Table 2 Pearson correlation between baseline urine cAMP concentration and physiological variables and measures of disease severity

	u-cAMP		u-cAMP/u-Cr	
	R (95 % CI)	*p*	*R* (95 % CI)	*p*
Age	−0.143 (−0.410 to 0.148)	0.334	0.096 (−0.193 to 0.370)	0.515
BMI	0.039 (−0.251 to 0.323)	0.794	−0.100 (−0.376 to 0.193)	0.505
Waist circumference	−0.086 (−0.445 to 0.297)	0.663	−0.292 (−0.600 to 0.091)	0.132
MAP	0.001 (−0.284 to 0.285)	0.997	0.050 (−0.238 to 0.329)	0.738
TKV	−0.104 (−0.377 to 0.186)	0.482	−0.006 (−0.290 to 0.278)	0.967
htTKV	−0.184 (−0.448 to 0.109)	0.215	−0.035 (−0.319 to 0.255)	0.817
eGFR	0.224 (−0.064 to 0.478)	0.126	0.077 (−0.212 to 0.354)	0.602
s-Cr	−0.209 (−0.465 to 0.080)	0.155	−0.150 (−0.416 to 0.141)	0.310
u-Cr	0.595 (0.374–0.752)	<0.001	−0.153 (−0.419 to 0.137)	0.299
Cystatin C	−0.245 (−0.508 to 0.060)	0.114	−0.113 (−0.400 to 0.194)	0.471
NAG	0.465 (0.209–0.662)	<0.001	−0.100 (−0.374 to 0.189)	0.498
s-OSM	−0.217 (−0.474 to 0.075)	0.144	−0.094 (−0.371 to 0.198)	0.528
u-OSM	0.520 (0.236–0.722)	<0.001	−0.193 (−0.486 to 0.140)	0.254
FENa	−0.460 (−0.658 to −0.202)	0.001	0.005 (−0.280 to 0.289)	0.973

CI Confidence interval

Table 3 Pearson correlation between baseline urine copeptin concentration and physiological variables and measures of disease severity

	u-copeptin		u-copeptin/u-Cr	
	R (95 % CI)	*p*	*R* (95 % CI)	*p*
Age	−0.023 (−0.305 to 0.449)	0.878	0.189 (−0.101 to 0.449)	0.198
BMI	0.111 (−0.283 to 0.386)	0.458	0.005 (−0.283 to 0.292)	0.974
Waist circumference	0.052 (−0.455 to 0.417)	0.792	−0.098 (−0.455 to 0.285)	0.618
MAP	0.098 (−0.156 to 0.372)	0.507	0.134 (−0.156 to 0.403)	0.363
TKV	0.261 (0.075–0.508)	0.073	0.351 (0.075–0.578)	0.014
htTKV	0.261 (−0.028 to 0.510)	0.076	0.383 (0.107–0.604)	0.008
eGFR	−0.153 (−0.542 to 0.138)	0.301	−0.304 (−0.542 to −0.022)	0.036
s-Cr	0.114 (−0.094 to 0.386)	0.441	0.195 (−0.094 to 0.454)	0.184
u-Cr	0.324 (−0.592 to 0.557)	0.025	−0.370 (−0.592 to −0.096)	0.010
Cystatin C	0.183 (−0.003 to 0.458)	0.241	0.298 (−0.003 to 0.549)	0.052
NAG	0.465 (−0.344 to 0.662)	<0.001	−0.066 (−0.344 to 0.222)	0.654
s-OSM	0.198 (0.020–0.459)	0.183	0.306 (0.020–0.545)	0.037
u-OSM	0.200 (−0.593 to 0.492)	0.234	−0.333 (−0.593 to −0.010)	0.044
FENa	−0.161 (0.002–0.129)	0.274	0.286 (0.002–0.527)	0.049
u-cAMP	0.527 (0.285–0.380)	<0.001	0.108 (−0.182 to 0.380)	0.467
u-cAMP/u-Cr	0.361 (0.086–0.658)	0.012	0.460 (0.202–0.658)	0.001

CI Confidence interval

and NAG ($R = 0.465$, $p < 0.001$). U-copeptin/u-Cr was significantly inversely correlated with u-Cr ($R = -0.370$, $p = 0.010$).

