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Hyperfiltration in Diabetic Patients Associated With Mild Hyponatremia

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Abstract

Glomerular hyperfiltration found in diabetic patients is recognized as an early renal alteration and reversible stage of kidney damage, but details have not yet been studied. We investigated the relation among estimated glomerular filtration rate (eGFR) and many factors such as age, HbA1cvalue, blood urea nitrogen (BUN) concentration, Na and K concentrations in serum of Japanese diabetic patients to investigate the characteristics of hyperfiltration [1]. Hyperfiltration (eGFR ≥ 120 ml/mini/1.73 m^2) was found in six among 60 diabetic patients investigated, and Na concentrations in five patients with hyperfiltration were slightly lower than the reference range of Na concentration (138-145 nmol/L), whereas their K concentrations were within the reference range (3.6-4.9 nmol/L), but significantly lower than those of diabetic patients with normal- and hypofiltration. In contrast, the Na and K concentrations in more than half of patients with normal-and hypofiltration have low Na concentration and high K concentration as compared with these reference ranges. Thus, mild hyponatremia with a relatively lower concentration of K seems to be the characteristic symptoms of hyperfiltration among diabetic patients [2]. BUN concentrations in five patients with hyperfiltration were normal level (below 20 mg/dL), whereas those in the patients with severe hypofiltration (eGFR < 30 ml/mini/1.73 m^2, n=4) were higher than 50 mg/dL. Thus, renal dysfunction estimated by BUN concentration could not be seen in most patients with hyperfiltration, whereas the patients with severe hypofiltration are thought to have chronic kidney disease [3]. No correlation was found between eGFR and HbA1c values of the patients with hyperfiltration. These results are consistent with previous findings that renal dysfunction of diabetic patients with hyperfiltration is mild, an early stage and recoverable.

Introduction

Diabetes mellitus (DM), commonly known as diabetes, is a group of metabolic disorders characterized by a high blood sugar level over a prolonged period of time. There are two main types of diabetes: type 1 (T1 DM) and type 2 (T2 DM). T1 DM results from the pancreas's failure to produce enough insulin due to the loss of beta cells in the pancreas. T2 DM begins with insulin resistance, a condition in which the cells fail to respond to insulin properly, and a lack of insulin may also develop as the disease progresses.

Glomerular filtration rate (GFR) in healthy subjects generally declines with an increase of age. The 5th and 95th percentiles of estimated GFR (eGFR), calculated from control subjects of Japanese without pre-diabetes and pre-hypertension, decrease 0.5-0.6 mL/min/1.73 m^2 per year, during 20 and 89 years [4-7]. In contrast, the decrease of eGFR is faster in diabetic patients (1.34 mL/min/1.73 m^2 per year) than healthy subjects, and resulted in subsequent kidney damage which is characteristic of hypofiltration in chronic kidney disease (CKD) and end-stage renal disease [1,7,12].

Glomerular hyperfiltration is well-recognized as an early renal alteration and reversible stage of kidney damage, which precedes the onset of albuminuria, following the decline of GFR and CKD [19]. Hyperfiltration is frequently found in T1 DM and T2 DM [1,8,15,19], and prevalence of hyperfiltration occurred in T1 DM and T2 DM were 27 % and 16 %, respectively [19]. There is no widely accepted threshold of hyperfiltration: so far we know, the lowest threshold is above 120 ml/min/1.73 m^2, and the highest threshold is above 140 ml/min/1.73 m^2 [19]. Mechanisms underlying the hyperfiltration in DM have not yet been well understood [8,16,19], but one plausible mechanism is increased proximal tubular reabsorption of glucose and Na [1,15,16].

As glucose is an osmotically active substance, hyperglycemia increases serum osmolarity, resulting in movement of water out of the cells and subsequently in a decrease of serum Na concentration by dilution, where glucosuria-induced osmolarity increases serum K concentration by the redistribution of K from the intracellular to the extracellular compartment [9,18]. The alteration of Na and K concentrations in the serum of diabetic patients is closely linked to one another, namely hyponatremia with hyperkalemia, and hypernatremia with hypokalemia, and those changes are found in the patients before tight control of glycemic levels [18]. On the other hand, so far we know, the changes of Na and K concentrations owing to hyperfiltration, which occurred in an early stage of renal disfunction, have not yet been reported.

Hyperkalemia is associated with not only hyperglycemia but also reduced glomerular filtration of K due to acute kidney injury and CKD [9]. Furthermore, taking drugs of antihypertensive and potassium-sparing diuretics which decrease the K excretion induce hyperkalemia, whereas some diuretic drugs increase the K excretion resulting in hypokalemia and taking exogenous insulin can induce mild hypokalemia. In contrast, taking drugs such as hypoglycemics, and diuretics could induce hyponatremia [9].

Blood urea nitrogen (BUN) and creatinine (Cre) are useful and simple biomarkers used as indexes of diabetic nephropathy [2,3,22]. According to Chutani and Pande (2017), BUN and Cre

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concentrations are correlated with the HbA1c values. The ratio of BUN to Cre concentration (BUN/Cre) is used to estimate the type of azotemia: This ratio of more than 20 indicates the possibility of prerenal failure, the ratio between 10 and 20 indicates the possibility of normal or postrenal failure, and below 10 indicates the possibility of renal failure [4,20].

