Glycemic disorders are positively associated with asymptomatic pyuria in females but not in males

Hui-Ming Chung, a,b *, Min-Chen Liu, c Chun-Lin Yeh, d Yung-Chen Tsai a,b

a Department of Medical Research, Mennonite Christian Hospital, Hualien, Taiwan
b Department of Urology, Mennonite Christian Hospital, Hualien, Taiwan
c Department of Nephrology, Mennonite Christian Hospital, Hualien, Taiwan
d Department of Endocrinology, Mennonite Christian Hospital, Hualien, Taiwan

Abstract

Objective: Asymptomatic pyuria (ASP) is associated with a higher risk of complicated urinary tract infections among diabetic patients. We investigated the association between glycemic status and ASP in an adult population undergoing a health checkup in Hualien, east-central Taiwan.

Materials and Methods: We reviewed the records of 9229 participants who had their first health checkup in this hospital between June 1, 2001 and September 1, 2006. All cases (n = 979) had pyuria as defined by the presence of more than 10 leukocytes per high-power field in urinalysis. Controls (n = 8250) included all other patients who had no pyuria. The glycemic status was classified as normal [fasting blood glucose (FBG) <100 mg/dl and no diabetes history], prediabetic (FBG, 100–125 mg/dl and no diabetes history), and diabetic (FBG >125 mg/dl or a history of diabetes). A case-control analysis was performed. Odds ratios (ORs) were calculated by logistic regression.

Results: The prevalences of ASP for diabetic, prediabetic, and normal adults were 23.4%, 18.0%, and 13.4% in women, and 5.6%, 4.2%, and 4.6% in men, respectively. Among women, the age-adjusted OR for ASP was 1.34 (p < 0.01) for prediabetics and 1.77 (p < 0.01) for diabetics, relative to the controls (p for trend <0.01). Among men, the corresponding OR was 0.91 (p = 0.59) for prediabetics and 1.15 (p = 0.44) for diabetics. The effects of glycemic status on ASP significantly differed among women versus those among men (p for interaction <0.01). The associations remained unchanged after further adjustments for other potential confounding factors.

Conclusion: An abnormal glycemic status has a significant positive dose-response relation with the presence of ASP; however, the association is only in women and not in men. Further research is required to protect diabetic women from this complication.

* Corresponding author. Department of Medical Research and Department of Urology, Mennonite Christian Hospital, 44 Min-Chuan Road, Hualien 970, Taiwan. E-mail address: hchung@jhsph.edu (H.-M. Chung).

Original article

1. Introduction

Diabetic patients have an increased risk of symptomatic urinary tract infections (UTIs) and UTI complications (e.g., bacteremia, renal abscesses, and renal papillary necrosis), especially among women. It has been suggested that asymptomatic bacteriuria (ASB) is a major risk factor of developing symptomatic UTIs and subsequent renal dysfunction. Several reports have shown that people with diabetes have a higher prevalence of ASB compared with those without diabetes, especially among women. ASB has been shown to be a predictor for hospitalization with a UTI in diabetic adults. Some investigators have even suggested that ASB is a complication of diabetes in women. However, data are conflicting as to whether people with diabetes do have a higher prevalence of ASB. Furthermore, most of the research has been conducted among women in Western countries, and mostly in clinic- or hospital-based populations. There is evidence suggesting that the association between diabetes and ASB may differ among different ethnic groups. For example, a study in an Asian population failed to show a higher prevalence of ASB in diabetic women. In addition, data are limited regarding the proposed association in men. To our knowledge, there are no reports on whether ASB is more prevalent among people with diabetes in Taiwan, either male or female. To further investigate these issues, we conducted this research in a population of Taiwanese people undergoing a health checkup that included adult men and women to assess the relationship between diabetes and ASB. Urine culture and urinary tract infections (UTIs) and UTI complications (e.g., bacteremia, renal abscesses, and renal papillary necrosis), especially among wom-
leukocyte counts (pyuria) are both suitable diagnostic tests for ASB. We used pyuria as a surrogate for bacteriuria in this study.

