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Asymptomatic Pyuria in Diabetic Women

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Abstract

The aim of the present study was to determine the prevalence of and the host factors for asymptomatic pyuria (ASP) in women with type 2 diabetes. The study included 179 type 2 diabetic women and consecutive 455 non-diabetic women attending as out-patients in 1996. Patients with symptoms of a urinary tract infection were excluded. ASP was defined as the presence of more than 10 leukocytes/high-power field in a random urine sample. Diabetic women more often had ASP than non-diabetic women (27.9 vs. 15.8%, P<0.001). The prevalence of ASP was significantly increased in patients with a duration of diabetes exceeding 15 years (0～4 years; 20.3%, 5～9 years; 24.3%, 10～14 years; 23.8%, and≧15 years; 46.3%). No differences were evident in HbA_{1C} between diabetic patients without ASP and those with ASP. Diabetic women with ASP more often had diabetic retinopathy, neuropathy, nephropathy, cerebrovascular disease, ischemic heart disease, and hyperlipidemia than those witout ASP. However, no statistically significant differences were evident in the prevalence of hypertension, constipation, or dementia. As the degree of neuropathy increases, it is accompanied by an increasing prevalence of ASP (none, 21.4 %; blunt tendon reflexes, 24.5%; symptomatic, 50.0%; and gangrene, 66.6%). The prevalence of ASP was significantly increased in the patients with proliferative diabetic retinopathy (none, 23.2 %; background, 29.4%; preproliferative, 18.2%; and proliferative, 50.0%). As the degree of nephropathy increases, it is accompanied by an increasing prevalence of ASP (none, 20.0%; microalbuminuria, 31.9%; macroalbuminuria, 37.0%; and renal failure, 60.0%). Thus, the prevalence of ASP is increased in women with diabetes and increased with longer duration of diabetes but was not affected by glucose control. The incidence of ASP increases significantly as diabetic microangiopathy becomes severer. (J Nippon Med Sch 2001; 68: 405—410)

Key words: asymptomatic pyuria, type 2 diabetes, duration of diabetes, diabetic microangiopathy, glucose control

Introduction

Patients with diabetes have an increased risk of bacterial infection, with the urinary tract being the most prevalent infection site[1]. An increased prevalence of asymptomatic bacteriuria (ASB) has been described in women with diabetes compared with women without diabetes in Europe and America[2-6]. However, the risk factors for developing ASB have

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not been defined in women with diabetes, and it is unknown whether ASB becomes symptomatic and affects renal function in diabetic patients or whether treatment of ASB is warranted. Further, various risk factors for ASB in women with diabetes have been suggested, including age, duration of diabetes, glucose control, complications of diabetes, sexual intercourse, and previous instrumentation of the urinary tract[4-9]. However, studies analyzing the correlation among these factors and ASB yielded conflicting results.

There is no consensus in the literature on whether diabetes mellitus increases the rate of ASB in Japanese women. This study examined whether type 2 diabetic patients have an increased prevalence of asymptomatic pyuria (ASP) compared with non-diabetic patients among Japanese women. In addition, the host factors of the patients with ASP were analyzed.

Materials and Methods

The present study included 179 type 2 out-patient diabetic women. By following the criteria, we defined diabetes as a fasting plasma glucose concentration of ≧140 mg/dl, a 2-h plasma glucose concentration of ≧200 mg/dl, or the use of glucose-lowering medications (oral agents or insulin). To investigate the prevalence of ASP in women without diabetes, all 455 non-diabetic women attending the out-patient clinic consecutively during the period February-December, 1996 were included. Patients with known urinary tract abnormalities, recent urinary tract instrumentation, symptoms of a urinary tract infection (UTI) (dysuria, increased frequency of urination, stranguria, and/or increased urgency of urination), or the use of antimicrobial drugs within the previous one month were excluded. The subjects were weighed and their BMI was calculated. Glycosylated hemoglobin A_{1C} (HbA_{1C}) was measured by the HPLC method. ASP was defined as the presence of more than 10 leukocytes/high-power field (HPF) in a random urine sample.