In the present study, we investigated the medical chart of 60 diabetic patients, calculated their eGFR from the Cre concentrations in serum, and classified to the patients with hyper-, normal- and hypofiltration. We compared many factors, such as the Na, K, BUN, and Cre concentrations, BMI and HbA1c values in serum, and age of the patients with hyper-, normal-, and hypofiltration, respectively, and investigated the typical symptom related to the hyperfiltration.

Material and Methods

Ethics statement

This research project and associated consent procedures were approved by the Human Research Ethics Committee of the Graduate School of Pharmaceutical Sciences, Health Sciences University of Hokkaido (No.15P004), and the Nikko Memorial Hospital (No. 80). All participants of DM provided their written informed consent to participate in this study.

Diabetic patients

Surveys from medical charts of diabetic patients from males (n=36) and females (n=24) were conducted mostly in August 2014 from Nikko Memorial Hospital (Hokkaido prefecture, Japan). Information on diabetic males and females is shown in supplemental Tables 1 and 2, respectively. All patients investigated were T2 DM, but the duration of DM therapy was unknown. Most DM patients participated in our previous studies of hair analyses [5]. All patients except for one (RF14B, see Table 1) took an antihyperglycemic drug, and some patients took the diuretic and/or antihypertensive drugs.

eGFR was calculated by serum Cre concentration (mg/dL) and age (years), according to the following equation for Japanese [11].

$$eGFR = 194 \times Cre^{-1.094} \times Age^{-0.287} \text{ (x 0.739 if the subject is female)}$$

The values of eGFR were considered “very low” (severe hypofiltration) and “very high (hyperfiltration)” when eGFR was less than 30 mL/min/1.73 m^2 and above 120 mL/min/1.73m^2, respectively [2,5,17].

Statistical analyses

Data were analyzed by student-t test using the Statcel 2 program (add-in software on Excel, OMS, Japan), with a value of $p<0.05$ considered to be significant. Data were expressed by the mean ± S.D. with outlier (s).

Results

General information

Figure 1 illustrates the data of male and female patients (age, BMI, HbA1c, eGFR, Na, K, Cre, and BUN) using box plots with outlier (s) which are listed in Tables 1 and 2. Patients with outliers in K concentration and eGFR value are listed in Tables 3-6. No significant difference between male and female patients was observed in those items, even considering some outliers.

The ages of male and female patients were 63.1 ± 12.2 (36-85, n=36) years and 68.9 ± 13.6 (40 -95, n=24) years, respectively (Figure 1).

The BMI of female patients (16.8-39.5 kg/m^2) was widely ranged than that of male patients (16.5-34.2 kg/m^2): The BMI of males was 23.3 ± 3.5kg/m^2 (n=35) with an outlier (RF14I, 34.2kg/m^2) and that of females was 26.2 ±6.8 (n=24) kg/m^2, respectively; twelve males and eleven females exceeded the reference range of BMI (17.5-25.0 kg/m^2), respectively. Especially, one male and eight females exceeded 30 kg/m^2. On the other hand, one male (RF14A7, 16.5 kg/m^2) and two females (RF14II, 16.8 kg/m^2; RF14BB, 17.1 kg/m^2) were below the reference range.

The HbA1c values of male and female patients were 9.5 ± 2.3 (6.8-15.3, n=36) % and 9.8 ± 2.1 (6.7-14.3, n=24) %, respectively; eleven males and nine females exceeded 10 %, and the highest value was found in the male patient at 15.3 % (RF14EE).

The Na concentrations in serum of male patients were 137±3.3 (n=35) nmol/L with an outlier (RF14EE, 125nmol/L) and those of

Table 1: Information for the Male Diabetic Patients.

