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HYPOURICEMIA IN HOSPITALIZED DIABETIC PATIENTS

MASAO KANAUCHI, TADATOSHI KIKAWA, HISAYUKI NISHIOKA, TAKAHIRO KAWANO, TAKASHI FUJIMOTO, HIDEO SHIIKI and KAZUHIRO DOHI

First Department of Internal Medicine, Nara Medical University

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Abstract: To determine the incidence and clinicopathological characteristics of hypouricemia in patients with diabetes mellitus, we studied 473 consecutive hospitalized diabetic patients. The incidence of hypouricemia, defined as a serum urate concentration below 2.0 mg/dl, was 1.9% (9 patients). In this group (2 males, 7 females), there were no patients receiving drugs known to reduce serum urate concentration. Two of the 9 patients had neoplastic disease, while the others suffered from no other disorder known to affect serum urate levels. Four patients exhibited glomerular hyperfiltration. Three of the 9 patients were studied in more detail by renal biopsy, and all had mild to moderate glomerular diffuse lesions and tubulointerstitial lesions, such as interstitial fibrosis or mononuclear cell infiltration. These findings suggest that the glomerular hyperfiltration which accompanies diabetic nephropathy and functional abnormality of tubular urate handling due to tubulointerstitial involvement contribute to hypouricemia in diabetic patients.

Index Terms

diabetes mellitus, hypouricemia, uric acid

INTRODUCTION

Hypouricemia is found in approximately 1～2% of hospitalized patients[1,2]. There are various causes of hypouricemia, including Fanconi's syndrome[3], Wilson's disease[4], neoplastic disease[5], liver cirrhosis[6], xanthine dehydrogenase deficiency[7], purine nucleoside phosphorylase deficiency[8], and familial renal hypouricemia[9]. Diabetes mellitus is also known to cause hypouricemia[10-12]. However, the clinicopathological significance of hypouricemia in diabetics has not been fully determined. The purpose of this study was to clarify the incidence and clinicopathological features of hypouricemia in hospitalized diabetic patients.

SUBJECTS AND METHODS

A total of 473 consecutive diabetic patients hospitalized in the First Department of Internal Medicine of Nara Medical University Hospital were evaluated retrospectively. Clinical backgrounds for these subjects are listed in Table 1. Serum urate concentrations were determined by uricase peroxidase assay at the time of admisson as part of initial assessment. The distribution of serum urate concentrations was examined; patients receiving medications known to affect serum urate concentration, including allopurinol, benzbromarone, and probenecid, were evaluated separatedly. Hypouricemia was defined as a serum urate concentration below 2.0 mg/dl. When significant hypouricemia was noted, the medical records of the patient were examined to determine the condition responsible for hypouricemia. If an obvious

cause of hypouricemia other than diabetes could be ascertained, the patient was excluded from the study. The clinical manifestations of hypouricemic patients were summarized, and pathological findings were evaluated for patients who underwent renal biopsy.

RESULTS

The distribution of serum urate concentrations is shown in Fig. 1. The incidence of hypouricemia was 1.9% (9 patients). In this group (2 males, 7 females), there were no patients receiving drugs known to reduce serum urate concentration. The diabetic patients with hypouricemia were separated into two groups, those with (2 patients) and those without (7 patients) known causes of hypouricemia. In the former group, both patients had neoplastic disease (one had a mediastinal tumor, probably malignant lymphoma, and the other had renal pelvic cancer). Table 2 shows the clinical characteristics of the 7 diabetic patients with hypouricemia who suffered from no other disorder affecting serum urate levels. Only one patient (case 1) exhibited poor glycemic control at the time of admission. Four patients (cases 1, 2, 4 and 9) had glomerular hyperfiltration, considering their elderly age. Three of the 7 subjects (cases 1, 2, 3) were studied in more detail by renal biopsy (Table 3). All three of these patients had both mild to moderate glomerular diffuse lesions, and tubulointerstitial lesions, such as interstitial fibrosis or mononuclear cell infiltration.

Table 1. Patient characteristics

Items		Number	(%)
Gender	Male	286	(60.5)
	Female	187	(39.5)
Age (yo)	10-19	2	(0.4)
	20-29	2	(0.4)
	30-39	14	(3.0)
	40-49	68	(14.4)
	50-59	130	(27.5)
	60-69	145	(30.7)
	70-79	100	(21.1)
	>80	12	(2.5)
Type	NIDDM	464	(98.1)
	IDDM	9	(1.9)
Duration of diabetes (yrs)	<5	165	(34.9)
	5- 9	90	(19.0)
	10-14	80	(16.9)
	15-19	39	(8.2)
	20-24	22	(4.7)
	>25	19	(4.0)
	unknown	58	(12.3)
Therapy	Diet alone	100	(21.2)
	Oral agent	171	(36.1)
	Insulin	202	(42.7)

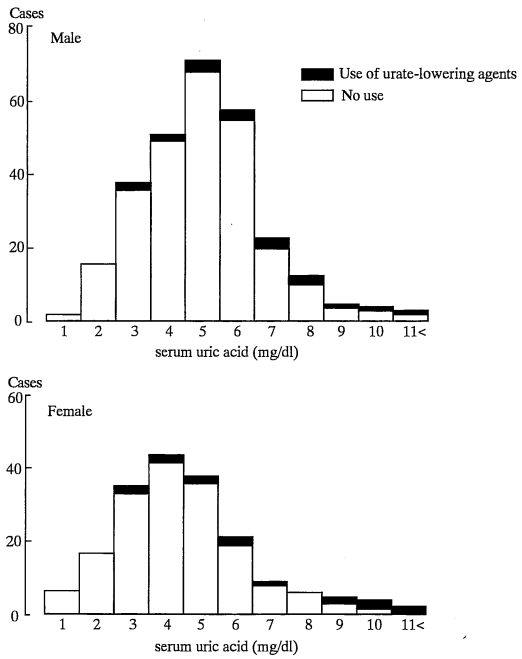

Fig. 1. The distribution of serum urate concentrations.