The patients with hypertension or hyperlipidemia were being treated with antihypertensive drugs or lipid-lowering therapy. The patients with constipation were being treated with laxatives. Diagnose of cerebrovascular disease (CVD), ischemic heart disease (IHD), or dementia were based on a physical examination, past history, and electrocardiogram. Diabetic complications were categorized and defined as follows. Retinopathy (as determined by ophthalmologists): none, background, preproliferative, and proliferative. Nephropathy: none, microalbuminuria (30－300 mg/g・Cr), macroalbuminuria (≧300 mg/g・Cr), and chronic renal failure (serum creatinine level ≧2 mg/dl) when measured on at least 2 occasions 2 months apart with random urine and blood samples. Neuropathy: none, blunt tendon reflexes, symptomatic (clinically apparent disturbance of sensory functions), and diabetic gangrene.

Statistical analysis was carried out using the chi-squared, Student *t* test and one way analysis of variance. Data in the text, tables, and figures were expressed as mean ± SD.

Results

The patients' characteristics in this study are shown in **Table 1**. Mean age was significantly higher in the non-diabetic women than in the diabetic women ($P<0.05$). The diabetic women more often had hypertension, hyperlipidemia, constipation, and IHD than the non-diabetic women ($P<0.001$, $P<0.001$, $P<0.001$, and $P<0.01$, respectively). However, no statistically significant differences were evident in the prevalence of CVD or dementia between the two groups. The prevalence of ASP was significantly higher in the diabetic women than in the non-diabetic women (27.9 vs. 15.8%, $P<0.001$).

The differences in clinical characteristics between the diabetic women without ASP and those with ASP are shown in **Table 2**. Mean age was significantly higher in the diabetic women with ASP than in those without ASP ($P<0.05$). Although a trend was evident toward longer duration of diabetes in the diabetic women with ASP, this did not reach statistical significance ($P=0.10$). The prevalence of diabetic retinopathy, neuropathy, or nephropathy all tended to be severer in the diabetic women with ASP than in those without ASP ($P<0.05$, $P<0.01$, and $P<0.05$, respectively). The diabetic women with ASP more often had hyperlipidemia, CVD, and IHD than those without ASP. However, no statistically significant differences

Table 1 Differences in clinical characteristics between the non-diabetic women and diabetic women

	Non-diabetic women	Diabetic women
n	455	179
age (years)	67.3 ± 13.9	64.8 ± 10.3*
Therapy for hypertension	131 (28.8)	78 (43.6) ***
Therapy for hyperlipidemia	81 (17.8)	54 (30.2) ***
Therapy fo constipation	65 (14.3)	61 (34.1) ***
Cerebrovascular disease	52 (11.4)	26 (14.5)
Ischemic heart disease	51 (11.2)	36 (20.1) **
Dementia	16 (3.5)	8 (4.5)
Asymptomatic pyuria	72 (15.8)	50 (27.9) ***

Data are mean ± SD, or n (%).
*P < 0.05, **P < 0.01, ***P < 0.001 : non-diabetic women vs. diabetic women

Table 2 Differences in clinical characteristics between the patients without asymptomatic pyuria (ASP) and those with ASP in diabetic women

	Without ASP	With ASP
n	129	50
Age	63.7 ± 10.0	67.8 ± 10.6*
BMI (kg/m^2)	23.8 ± 4.0	24.5 ± 4.6
Duration of diabetes (years)	9.3 ± 8.2	11.9 ± 11.1
HbA_{1c} (%)	7.7 ± 1.6	8.0 ± 1.9
Diabetic retinopathy (none/background/preproliferative/proliferative)	73/24/18/14	22/10/4/14*
Diabetic neuropathy (none/blunt tendon reflexes/symptomatic/gangrene)	77/37/13/2	21/12/13/4**
Diabetic nephropathy (none/micro-/macro-albuminuria/renal failure)	76/32/17/4	19/15/10/6*
Therapy (diet/OHA/insulin)	48/71/10	15/30/5
Therapy for hypertension	53 (41.1)	25 (50.0)
Therapy for hyperlipidemia	33 (25.6)	21 (42.0) *
Therapy for constipation	42 (32.6)	19 (38.0)
Cerebrovascular disease	12 (9.3)	14 (28.0) **
Ischemic heart disease	14 (10.9)	14 (28.0) **
Dementia	4 (3.1)	4 (8.0)

Data are mean ± SD, or n (%).
*P < 0.05, **P < 0.01 : without ASP vs. with ASP

were evident in the prevalence of hypertension and dementia between the two groups.