	Sex	Age (y)	BMI (kg/m^2)	HbA1c (%)	Na (nmol/L)	K (nmol/L)	BUN (mg/dL)	Creatine (mg/dL)	eGFR (mL/min/1.73m^2)
RF14A	M	75	23.0	8.7	139	**5.4**	**27.0**	1.09	51.1
RF14B	M	54	19.9	8.2	**134**	4.0	9.7	0.56	116.4
RF14I	M	43	**34.2**	8.6	140	4.1	12.6	0.85	78.7
RF14J	M	63	22.5	9.2	**134**	4.1	17.7	0.70	85.0
RF14N	M	70	23.9	8.3	143	**3.4**	15.5	**1.28**	43.7
RF14O	M	55	**27.5**	8.2	138	4.1	10.8	0.61	105.5
RF14R	M	77	21.8	11.3	140	**3.5**	**54.7**	**3.86**	**12.7**
RF14S*	M	61	23.1	12.9	**134**	**5.1**	16.4	0.72	116.7
RF14V*	M	40	**25.2**	9.6	**135**	3.9	14.0	**0.55**	**129.4**
RF14W	M	65	23.1	8.0	140	4.2	15.2	0.75	80.2
RF14X	M	67	22.2	8.7	**135**	**5.0**	**28.1**	**1.15**	49.8
RF14Y	M	36	**26.2**	14.4	138	4.1	8.5	**0.50**	**148.1**
RF14Z	M	66	**25.4**	10.2	140	3.8	19.0	0.62	98.3
RF14AA	M	47	**26.6**	12.0	**136**	4.8	19.5	0.93	69.6
RF14EE	M	56	22.8	15.3	**125**	4.7	17.3	0.73	90.3
RF14GG	M	56	**29.3**	7.6	**136**	4.7	19.5	1.02	44.7
RF14HH	M	52	23.7	12.7	**130**	**5.0**	16.1	0.68	95.2
RF14KK	M	75	21.5	14.3	143	3.8	16.6	**0.57**	103.9
RF14LL	M	85	17.7	8.2	134	4.9	**23.2**	0.78	71.1
RF14MM	M	84	22.6	7.5	138	3.9	12.9	0.78	71.4
RF14NN	M	71	24.3	11.0	**136**	4.2	15.3	0.70	84.3
RF14PP	M	61	20.3	8.9	138	4.2	19.4	**0.57**	104.3
RF14QQ*	M	82	19.9	7.7	**133**	**5.2**	**79.0**	**1.83**	**28.8**
RF14RR*	M	70	21.3	8.3	138	4.3	20.0	**1.73**	32.1
RF14SS	M	74	21.6	8.7	141	**5.2**	16.2	0.92	63.3
RF14VV*	M	72	**28.0**	8.2	139	4.2	19.1	0.65	84.0
RF14WW*	M	70	17.7	6.8	**136**	3.7	12.6	**0.50**	**122.3**
RF14YY*	M	50	**29.8**	9.3	**134**	3.7	**21.5**	**1.83**	32.6
RF14ZZ*	M	79	18.8	7.0	**136**	3.7	13.6	0.65	96.8
RF14AAA	M	66	**26.0**	10.6	**137**	4.0	8.7	0.65	86.1
RF14BBB	M	67	23.6	8.6	**137**	4.4	13.3	0.70	85.7
RF14EEE	M	37	20.1	12.9	**135**	4.5	14.1	0.65	101.7
RF14A3	M	44	**27.2**	8.3	140	4.3	**26.6**	**1.78**	34.4
RF14A4	M	63	**29.7**	7.9	145	**5.0**	**50.9**	**2.77**	**19.2**
RF14A5	M	70	18.6	8.0	142	4.6	14.8	0.87	66.7
RF14A7	M	68	**16.5**	7.1	**136**	4.0	**28.4**	0.44	**141.9**
	Mean	63.1	23.3	9.5	137	4.4	17.1	0.86	78.5
	SD	12.2	3.5	2.3	3.3	0.5	5.3	0.39	34.7

*The patient who took diuretic and/or antihypertensive agent

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Table 2: Information for the female diabetic patients.

	Sex	Age (y)	BMI (kg/m²)	HbA1c (%)	Na (nmol/L)	K (nmol/L)	BUN (mg/dL)	Creatine (mg/dL)	eGFR (mL/min/1.73m²)
RF14C	F	69	**35.9**	8.3	139	**5.4**	15.4	0.64	39.0
RF14D	F	79	24.2	6.7	144	3.7	19.2	0.51	87.3
RF14F	F	66	**30.7**	7.9	141	4.2	9.2	0.59	75.3
RF14G	F	55	**32.9**	13.8	**137**	4.3	12.3	0.45	108.7
RF14H	F	59	**33.9**	11.8	140	4.6	12.6	0.48	99.3
RF14K	F	71	24.2	8.9	**137**	4.1	15.7	**1.09**	38.0
RF14L	F	56	28.1	9.9	**132**	4.6	11.1	0.44	110.9
RF14P*	F	84	**29.3**	8.8	140	4.0	18.1	**1.06**	37.7
RF14Q	F	66	18.9	11.5	139	4.7	17.1	0.53	92.0
RF14T	F	83	**33.6**	8.1	144	**3.4**	19.0	**0.90**	45.3
RF14U	F	49	20.8	10.1	141	4.0	13.2	0.47	107.2
RF14BB	F	46	**17.1**	10.1	**125**	**3.5**	**61.0**	**4.29**	**9.7**
RF14CC	F	66	**25.9**	9.8	**137**	3.9	11.9	**0.34**	**140.2**
RF14DD	F	60	**33.3**	10.3	140	4.4	**23.5**	**1.15**	36.3
RF14II	F	73	**16.8**	14.3	**137**	4.8	14.3	0.54	82.1
RF14JJ	F	75	20.1	7.9	139	4.1	16.5	0.48	92.7
RF14OO*	F	66	23.4	9.8	**136**	3.7	**21.3**	0.81	55.0
RF14TT	F	79	**35.2**	9.2	**136**	4.1	14.6	0.56	71.5
RF14UU	F	40	21.4	13.1	**135**	4.1	11.4	**0.28**	**200.2**
RF14XX	F	78	20.8	7.3	142	3.8	16.5	0.75	52.4
RF14DDD	F	75	22.1	7.8	144	**3.3**	4.9	0.54	88.6
RF14A1	F	95	17.6	7.5	**137**	4.2	**29.0**	**0.86**	43.5
RF14A2	F	76	**39.5**	8.9	139	3.7	12.1	0.75	52.8
RF14A6	F	88	22.8	12.2	139	4.5	16.5	0.57	69.4
	Mean	68.9	26.2	9.8	139	4.1	15.4	0.64	71.1
	SD	13.6	6.8	2.1	3.0	0.5	5.2	0.24	31.7