Table 2. Clinical characteristics of diabetic patients with hypouricemia

Case	Age	Sex	UA (mg/dl)	Duration of diabetes (yrs)	FBS (mg/dl)	HbA1c (%)	Scr (mg/dl)	Ccr (ml/min)	Therapy	Underlying disease
1	46	F	1.9	20	133	15.8	0.3	122	insulin	none
2	63	M	1.8	5	236	7.9	0.6	125	insulin	none
3	49	F	1.7	12	233	8.5	0.3	85	SU	none
4	62	F	1.5	17	291	6.4	0.3	126	insulin	none
5	71	F	1.6	12	137	6.4	0.4	75	SU	none
6	51	M	1.8	unknown	116	6.6	1.4	92	diet	none
7	74	F	1.4	unknown	169	7.1	1.0	ND	diet	mediastinal tumor
8	62	F	1.5	4	155	7.2	0.7	54	diet	pelvic cancer
9	45	F	1.6	3	79	5.7	0.2	177	diet	none

Abbreviations are : UA, uric acid ; FBS, fasting blood suger ; Scr, serum creatinine ; Ccr, creatinine clearance ; SU, sulfonyl urea ; ND, not determined.

Table 3. Summary of light microscopic findings

Case	Glomerular lesions		Tubulointerstitial lesions		Vascular lesions
	Diffuse	Nodular	Fibrosis	Cellular infiltration	
1	III	I	+	++	III
2	II	I	+	++	II
3	II	0	+	+	II

The severity of glomerular diffuse lesions was graded using Gellman's criteria as D I (segmental widening of mesangial area) ; DII (moderate enlargement of mesangial area observed in a diffuse pattern) ; DIII (mesangial area increased and capillary wall diffusely thickened). The severity of nodular lesions was also graded using Gellman's criteria as N0 (no nodule) or N I (a single nodule in occasional glomeruli).

Tubulointerstitial fibrosis and mononuclear cell infiltration : +, mild ; ++, moderate.

Vascular lesions : V I , PAS-positive thickening observed, but over less than half of circumference ; V II, most vessel walls moderately thicked with PAS-positive deposition ; VIII, heavy thickening of majority of vessel walls, with luminal narrowing.

DISCUSSION

The incidence of hypouricemia in the general population is very low. Hisatome et al.[13] measured serum urate concentration in 3,258 outpatients, and reported an incidence of hypouricemia of 0.40%. Ogino et al.[2] found an incidence of hypouricemia of 0.34% in 586 healthy subjects. Van Peenen[14] also found an incidence of 0.72% in a community population. On the other hand, the incidence of hypouricemia in hospitalized patients, especially in diabetics, is relatively high. Ramsdel and Kelly[1] reported an incidence of 0.97% in 6,129 hospitalized patients. Ogino et al.[2] found an incidence of hypouricemia of 2.54% in 1,220 hospitalized patients. Shichiri et al.[12] found that 6.5% of diabetic subjects exhibited hypouricemia. In our study, hypouricemia was found in 1.9% of hospitalized diabetic patients. Our resusts are thus compatible with those of the above studies.

A four-stage process has been postulated to explain renal urate transport : (1) filtration of urate by the glomerulus, (2) reabsorption in the proximal tubule, (3) additional tubular secretion, and (4) post-secretory reabsorption[15]. In diabetes mellitus, the reason for hypour-

icemia has been postulated to be the following. First, urate clearance in diabetics with hyperglycemia and/or hyperfiltration is significantly higher than that in non-diabetics[11]. In volume-expanded states such as hyperglycemia, increased urate secretion is likely to result in increased urate clearance. In one of our patients with hyperglycemia at the time of admission (case 1), hypouricemia continued even after serum glucose level was well controlled. Thus, hyperglycemia does not appear to be principally responsible for hypouricemia in diabetics. Four of our patients had glomerular hyperfiltration (122 to 177 ml/min). Second, hypouricemia may result from tubular urate handling abnormality. Shichiri et al.[11] reported hypouricemic diabetic patients whose urate clearance changed in response to the pyrazinamide suppression test and probenecid loading test. Pyrazinamide is thought to inhibit tubular secretion of urate, and probenecid to inhibit post-secretory reabsorption. The findings obtained by Shichiri et al. were compatible with increased secresion of urate. In the present study, we were unable to determine the location of defect in tubular urate transport using the pyrazinamide suppression test and probenecid loading test. However, we found all 3 patients had tubulointerstitial changes in renal biopsy specimen. Although these changes, which included interstitial fibrosis and mononuclear cell infiltration, are not specific for diabetic nephropathy, their presence suggests that they may have contributed to tubular dysfunction in these patients. These considerations suggest the possibility that the glomerular hyperfiltration which accompanies diabetic nephropathy and functional abnormality of tubular urate handling due to tubulointerstitial involvement contributes to hypouricemia in diabetic patients.

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