, n = 47)*
Age (years)	66.1 ± 14.2	69.2 ± 10.6
BMI ($kg\,m^{-2}$)	24.6 ± 3.2	24.5 ± 4.0
SBP (mm Hg)	157.6 ± 14.7	152.3 ± 14.8
DBP (mm Hg)	93.0 ± 11.6	80.9 ± 9.4**
Incidence of diabetes (*n*)	11 (22.0%)	9 (20.9%)
eGFR ($ml\,min^{-1}$)	85.4 ± 26.6	77.9 ± 28.0
Uric acid ($mg\,dl^{-1}$)	5.6 ± 1.6	5.6 ± 1.8
Na ($mEq\,l^{-1}$)	140.9 ± 1.8	141.3 ± 1.6
K ($mEq\,l^{-1}$)	4.22 ± 0.45	4.29 ± 0.61
BNP ($pg\,ml^{-1}$)	23.6 (10.3, 50.3)	22.9 (10.9, 34.96)
A1c (%)	5.34 ± 0.77	5.51 ± 1.24
ACR (μg per mg of Cr)	17.1 (6.0, 53.3)	10.0 (5.6, 26.8)
eSE (g per day)	10.8 ± 2.9	9.2 ± 2.3*

Abbreviations: ACR, albumin-to-creatinine ratio; BMI, body mass index; BNP, brain natriuretic peptide; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; eSE, estimated salt excretion; MBP, mean blood pressure; SBP, systolic blood pressure.
High responders were defined as those with a decline in mean blood pressure of >11 mm Hg over the first 3 months. Values of BNP and ACR indicate median value in addition with 1st and 3rd quartile values in the parenthesis as distribution of those values do not show normal distribution.
*$P<0.05$, **$P<0.01$.

Table 4 Univariate and multivariate analyses the decline of mean blood pressure over a 3-month observation

	Univariate analysis		*Multivariate analysis*		
Parameters (at 0 M)	*Correlation coefficient (R)*	*P-value*	*Partial regression coefficient*	*s.e.*	*P-value*
Age (years)	0.050	n.s.			
BMI ($kg\,m^{-2}$)	0.008	n.s.	0.050	0.336	n.s.
Baseline SBP (mm Hg)	−0.179	n.s.			
Baseline DBP (mm Hg)	−0.565	<0.001	−0.570	0.087	<0.001
Baseline MBP (mm Hg)	−0.511	<0.001			
eGFR ($ml\,min^{-1}$)	−0.067	n.s.	−0.026	0.045	n.s.
Uric acid ($mg\,dl^{-1}$)	0.154	n.s.			
Na ($mEq\,l^{-1}$)	0.009	n.s.			
K ($mEq\,l^{-1}$)	0.149	n.s.			
BNP ($pg\,ml^{-1}$)	−0.064	n.s.	−0.139	2.712	n.s.
A1c	0.001	n.s.			
ACR (μg per mg of Cr)	−0.150	n.s.	−0.061	1.595	n.s.
eSE (g per day)	−0.287	0.007	−0.224	0.412	0.021

Abbreviations: ACR, albumin-to-creatinine ratio; BMI, body mass index; BNP, brain natriuretic peptide; DBP, diastolic blood pressure; eSE, estimated salt excretion; MBP, mean blood pressure; n.s., not significant; SBP, systolic blood pressure.
Coefficient of determination in this model = 0.42.

(17.7, 7.6, 61.4 *vs.* 7.5, 4.9, 16.9 μg per mgCr, indicating median, 1st and 3rd quartile values, $P=0.012$) were significantly higher than in the low eSE group. The efficacy of the urine Na-to-creatinine ratio (NCR) as a substitutional parameter for eSE was also assessed because eSE calculation using Tanaka's formula is still fairly complex for use in clinical settings. The univariate analysis showed a significantly high correlation between eSE and NCR, as shown in Figure 2c. As expected from the correlation between NCR and eSE, significant correlation between NCR and MBP change in the 3rd month was also demonstrated by the univariate analysis, suggesting that the NCR was also useful as a predicting parameter of the efficacy of the losartan/thiazide combination therapy.