Discussion

The relationship between renal function, TKV and cAMP, plasma copeptin in ADPKD patients

In ADPKD, disease progression causes decreased urinary concentrating capacity [12]. Binding of AVP to the V2R at collecting duct cells causes an increase in intracellular cAMP, which then leads to proliferation of epithelial cells and fluid secretion into cysts. However, the use of u-cAMP as a marker of AVP activity remains controversial [17]. Hypertonic saline infusion does not affect u-cAMP in patients with ADPKD [20]. In this study, we failed to show statistical correlations between u-cAMP, u-cAMP/u-Cr and markers of disease severity including TKV, htTKV and eGFR. Therefore, we regretfully conclude that cAMP is not useful as a surrogate marker of ADPKD disease progression.

Plasma copeptin and GFR were significantly associated in ADPKD patients, but not in renal donors without

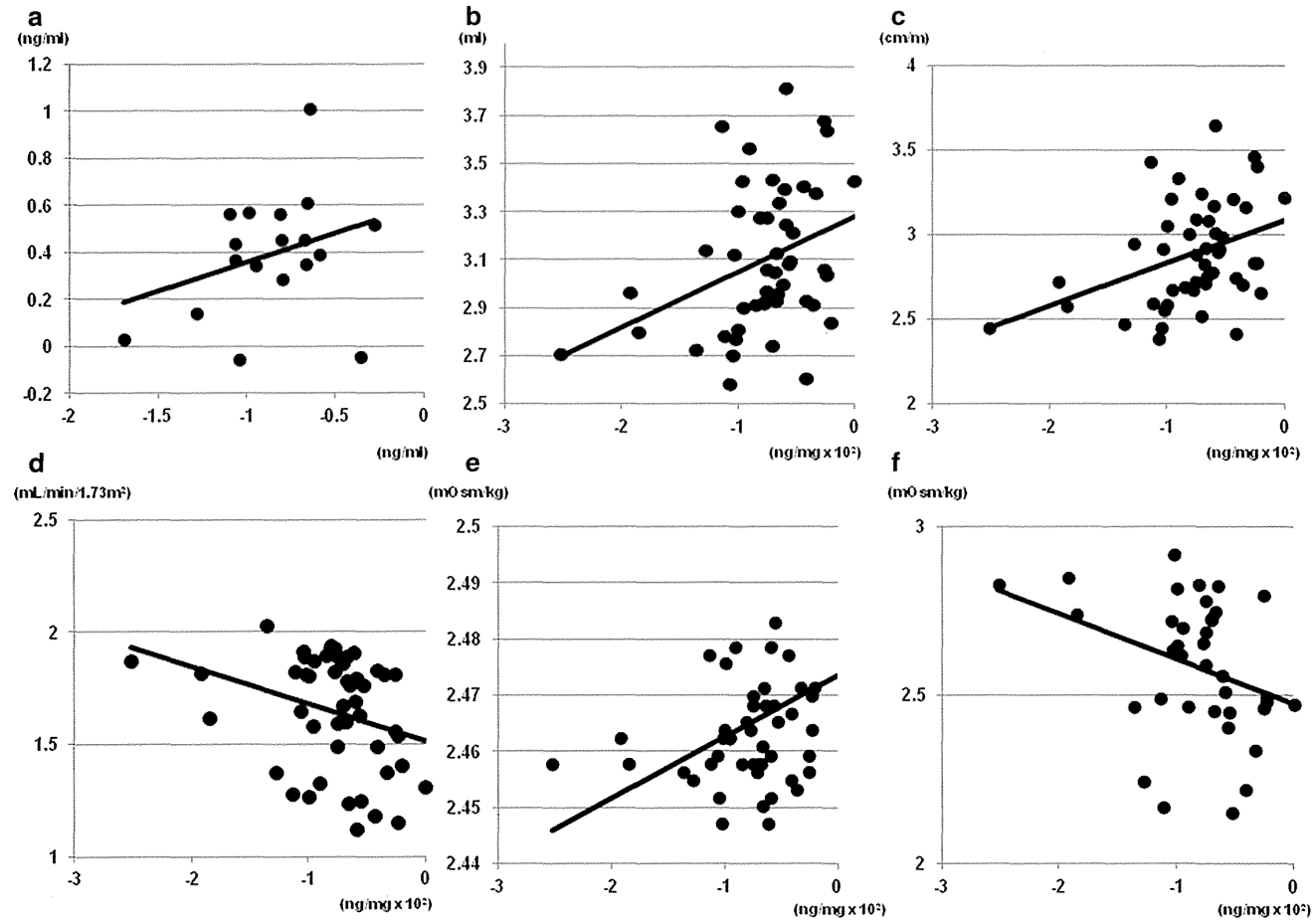

Fig. 1 Scatter plots for correlation between u-copeptin/u-Cr and markers of disease severity. **a** plasma copeptin: $R = 0.318$ (95 % CI; −0.174 to 0.684) $p = 0.198$. **b** TKV: $R = 0.351$ (95 % CI; 0.075–0.578) $p = 0.014$. **c** htTKV: $R = 0.383$ (95 % CI; 0.107–0.604) $p = 0.008$. **d** eGFR: $R = -0.304$ (95 % CI; −0.542 to −0.022) $p = 0.036$. **e** s-OSM: $R = 0.306$ (95 % CI; 0.020–0.545) $p = 0.037$. **f** u-OSM: $R = -0.333$ (95 % CI; −0.593 to −0.010) $p = 0.044$

ADPKD [13]. Several previous studies reported that in ADPKD patients, plasma copeptin level is associated with rate of kidney function decrease [12, 21–23]. As indicated in this study, it was also reported that a higher TKV was independently associated with higher plasma copeptin levels [11]. Boertien WE et al. [10] reported that the higher the baseline copeptin concentration, the more measured GFR decreased and the more TKV increased, independent of age, sex, and kidney risk factors.

Validity of u-copeptin as a surrogate marker of ADPKD

Analysis of urine can offer a non invasive means to detect changes in the expression of proteins [24]. In contrast to other body fluids such as serum or plasma, urinary proteins do not undergo detectable degradation by endogenous proteases after voiding, thus minimizing the bias introduced by preanalytical sample handling [24].