Fig. 1 shows the percentage distribution of ASP in relation to the duration of diabetes. The prevalence of ASP in patients with a duration of diabetes exceeding 15 years was significantly increased compared with the prevalence in patients with a duration of diabetes of 0～4 years, patients with a duration of diabetes of 5～9 years, and patients with a duration of diabetes of 10～14 years (46.3% vs. 20.3%, 24.3%, and 23.8%, P<0.01, P<0.05, and P<0.05, respectively).

Fig. 2 shows the percentage distribution of ASP in relation to the degree of the diabetic neuropathy. As the degree of neuropathy increases, it is accompanied by an increasing prevalence of ASP. The prevalence of ASP in patients with symptomatic diabetic neuropathy was significantly increased compared with the prevalence in patients without diabetic neuropathy and patients with blunt tendon reflexes (50.0 % vs. 21.4% and 24.5%, P<0.01 and P<0.05, respectively). The prevalence of ASP in patients with diabetic gangrene was significantly increased compared with patients without diabetic neuropathy (66.6% vs. 21.4%, P<0.05).

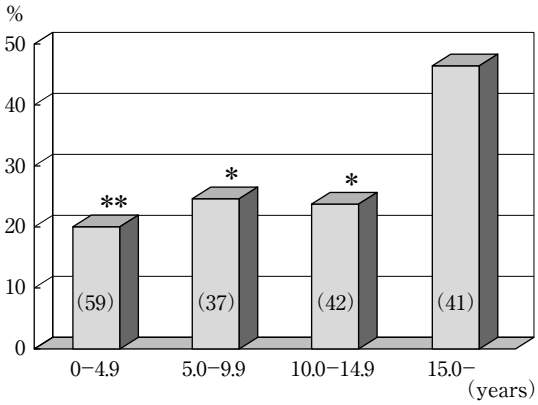

Fig. 1 The percentage distribution of asymptomatic pyuria in relation to the duration of diabetes. The duration of diabetes is on the horizontal axis. *P<0.05, **P<0.01 vs. the patients with a duration of diabetes exceeding 15 years.( ); number of subjects.

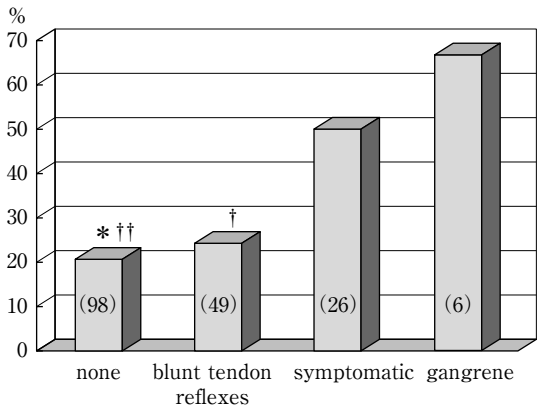

Fig. 2 The percentage distribution of asymptomatic pyuria in relation to diabetic neuropathy (none, patients without diabetic neuropathy; blunt tendon reflex, patients with blunt tendon reflex; symptomatic, patients with symptomatic diabetic neuropathy; gangrene, patients with diabetic gangrene). *P<0.05 vs. the patients with diabetic gangrene, †P<0.05, ††P<0.01 vs. the patients with symptomatic diabetic neuropathy.( ); number of subjects.