*The patient who took diuretic and/or antihypertensive agent

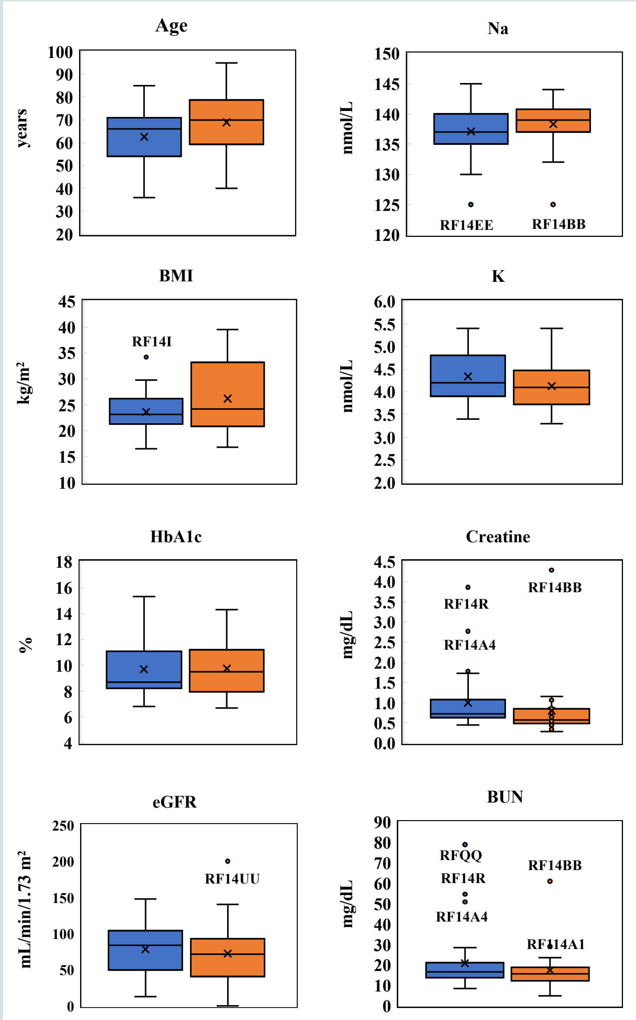

Figure 1: Comparison of age, BMI, HbA1c, Na, K, eGFR, creatine and BUN between the diabetic males (blue, n=36) and females (orange, n=24).

female patients were 139±3.0 (n=23) nmol/L with an outlier (RF14BB, 125 nmol/L); nineteen males and ten females including RF14EE and RF14BB were below the reference range of Na concentration (138-145 nmol/L). On the other hand, none of patients exceeded the reference range of Na concentration.

The K concentrations in serum of male and female patients were 4.4± 0.5 (3.4-5.4, n=36) nmol/L and 4.1 ± 0.5 (3.3-5.4, n=24) nmol/L, respectively; seven males and one female exceeded the reference range of K concentration (3.6 -4.9 nmol/L), whereas two males and three females were below the reference range. Those patients with hyper- and hypokalemia were listed in Tables 3 and 4, respectively.

The eGFR v alues of male patients, calculated from their Cre concentrations, were79 ± 35 (12.7-148, n=36) mL/min/1.73 m², and those of female patients were 71 ± 32 (9.7-140, n=23)mL/min/1.73 m² with an outlier (RF14UU, 200.2mL/min/1.73 m²).

Hyperfiltration (eGFR ≥120 mL/min/1.73 m²) was found in four male and two female patients (Table 5). The highest eGFR value (200.2mL/min/1.73m²) was found in the youngest female patient with HbA1c value and Na concentration being 13.1 % and 135 nmol/L (RF14UU, 40 years), respectively, and the second highest (148.1mL/min/1.73m²) was found in the youngest male patient with HbA1c and BMI values being 14.4% and 26.2 kg/m² (RF14Y, 36 years), respectively. The HbA1c values of patients with hyperfiltration (n=6) scattered a relatively wide range of 6.8-14.4 % (Table 5).

Hypofiltration (less than 60 mL/min/1.73 m²) was found in 10 male and 10 female patients. Especially, severe hypofiltration (less than 30 mL/min/1.73m²) was found in three male patients and one female patient (Table 6), and their HbA1c values were scattered relatively in a narrow range (7.7-11.3 %). The lowest eGFR value at 9.7 mL/min/1.73 m² was found in the female patient (RF14BB): BUN concentration and HbA1c value in her serum were 61.0 mg/dL and 10.1 %, respectively, but she hadn't had artificial dialysis yet.