Unfortunately, there is no literature concluding how copeptin is cleared from the body. Copeptin has a molecular weight of 5 kDa [6] and consequently is subjected to glomerular filtration. Taking the undeniable effect of urine volume into account, we evaluated not only u-copeptin but also u-copeptin/u-Cr, as has been done with albuminuria. Results of this study and previous reports suggest that decreased renal clearance may lead to higher plasma copeptin values and, consequently, higher u-copeptin/u-Cr values.

With respect to TKV, urinary copeptin and urinary copeptin/u-Cr correlated with TKV in this study, although these correlations were moderate. We therefore chose htTKV as a surrogate marker, as it has recently been shown to be a strong predictor of the development of stage 3 and 4 KDOQI CKD within 8 years in ADPKD patients [25]. In this study, a linear model to predict htTKV achieved a high accuracy.

It is a clinically accepted fact that patients with ADPKD already have decreased urinary concentrating capacity [26] at a young age [27], and that plasma osmolality is maintained within the normal range at the cost of higher plasma copeptin and AVP levels [18]. Boertien et al. [10] show that in relatively early stage ADPKD, plasma copeptin levels, as a marker for AVP, are not associated with plasma osmolality. However, in another study involving different populations, the same group found a significant association between plasma copeptin level and plasma osmolality [11]. On the other hand, two other studies performed in patients without ADPKD investigating the association between plasma osmolality and plasma copeptin level showed that in accordance with normal physiology, the higher the plasma osmolality, the higher the plasma copeptin level [21, 28]. Given these previous observations, it is difficult to conclude whether or not there is statistical relationship between plasma osmolality and plasma copeptin level in ADPKD. Our data indicated that u-copeptin/u-Cr was significantly positively associated with s-OSM and negatively associated with u-OSM. Previous report that maximal urinary concentration capacity was lower in ADPKD patients [18] may be consistent with our data of inversely significant correlation between u-copeptin/u-Cr and u-OSM.