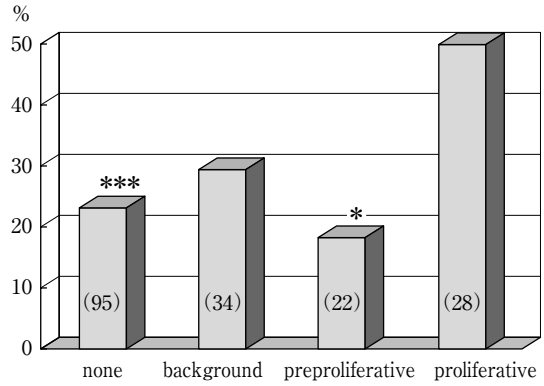

Fig. 3 The percentage distribution of asymptomatic pyuria in relation to diabetic retinopahy (none, without retinopathy; background, patients with background retinopathy; preproliferative, patients with preproliferative retinopathy; proliferative, patients with proliferative retinopathy).
*P<0.05, ***P<0.001 vs. the patients with proliferative retinopathy.( ); number of subjects.

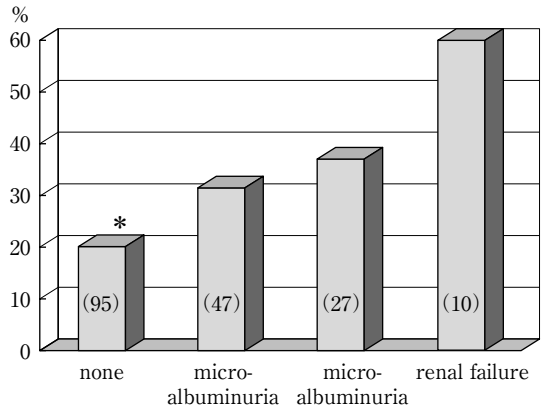

Fig. 4 The percentage distribution of asymptomatic pyuria in relation to diabetic nephropahy (none, without nephropathy; microalbuminuria, patients with microalbuminuria (30−300 mg/g・Cr); macroalbuminuria, patients with macroalbuminuria (300 mg/g・Cr); renal failure, patients with serum creatinine level ≧2 mg/dl.)
*P<0.05 vs. patients with renal failure.( ); number of subjects.

Fig. 3 shows the percentage distribution of ASP in relation to the degree of diabetic retinopathy. The prevalence of ASP in patients with proliferative diabetic retinopathy was significantly increased compared with patients without diabetic retinopathy and patients with preproliferative diabetic retinopathy (50.0% vs. 23.2% and 18.2%, P<0.001 and P<0.05, respectively).

Fig. 4 shows the percentage distribution of ASP in relation to the degree of diabetic nephropathy. As the degree of nephropathy increases, it is accompanied by an increasing prevalence of ASP. The prevalence of ASP in patients with renal failure was significantly increased compared with patients without diabetic nephropathy (60.0% vs. 20.0%, P<0.05).

Discussion

In this study, we found that the prevalence of ASP is higher in diabetic women than in non-diabetic women (27.9 vs. 15.8%). Some studies demonstrated no differences in the prevalence of ASB between diabetic and non-diabetic women[1,10], but the majority of investigators reported a twofold or threefold higher prevalence of ASB in diabetic women[2-6]. The three largest studies previously described, in which 400, 341, and 1,072 out-patient diabetic women were studied and the prevalence of ASB was reported as 9.5%, 9.1%, and 7.9%, respectively[4,7,8].

Our prevalence of ASP of 27.9% is remarkable, and it is inconsistent with the prevalence in these previous studies. The reason for this discrepancy may lie in the far greater number of aged patients examined in the present study. Geerlings et al[6] reported a prevalence of ASB of 26% in 378 diabetic women; the mean age of the subjects was about 60 years. This prevalence is similar to our result. The observation that age is associated with ASB is consistent for all ambulatory populations, regardless of whether or not they have diabetes[6,7,11]. The effect of age might be explained by an increased prevalence of mechanical or functional bladder outlet disorders in the elderly, perhaps combined with postmenopausal uroepithelial changes[7,12]. In our study of 80 middle-aged (<65 years) diabetic women, the prevalence of ASP was 12.5% (data not shown). The prevalence found in middle-aged women corresponds approximately to the results obtained by others[4,7,8].

In this study, the prevalence of ASP increased with advancing severity of diabetic microangiopathies, especially diabetic neuropathy, but was not affected by measures of glucose control. And this prevalence was increased in patients with a duration of diabetes exceeding 15 years. Many of these factors seem contradictory because it is generally assumed that the longer diabetes exists, the greater the chance of micro- and macroangiopathy.