The BUN concentrations of male patients were 17.1 ± 5.3 mg/dL (n=33) with three outliers (RF14A4, 50.9mg/dL; RF14R, 54.7 mg/dL; RF14QQ, 79.0 mg/dL) and those of female patients were 15.4 ± 5.2 (n=22) with two outliers (RF14A1,29.0 mg/dL; FR14BB, 61.0 mg/dL). Among those five outliers, nine were the same patients with hypofiltration as listed in Table 4. Nine male and four female patients exceeded the upper range of BUN concentration (8-20 mg/dL). On the other hand, the lowest BUN concentration (4.9 mg/dL) was found in a female patient (RF14DDD) with K concentration being 3.3 mg/dL (hypokalemia) and the ratio of BUN to Cre (BUN/Cre) is being 9.1.

The Cre concentration of male patients was 0.86 ± 0.39 mg/dL(n=34) with two outliers (RF14A4, 2.77 mg/dL; RF14R, 3.86mg/

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Table 3: List of patients with hyperkalemia.

		Age (y)	BMI (kg/m$^{2)}$	HbA1c (%)	Na (nmol/L)	K (nmol/L)	BUN (mg/dL)	Cre (mg/dL)	BUN/Cre	eGFR (mL/min/1.73m^2)
Male	RF14A	75	23.0	8.7	139	5.4	27.0	1.09	24.8	51.1
	RF14X	67	22.2	8.7	135	5.0	28.1	1.15	24.4	49.8
	RF14HH	52	23.7	12.7	130	5.0	16.1	0.68	23.7	95.2
	RF14QQ	82	19.9	7.7	133	5.2	79.0	1.83	43.2	28.3
	RF14SS	74	21.6	8.7	141	5.2	16.2	0.92	17.6	63.3
	RF14A4	63	29.7	7.9	145	5.0	50.9	2.77	18.4	19.2
Female	RF14C	69	35.9	8.3	139	5.4	15.4	0.64	24.1	39.0

Table 4: List of patients with hypokalemia.

		Age (y)	BMI (kg/m$^{2)}$	HbA1c (%)	Na (nmol/L)	K (nmol/L)	BUN (mg/dL)	Cre (mg/dL)	BUN/Cre	eGFR (mL/min/1.73m^2)
Male	RF14N	70	23.□	8.3	143	3.4	15.5	1.28	12.1	43.7
	RF14R	77	21.8	11.3	140	3.5	54.7	3.86	14.2	12.7
Female	RF14T	83	33.6	8.1	144	3.4	19.0	0.90	21.1	45.3
	RF14BB	46	17.1	10.1	125	3.5	61.0	4.29	14.2	9.7
	RF14DDD	75	22.1	7.8	144	3.3	4.9	0.54	9.1	88.6

Table 5: List of patients with hyperfiltration.

		Age (y)	BMI (kg/m$^{2)}$	HbA1c (%)	Na (nmol/L)	K (nmol/L)	BUN (mg/dL)	Cre (mg/dL)	BUN/Cre	eGFR (mL/min/1.73m^2)
Male	RF14V	46	25.2	9.6	135	3.9	14.0	0.55	25.5	129.4
	RF14WW	70	17.7	6.8	136	3.7	12.6	0.50	25.2	122.3
	RF14A7	68	16.5	7.1	136	4.0	28.4	0.44	64.5	141.9
	RF14Y	36	26.2	14.4	138	4.1	8.5	0.55	15.5	148.1
Female	RF14CC	66	25.9	9.8	137	3.9	11.9	0.34	35.0	140.2
	RF14UU	40	21.4	13.1	135	4.1	11.4	0.28	6.5	200.2

Table 6: List of patients with severe hypofiltration.

		Age (y)	BMI (kg/m$^{2)}$	HbA1c (%)	Na (nmol/L)	K (nmol/L)	BUN (mg/dL)	Cre (mg/dL)	BUN/Cre	eGFR (mL/min/1.73m^2)
Male	RF14R	77	21.8	11.3	140	3.5	54.7	3.86	14.2	12.7
	RF14A4	63	29.7	7.9	145	5.0	50.9	2.77	18.4	19.2
	RF14QQ	82	19.9	7.7	133	5.2	79.0	1.83	43.2	28.8
Female	RF14BB	46	17.1	10.1	125	3.5	61.0	4.29	14.2	9.7

dL) and that of female patients was 0.64 ± 0.24 mg/dL (n=23) with an outlier (RF14BB, 4.29mg/dL). Seven males were below the lower range of Cre concentration for males (0.6-1.1 mg/dL), and two females were below that of females (0.4-0.8 mg/dL); as a matter of course, most of those patients having low Cre concentrations were the patients with hyperfiltration (Table 5).

Sodium and potassium concentrations in serum of diabetic patients and classified by HbA1c and eGFR values

Figure 2 shows the scatter plot of Na and K concentrations in serum of male and female diabetic patients. The dotted square indicates the normal ranges of Na concentration (138-145 nmol/L) and K concentration (3.6-4.9 nmol/L) in serum, and the plotted patients were classified by HbA1c levels (left figure) and eGFR levels (right figure).