2. Materials and methods

2.1. Study group

The study group comprised participants who had a health checkup sponsored by the National Health Insurance in our hospital between June 1, 2001 and September 1, 2006. The NHI-sponsored health checkup program is a nationwide project that offers a periodic free comprehensive health exam to beneficiaries aged 40 years and older. The free health checkup service is offered annually to people aged 65 years and older, but every 3 years to those aged 40–64 years. Some participants had more than one health checkup in this hospital during the study period, but we analyzed only data from the first health checkup.

2.2. Definition of pyuria and glycemic disorders

There were 9229 participants in the study. A case-control analysis was conducted. Cases (n = 979) were patients who had pyuria, which was defined as the presence of more than 10 leukocytes per high-power field in the urine analysis. Controls (n = 8250) comprised the other patients who had no pyuria. As a health checkup population, these patients were assumed to be asymptomatic. Their glycemic status was classified as normal [with a fasting blood glucose (FBG) of <100 mg/dL and no history of diabetes], prediabetic (with a FBG of 100–125 mg/dL and no history of diabetes), or diabetic (with a FBG of >125 mg/dL or with a history of diabetes).

2.3. Data collection

After a fasting period of at least 8 hours, a complete blood count, fasting blood sugar, renal function, liver function, uric acid, lipid profile, and sediment urinalysis were conducted in participants. They then completed questionnaires regarding their medical history (diabetes, hypertension, and hyperlipidemia), smoking, alcohol consumption, betel nut chewing, demographic factors, and family history of major cardiovascular diseases. A physician then carried out a physical examination of the participants. Data on their blood tests were automatically entered into an electronic database, while data from the questionnaires were manually entered into the same database. Participants were enrolled in this study if they had complete data on their glycemic status (a history of diabetes and FBG) and urinalysis. We used the database to explore the relationship between glycemic status and asymptomatic pyuria (ASP). The potential confounding factors considered were age, sex, body mass index (BMI), smoking, alcohol consumption, betel nut chewing, a history of hypertension or hyperlipidemia, hyperuricemia (serum uric acid >7.2 mg/dL), liver dysfunction (glutamyl transaminase >42 mg/dL), and nephropathy (serum creatinine >1.5 mg/dL). BMI and age were considered as continuous variables, while all others were treated as categorical variables. This study was approved by the institutional review committee of the hospital.

2.4. Statistical analysis

Logistic regression was used to analyze the relation between glycemic status and ASP while adjusting for other potential confounding factors, including age, sex, history of hypertension, smoking, alcohol consumption and nephropathy. Other factors were tested for their effects on the odds ratio (OR) estimate and were not included in the model, since they did not change the OR estimate for diabetes by 10% or more. We first examined whether the glycemic status of the cases and controls differed, as well as other potential confounding factors. Because sex was found to have different effects on the glycemia–ASP association, we then assessed the glycemia–ASP association stratified by sex. The ORs were calculated with 2005 Stata statistical software (Intercooled Stata 8.2; Stata Corporation, College Station, TX, USA).

3. Results

The prevalence of ASP was 10.6% [95% confidence interval (CI): 9.9–11.2%] in this population, with 15.9% (95% CI: 14.9–16.9%) for women and 4.7% (95% CI: 4.1–5.3%) for men. The prevalences of ASP in adults with glycemic statuses classified as diabetic, prediabetic, and normal were 23.4%, 18.0%, and 13.4% in women, and 5.6%, 4.2%, and 4.6% in men, respectively. Of the 9229 participants, 1572 had a diabetic, 2024 had a prediabetic, and 5633 had a normal glycemic status.

Table 1 shows the characteristics of the cases and controls. The two groups had no differences in terms of BMI, betel nut chewing, hypertensive status, hyperuricemia, or liver dysfunction. The cases were more likely to be older, female, dyslipidemic, and nephropathic, but they were less likely to be smokers or drink alcohol. The prevalence of prediabetes and/or diabetes tended to be higher in the cases than in controls.