Many studies found a correlation among the duration of diabetes[4-6,8,9], the presence of microvascular diseases, and the presence of ASB in diabetic patients[5-7]. In the majority of these studies[4,5,7-9], the subjects investigated included only a number of type 2 diabetic patients or a number of patients with type 1 and type 2 diabetes unspecified. Vejlsgaard[9] found an increased prevalence of bacteriuria in patients with diabetes mellitus for >20 yr compared with patients having the disease for a shorter time and found an association between bacteriuria and the diabetic complications of retinopathy, neuropathy, IHD, and peripheral vascular disease. Geerlings et al[6] investigated the prevalence of and the risk factors for ASB in a large number of women with either type 1 or type 2 diabetes. When women with type 1 diabetes were studied separately, they found that the prevalence of ASB was higher than in women without diabetes and that the risk factors for ASB were a longer duration of diabetes and presence of diabetic nephropathy and neuropathy. These findings were compatible with those of other studies of women with type 2 diabetes or with combined analyses of women with type 1 and type 2 diabetes.

ASP in diabetic women is most strongly associated with diabetic neuropathy in this study. Ellenberg et al.[13] performed urological investigations on diabetic patients with and without neuropathy and non-diabetic controls, all of whom were completely free of symptoms and signs referable to the urinary tract. The non-diabetic controls and the diabetics without neuropathy were normal. In striking contrast, 83 per cent of the diabetic patients with neuropathy had clear, objective evidence of neurogenic bladder involvement as manifested by abnormal cystometrograms, and grossly enlarged bladders. They suggested that bacteriuria is due to stasis of urine in the incipient asymptomatic diabetic bladder. However, Geerlings et al[6] were unable to show a correlation among the presence of diabetic neuropathy, bladder residue, and ASB.

Our findings are in agreement with whose in previous reports suggesting glucose control is not associated with bacteriuria[4-8]. Hyperglycemia impairs host response to microorganisms by several mechanisms. Defects in polymorphonuclear leukocyte functions such as chemotaxis, phagocytosis, intracellular bactericidal activity, and serum opsonic activity have all been reported in diabetic patients, but their significance has not yet been fully confirmed in clinical studies[11,14].

The most important limitation of this study is that we did not culture the urine samples. Obtaining reliable urine specimens for culture from elderly patients is difficult because of physical disabilities and lack of cooperation. The criteria adopted in the clinical studies for diagnosing infections of the urinary tract have varied from study to study. However, the Dutch Institute for Quality Assurance guidelines advise diagnosing UTIs with either sediment microscopy or a nitrite test[15]. Although urine cultures and urinary leukocyte counts may both be suitable diagnostic methods for ASB, the urinary leukocyte count is strongly recommended because it is easier and faster to perform, more convenient and acceptable to patients, more reproducible, and less expensive. Cutoff values for urinary leukocyte counts for bacteriuria have not been completely established for clinical settings. In a study by Zhanel et al.[8], in which urinary leukocytes were measured by the more accurate hemocytometer method, absolute urinary leukocyte counts were $\geqq 10/mm^3$ in 77.6% of the urine specimens from 85 patients with bacteriuria proven by two consecutive cultures.

Whether symptomatic UTIs are preceded by ASB is not known [2,3,11]. Many experts in the U.S. recommended treating ASB in diabetic patients because of the frequency and severity of upper UTIs[11]. On the other hand, European experts believe that the benefit of treatment is doubtful, and therefore most diabetic women with ASB are not treated in Europe[11]. This contrast is the result of a lack of follow-up studies of diabetic women with untreated ASB. Long-term prospective intervention studies are needed to clarify the risks and benefits of treatment for ASB.

In conclusion, we have shown in this study of diabetic women that the prevalence of ASP is higher in women with diabetes than in women without diabetes. It appears that ASP cannot be correlated with diabetes mellitus per se, but the present study suggests diabetic complications, especially neuropathy, are contributory factors in the development of ASP in diabetic women.

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