Although several reports evaluate urine copeptin in model animals [29, 30], as far as we know, ours is the first report indicating the usefulness of u-copeptin as a valuable novel biomarker to identify ADPKD disease progression. Unlike previous studies involving plasma copeptin in patients in a relatively early phase of disease [18], ours enrolled ADPKD patients with CKD stage ≤ 4. As mentioned above, the novel treatment of V2R antagonist for ADPKD with CKD stage ≤ 4 began in Japan under national health insurance in 2014. Therefore, it may be possible to use u-copeptin/u-Cr as a therapeutic response evaluation of this therapy.

We acknowledge that this study has limitations. First, little is known about the freeze–thaw durability of urine copeptin. Second, patients were allowed to drink ad libitum in this study. After 14 h of water deprivation, ADPKD patients tended to have higher plasma osmolality and significantly higher plasma AVP and copeptin levels, whereas u-OSM was similar in ADPKD patients and controls [18]. Differences in hydration status between individuals may be lead to variability in urine copeptin concentration. We do not yet know how urine copeptin values might change following water load or deprivation. On the other hand, it is known from previous studies that plasma copeptin values can decrease very quickly after a water load [6], suggesting extrarenal clearance as the predominant clearance mechanism [10]. The relationship between u-copeptin and limitations on liquid intake should be the subject of a future investigation. Third, we do not know about u-copeptin values in healthy controls and patients with CKD other than ADPKD. It was reported that plasma copeptin is unspecific for ADPKD and mostly shows considerable overlap with healthy controls [31]. Therefore, from this study, one may not be able to conclude whether or not urine copeptin is a specific marker for ADPKD, or a marker for chronic kidney disease progression in general. Fourth, mainly because of a small number cases with preserved blood plasma ($n = 18$), we could not show the significant correlations between u-copeptin and plasma copeptin. The relationship between plasma copeptin and u-copeptin will be one of the agenda to be examined in the future. Fifth, no sex-based differences in u-copeptin values were found in this study. On the other hand, it was reported that plasma copeptin concentration was higher in men than in women [11]. Unfortunately, at present, we cannot determine the cause of this outcome. Hereafter, we should explore the root causes of this difference. Sixth, as a matter of course, we should perform validation analysis. Replication of our findings must precede their clinical usage.

In conclusion, our results suggest that u-copeptin/u-Cr might be a convenient and easily measured surrogate marker to help predict disease progression in ADPKD. It is tempting to hypothesize that, in ADPKD patients, a u-copeptin increase could be used as a surrogate marker to predict the treatment efficacy with respect to renoprotection.

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Conflict of interest Honoraria: Satoru Muto, Shigeo Horie (Otsuka Pharmaceutical); Subsidies or Donations: Satoru Muto, Haruna Kawano, Shigeo Horie (Otsuka Pharmaceutical); Endowed departments by commercial entities: Shigeo Horie (Otsuka Pharmaceutical); Travel fees, gifts, and others: Satoru Muto, Shigeo Horie (Otsuka Pharmaceutical).

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厚生労働科学研究費補助金　難治性疾患等政策研究事業（難治性疾患政策研究事業）

資　料

市民公開講座

「腎臓を守ろう!」～腎臓病・糖尿病とともに生きる～

とき

9/20(土)

12:00開場　13:00開演
［15:25終了予定］

近ごろ「高血圧が続く」「タンパク尿が出ている」などといった症状はありませんか。腎臓病の症状は悪くなってもあまり自覚症状がなく見過ごされるケースが多くあります。腎臓病の早期発見と治療を呼びかける専門医による講演会を開催します。日常の注意点から治療方法まで、役立つ情報が満載です。