The effects of glycemic status on ASP appeared to differ among women versus men (p for interaction < 0.01). Table 2 shows the relationship between glycemic status and ASP stratified by sex. Among women, those with a prediabetic glycemic status had a 34% higher estimated risk of ASP (age-adjusted OR: 1.34; 95% CI: 1.11–1.64; p < 0.01), and those with diabetes had a 77% higher estimated risk of ASP compared with controls (age-adjusted OR: 1.77; 95% CI: 1.45–2.18; p < 0.01). A clear linear trend was present for this association among women (p < 0.01). In contrast, there was no association between glycemic status and ASP among men. The age-adjusted OR was 0.91 (p = 0.59) for those with a prediabetic glycemic status and 1.15 (p = 0.44) for those with diabetes compared with controls. Further adjustments for nephropathy, hypertension, smoking, and alcohol consumption did not significantly change the OR estimates.

Table 1: Characteristics of cases (with UTI) and controls (non-UTI) among the health checkup population in Hualien, 2001–2006

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases (n = 979)</th>
<th>Controls (n = 8250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at exam date, mean</td>
<td>62.2 (13.5)</td>
<td>60.1 (12.9)</td>
</tr>
<tr>
<td>(standard deviation)</td>
<td>(3.9)</td>
<td>(3.7)</td>
</tr>
<tr>
<td>Body mass index, mean</td>
<td>24.8 (3.9)</td>
<td>24.8 (3.7)</td>
</tr>
<tr>
<td>(standard deviation)</td>
<td>(3.9)</td>
<td>(3.7)</td>
</tr>
<tr>
<td>Sex (male), %</td>
<td>21.1*</td>
<td>30.5*</td>
</tr>
<tr>
<td>Smoking (ever), %</td>
<td>12.6*</td>
<td>18.7*</td>
</tr>
<tr>
<td>Alcohol consumption, %</td>
<td>18.0*</td>
<td>29.4*</td>
</tr>
<tr>
<td>Betel nut consumption, %</td>
<td>19.4*</td>
<td>11.5</td>
</tr>
<tr>
<td>Hypertension*, %</td>
<td>29.3*</td>
<td>30.0</td>
</tr>
<tr>
<td>Dyslipidemia*, %</td>
<td>33.5*</td>
<td>30.4</td>
</tr>
<tr>
<td>Hyperuricemia, %</td>
<td>18.4</td>
<td>18.0</td>
</tr>
<tr>
<td>Liver dysfunction, %</td>
<td>8.1</td>
<td>9.8</td>
</tr>
<tr>
<td>Renal insufficiency, %</td>
<td>7.0*</td>
<td>3.9</td>
</tr>
<tr>
<td>Glycemia status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal FS</td>
<td>54.6*</td>
<td>61.8</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>22.3*</td>
<td>21.9</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23.1*</td>
<td>16.3</td>
</tr>
</tbody>
</table>

*a p < 0.05.
*b weight (kg)/height (m)².
*c history of hypertension or BP >130/85 mmHg.
*d history of dyslipidemia or serum triglycerides >150 mg/dL.
FS = fasting sugar; UTI = urinary tract infection.
Our results suggest that glycemic disorders may increase the risk of ASB in a dose-response manner (p < 0.01), but the effect was limited to women, and was not detected in men (p < 0.01). Although the data are not totally consistent, several reports on Western populations have shown that diabetic women have a higher prevalence of ASB compared with women without the condition. The current study of a Taiwanese population supports the concept that the prevalence of ASB is higher in diabetic women (23.4%) than that in women with a normal glycemic index (13.4%), with an age-adjusted OR of 1.77 (p < 0.01). If diabetes does predispose to ASB, we can speculate that prediabetes also predisposes to ASB. Previous studies have rarely examined whether being prediabetic also increases the risk of ASB. Our data are unique in further showing that even a prediabetic status alone increases the estimated risk of ASB by 34% in women (OR: 1.34, 95% CI 1.11–1.64). If diabetes predisposes to ASB, we can speculate that prediabetes also predisposes to ASB. The linear trend we found between prediabetes and diabetes with ASB in women strongly supports the theory that glycemic disorders increase the risk of ASB, which in turn may increase the risk of symptomatic UTIs. Fourth, our data showed that glycemic disorders are associated with a higher risk of ASB in women, but not in men. Fifth, in contrast to most other reports, this study provides data from a non-Western population that support the proposed association.