Male and female patients tended to have low Na concentration (hyponatremia), and many male patients and one female patient have high K concentration (hyperkalemia): Twenty-three among 36 male patients and 13 among 24 female patients were scattered outside of the square. Some male patients with HbA1c value exceeded 10% were distributed outside the upper left corner of the square (hyponatremia and hyperkalemia), whereas one female patient with HbA1c value which exceeded 10% was distributed outside the low-left corner of the square. Negative correlations ($p < 0.05$) were found between Na concentration and HbA1c value of both male patients and female patients. A positive correlation ($p < 0.05$) was found between K concentration and HbA1c value of female patients, but not of male patients.

Of the four male patients with hyperfiltration (above 120 mL/min/1.73m^2, Table 5), three were distributed outside of the low-left corner of the square (RF14V, RF14WW and RF14A7) and one was distributed inside of the low-left corner of the square (RF14Y). Similarly, two female patients with hyperfiltration distributed outside of the low left corner of the square (RF14CC and RF14UU). The Na concentrations in the patients with hyperfiltration (n = 6) and those with normal- and hypofiltration (n =54) were similar (136 ± 1.1 vs 137 ± 4.1 nmol/L), whereas the K concentrations in the patients with hyperfiltration (n = 6) was significantly lower than those (n =54) (3.9± 0.1 vs 4.3 ± 0.5 nmol/L).

The Na concentrations of male (RF14EE) and female (RF14BB) patients were very low (125 mmol/L) which were shown as the

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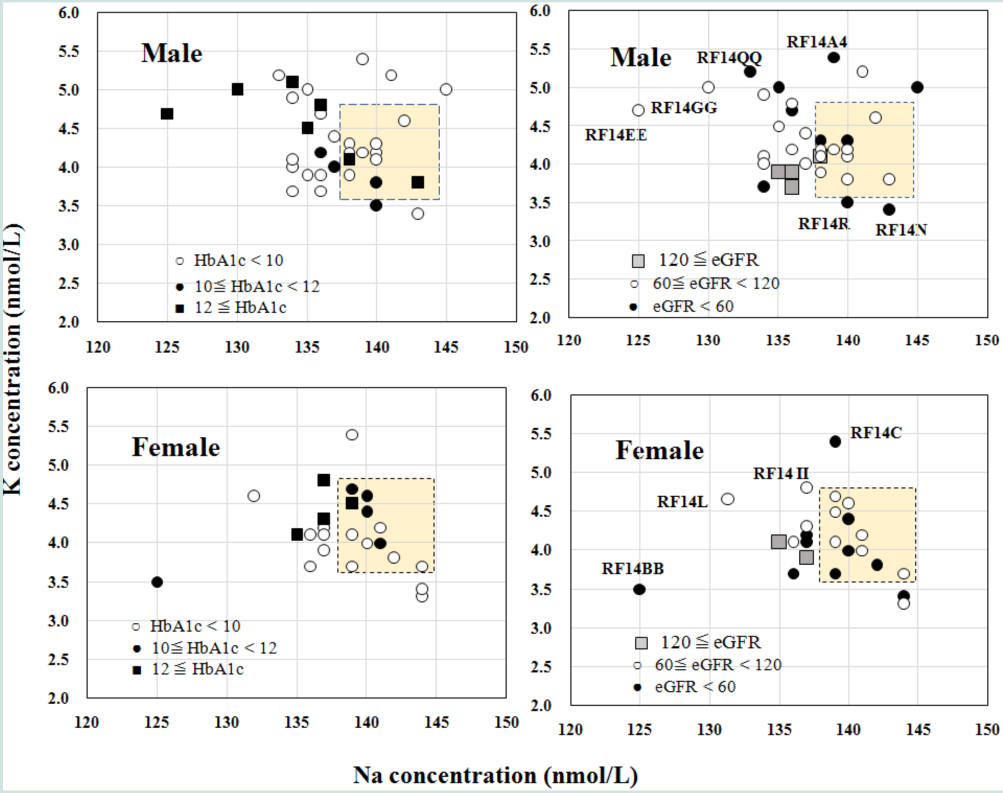

Figure 2: Na and K concentrations in serum related to HbA1c and eGFR values in diabetic male and female patients.

outliers of Na concentration (Figure 1). This male patient (RF14EE) had the highest HbA1c value (15.3 %), and the female patient (RF14BB) had the lowest eGFR value (9.7 mL/min/1.73 m^2). The male patient took insulin preparation, biguanide and sulfonylurea drugs and the female patient took DPP-4 inhibitor, without any diuretic and antihypertensive drugs.

Relationship among Cre, BUN and eGFR

Figure 3 shows scatter plot of Cre and BUN concentrations of male and female patients, and the numbers shown in this figure are eGFR values (mL/min/1.73m^2). In both male and female patients, strong positive correlations were found between Cre and BUN concentrations ($p < 0.01$), whereas, as data not shown in Figure, strong negative correlations were found between BUN concentration and eGFR value ($p < 0.01$) and between Cre concentration and eGFR value ($p < 0.01$).

All patients except for one (RF14BB) distributed the above area of the line of Y=10X (BUN/Cre>10), and about half were distributed the above area of the line of Y=20X (BUN/Cre>20).