ところ

朝日ホール

名古屋市中区栄1-3-3 朝日会館15階
＊地下鉄東山線・鶴舞線「伏見」駅下車
7番出口を西へ徒歩3分
＊JR「名古屋」駅下車徒歩15分

主な内容

＊腎臓病の各専門医による講演
＊食品サンプリング・
展示ブースの設置


坪井 直毅先生


古市 賢吾先生


丸山 彰一先生


小関 裕二先生


佐藤 和一先生


鈴木 富夫先生

プログラム

講演1 13:05	「気になる腎臓のはなし」(15分) 名古屋大学 腎臓内科 講師 坪井 直毅先生
講演2 13:20	「糖尿病からあなたの腎臓を守りましょう!」(20分) 金沢大学附属病院 血液浄化療法部 准教授 古市 賢吾先生
講演3 13:40	「腎炎・ネフローゼってどんな病気?」(20分) 名古屋大学 腎臓内科 准教授 丸山 彰一先生
14:00	～ 休 憩 (20分) ～
講演4 14:20	「より良く生活習慣を変えましょう!」(20分) 増子記念病院 リハビリテーション科 課長 小関 裕二先生
講演5 14:40	「腎不全を正しく知ろう!」(20分) 藤田保健衛生大学 腎内科 准教授 佐藤 和一先生
講演6 15:00	「腎臓にやさしい食事」(20分) 名古屋大学 栄養管理部 副部長 鈴木 富夫先生

セミナー参加者300名様無料ご招待!

応募方法

郵便番号、住所、氏名、年齢、電話番号、参加希望人数(5名様まで)を明記の上、往復はがき、FAX、e-mailのいずれかで下記のあて先までお送りください。
※往復はがきで応募の方は、返信用はがきにもあなたの郵便番号、住所、氏名を記入。

あて先

◎往復はがき　〒466-8550
名古屋市昭和区鶴舞65番地
名古屋大学医学部附属病院 腎臓内科
「腎臓病・糖尿病セミナー」係
◎FAX　052-744-2209
◎e-mail
jin-shogai@med.nagoya-u.ac.jp

※応募締め切り／9月12日(金)必着

応募多数の場合は抽選とします。
当選者の発表は招待状の発送をもってかえさせていただきます。
※お送りいただきました個人情報は、名古屋大学でとりまとめ、案内状の発送および個人を特定しないデータとして利用させていただきます。

お問い合わせ先

名古屋大学医学部附属病院 腎臓内科
TEL(052)741-2111(代表)
◎9:00～17:00(土・日・祝を除く)

◎主催　厚生労働科学研究費補助金難治性疾患等政策研究事業（難治性疾患政策研究事業）「難治性腎疾患に関する調査研究」班／厚生労働省科学研究費補助金難治性疾患等克服（腎疾患対策）研究事業「糖尿病性腎症ならびに腎硬化症の診療水準向上と重症化防止にむけた調査・研究」班／日本慢性腎臓病対策協議会(J-CKDI)
◎協賛　MSD、興和創薬、三和化学研究所、第一三共、大日本住友製薬、帝人ファーマ、バクスター
◎後援　朝日新聞社広告局

※プログラム及び講師につきましては変更する場合もありますので、あらかじめご了承ください。

jin-shogai.jp/mt/public/hp/

厚生労働科学研究費補助金難治性疾患政策研究事業

難治性腎疾患に関する調査研究

お問い合わせフォーム

文字サイズを変更 | 小 | 中 | 大 |

【IgA腎症・急速進行性糸球体腎炎・ネフローゼ症候群・多発性嚢胞腎】症例数が少なく、原因が不明で、治療法が確立されていない疾患で、長期間生活に支障を及ぼすものについて、研究班を設置し、原因の究明・治療法の確立に取り組む、厚生労働省の事業。

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- 疾患登録・調査研究分科会 【急速進行性糸球体腎炎ワーキンググループ】(12 / 8)

【病気の解説】

- IgA腎症 IgA nephropathy
- 急速進行性糸球体腎炎 Rapidly progressive glomerulonephritis; RPGN
- ネフローゼ症候群 Nephrotic syndrome
- 多発性嚢胞腎 Polycystic kidney disease

症例数が少なく、原因が不明で、治療法が確立されていない疾患で、長期間生活に支障を及ぼすものについて、研究班を設置し、原因の究明・治療法の確立に取り組む、厚生労働省の事業。

→ 詳細を見る

◆疾患登録・疫学調査研究分科会

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難治性腎疾患に関する調査研究班 班長 松尾清一

国民の皆さんや腎臓病と闘っておられる患者さんに貢献できるよう、活動しています。

→ 研究班班長のご挨拶

月別アーカイブ

- 2014年12月(12)
- 2013年7月(1)
- 2013年2月(2)
- 2012年11月(1)
- 2012年9月(1)
- 2012年3月(6)
- 2012年2月(4)
- 2012年1月(1)

患者様向けQ&A