All patients with severe hypofiltration (eGFR values of RF14BB, RF14R, RF14A4 and RF14QQ were 9.7, 12.7, 19.2 and 28.8 mL/min/1.73m^2, respectively) were distributed at the outside of normal ranges of Cre concentration (below 1.1 mg/dL for males and 0.8 mg/dL for females) and BUN concentration (below 20 mg/dL), and the ratios of BUN/Cre in those patients were 14.2-43.2.

All patients with hyperfiltration except for one (RF14A7, 141.9 mL/min/1.73m^2) were distributed in the normal ranges of BUN and Cre concentrations.

Of seven patients having high K concentration (5 ≤nmol/mL, Table 3), five were distributed in the area above the line of Y=20X (BUN/Cre > 20), and two were distributed in the areas lightly below this line. On the other hand, the patients having low K concentration (3.5 > nmol/mL, Table 4) were distributed in the area between two lines (Y = 10X and Y = 20 X). The ratios of BUN/Cre in both male patients and female patients have significantly correlated their K concentrations ($p < 0.05$).

Age-dependent decreases of HbA1c and eGFR values, and hyperfiltration

The age-dependent decreases of HbA1c and eGFR values in male and female diabetes are shown in upper and lower figures, respectively (Figure 4).

The HbA1c values of both male and female patients decreased with ages (upper figure, $p < 0.05$ and 0.01, respectively); about 0.7% of HbA1c values decreased per decade in male and female patients.

The eGFR of male and female patients shown by the solid lines decreased with the ages (lower figure). However, the slope of females ($Y = -1.38X + 171$, $p < 0.05$) was slightly steeper than that of males ($Y = -0.79X + 129$, $p < 0.10$). The dotted lines indicate the 5th and 95th percentiles of eGFR of combined control subjects from male

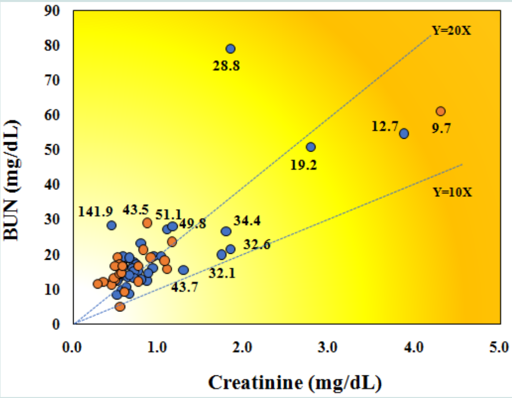

Figure 3: Relationship between creatinine and BUN concentrations in serum of male (●) and female (●) patients. The numbers in figure are eGFR values.

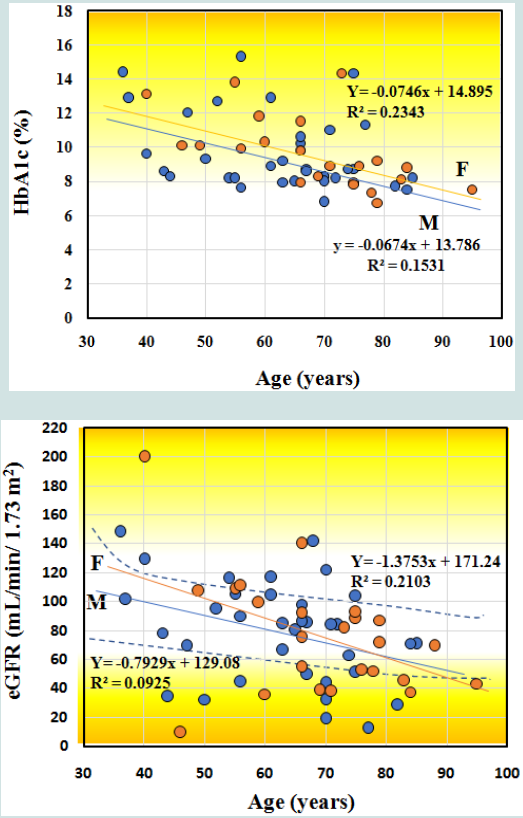

Figure 4: HbA1c and eGFR values of diabetic patients as a function of age. Solid lines in upper and lower figures represent the regression lines of males (M ●) and females (F ●). Broken lines in lower figure represent the 5% and 95% tiles of control subjects reported by Okada et al. (2012).

and female at 20-89 years without pre diabetes and pre hypertension (Okada et al., 2012). Those dotted lines showing the 5th and 95th percentiles of control subjects decreased slightly with age; those slopes were about from -0.5 to -0.6 mL/min/1.73 m^2/year. The slopes of diabetic patients of males and females in this study (-1.38 mL/min/1.73 m^2/year and -0.79 mL/min/1.73 m^2/year, respectively) were apparently steeper than those of 5th and 95th percentiles of control subjects.

Seven male patients and three female patients exceed the dotted line of 95th percentile of eGFR value, of which included three males (RF14KK, RF14B and RF14S had 103.9, 116.4 and 116.7 mL/min/1.73m^2, respectively) and one female (RF14G had 108.7 mL/min/1.73m^2), although their eGFR values were below 120 mL/min/1.73m^2. On the other hand, ten male and seven female patients were below the dotted line of the 5th percentile of eGFR value, respectively, although the eGFR values of seven males and six females were above30 mL/min/1.73m^2, respectively.

Discussion

All patients with hyperfiltration exceeded 120 mL/min/1.73 m^2 (four males and two females) characteristically have low Na concentration (135-138 nmol/L) (mild hyponatremia, whereas the K concentrations in the patients with hyperfiltration were normal range of K concentration, but significantly lower than those with normal- and hypofiltration (Figure 2). Three of six patients with hyperfiltration took antihyperglycemic drug (DPP-4 inhibitor, SGL2 inhibitor and/or metformin) and the other three took both insulin preparation and diuretic drug (furosemide, spironolactone and/or tolvaptan), and most of the patients with normal- and hypofiltration took the same or similar drugs. Thus, mild hyponatremia with a relative lower K concentration in the serum seems to be the characteristic symptoms of diabetes with hyperfiltration. So far we know, we first report the symptoms of hyperfiltration. The low Na concentration and high K concentration in serum were observed in many diabetic male patients (Figure 2). In agreement, Ishikawa et al. (1994) and Saito et al. (1999) found the hyponatremia with hyperkalemiaor the hypernatremia with hypokalemia in the patients of uncontrolled hyperglycemia.

The highest hyperfiltration was found in the youngest female, 40 years old (RF14UU, 200.2 mL/min/1.73m^2) among 24 female patients who participated in this study (40-90 years), and the second-highest was youngest male, 36 years old (RF14Y, 148.1 mL/min/1.73m^2) among 36 male patients (36-85 years). In agreement, Jerums et al. (2010) reported that the prevalence of hyperfiltration is markedly higher in T2 DM under 40 years than that over 65 years.

We found the negative correlation between Na concentration and HbA1c value in both male patients and female patients ($p < 0.05$) and the positive correlation between K concentration and HbA1c value in female patients ($p < 0.01$), although such correlations were not found in the patients with hyperfiltration (n = 6). Similarly, Saito et al. (1999) reported the negative correlation between serum Na concentration and fasting plasma glucose (FPG) of diabetic patients and the positive correlation between serum K concentration and FPG.

We choose the threshold of hyperfiltration above 120 mL/min/1.73 m^2 which is the lowest threshold among several thresholds so far defined previously (Tonneijack et al., 2017). All thresholds of hyperfiltration previously defined had not accounted for the age-related decrease in GFR values. Okada et al. (2012) advocated the use of 5th and 95th percentile of age-relate GFR values for the thresholds of hypofiltration and hyperfiltration, respectively (Figure 4). The slopes of decreasing eGFR values owing to the ageing of male and female patients in this study were slightly steeper than those of the 5th and 95th percentiles of control values which were calculated from enormous control subjects without prediabetes and prehypertension (Okada et al., 2012). If the exceeding 95th percentile is the threshold

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of hyperfiltration, three male patients (RF14B, RF14S and RF14KK) and one female patient (RF14G) will be additionally diagnosed to the diabetic patients with hyperfiltration even though their eGFR values were below 120 ml/min/1.73m^2 (Figure 4); two male patients had low Na concentration (134 nmol/L), and other male and female patients had high values of HbA1c (14.3 %) and BMI (32.9 kg/m^2), respectively. The renal function of all patients with hyperfiltration defined by exceeding 95th percentile is believed to be normal or reversible stage of kidney damage as their BUN values except for one (RF14A7) did not exceed the limit of 20 mg/dL. Okada et al. (2012) suggest that identifying patient with hyperfiltration is an important and effective preventative strategy of CKD.

BUN is widely used as index of diabetic nephropathy [2,3,20,22]. The four highest BUN values (50.9, 54.7, 61.0 and 79.0 mg/dL) were found in the patients with serve hypofiltration (eGFR was less than 30 mL/min/1.73 m^2, Table 4) and with hypo- or hyperkalemia (Tables 3 and 4). Significant negative correlations between eGFR and BUN values were found in both male patients and female patients ($p < 0.01$). Although we had expected the negative correlation between HbA1c and eGFR values, the negative correlation was not found, probably because the hyperfiltration found in early stage of diabetic patients does not relate to the HbA1c values.

Hyperkalemia was found in six male and one female patient (Table 3). Among those patients, four patients had BUN values exceeding the limit at 20 mg/dL and five patients had hypofiltration (less than 60 mL/min/1.73m^2). However, no correlation was found in the patients between BUN and eGFR values, probably because they took some antihypertensive drugs and/or diuretic drugs.

HbA1c values in diabetic patients of males (63.1 ± 12.2 years) and females (68.9 ±13.6 years) decreased with increases in age (Figure 4), which is thought to be the reduction of red blood cell numbers due to the aging [21]. In contrast, HbA1c value in control subjects tends to slightly increase with age, inferring the deterioration of glucose tolerance with age [10,14,23]. *i.e.* the average HbA1c value is about 5.0 % for control subjects under 40 years and 5.5 % over 70 years [14].

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