There are also some limitations to our study that deserve discussion. First, we were unable to differentiate between the two primary types of diabetes mellitus: insulin-dependent diabetes mellitus (type I) and non-insulin-dependent diabetes mellitus (type II). The metabolic profiles of the two types may differ, but Geerlings et al showed that women with type I diabetes also have a higher prevalence of ASB compared with normal controls. We believe that this difference between types may have had little effect on our results because the majority of diabetic patients in this study were aged 40 years or older, and therefore most likely to be of type II. Second, we used pyuria defined by urinary leukocyte counts instead of urine culture as a surrogate for bacteriuria. The use of this definition might have led us to observe a less strong association between ASB and diabetes. Third, we assumed that people in this health checkup program were asymptomatic. If that assumption was wrong, the bias might have resulted in a stronger association between ASB and diabetes. Another limitation is that as this was a retrospective study, we were unable to control for some other potential confounding factors pertaining to UTIs, including the presence of anomalies of the urinary tract and the consumption of cranberries, which may have reduced the risk of UTI.

Some authors have proposed the following mechanisms to explain why ASB may be more prevalent in people with diabetes, although none have been confirmed. First, the higher glucose concentration in the urine of diabetic patients may serve as a culture medium allowing bacteria to grow faster. Second, those with diabetes may have an impaired host defense system. Diabetic women have lower urinary interleukin-6 concentrations compared with other assays of the two types may differ, but our study provides data from a non-Western population that support the proposed association.

There are also some limitations to our study that deserve discussion. First, we were unable to differentiate between the two primary types of diabetes mellitus: insulin-dependent diabetes mellitus (type I) and non-insulin-dependent diabetes mellitus (type II). The metabolic profiles of the two types may differ, but Geerlings et al showed that women with type I diabetes also have a higher prevalence of ASB compared with normal controls. We believe that this difference between types may have had little effect on our results because the majority of diabetic patients in this study were aged 40 years or older, and therefore most likely to be of type II. Second, we used pyuria defined by urinary leukocyte counts instead of urine culture as a surrogate for bacteriuria. The use of this definition might have led us to observe a less strong association between ASB and diabetes. Third, we assumed that people in this health checkup program were asymptomatic. If that assumption was wrong, the bias might have resulted in a stronger association between ASB and diabetes. Another limitation is that as this was a retrospective study, we were unable to control for some other potential confounding factors pertaining to UTIs, including the presence of anomalies of the urinary tract and the consumption of cranberries, which may have reduced the risk of UTI.

Some authors have proposed the following mechanisms to explain why ASB may be more prevalent in people with diabetes, although none have been confirmed. First, the higher glucose concentration in the urine of diabetic patients may serve as a culture medium allowing bacteria to grow faster. Second, those with diabetes may have an impaired host defense system. Diabetic women have lower urinary interleukin-6 concentrations compared with other assays of the two types may differ, but our study provides data from a non-Western population that support the proposed association.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemia status (females)</td>
<td>n = 773</td>
<td>n = 4088</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>54.0</td>
<td>66.0</td>
<td>Reference</td>
<td>Reference</td>
<td>—</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>22.6</td>
<td>19.6</td>
<td>1.34</td>
<td>1.11–1.64</td>
<td>0.00</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23.4</td>
<td>14.5</td>
<td>1.77</td>
<td>1.45–2.18</td>
<td>0.00</td>
</tr>
<tr>
<td>Glycemia status (males)</td>
<td>n = 206</td>
<td>n = 4162</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>56.8</td>
<td>57.7</td>
<td>Reference</td>
<td>Reference</td>
<td>—</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>21.4</td>
<td>24.2</td>
<td>0.91</td>
<td>0.63–1.29</td>
<td>0.59</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21.8</td>
<td>18.1</td>
<td>1.15</td>
<td>0.80–1.64</td>
<td>0.44</td>
</tr>
</tbody>
</table>

* Adjusted for age: the association remained similar after further adjustment for renal insufficiency, hypertension, smoking, and alcohol.

ASP = asymptomatic pyuria; CI = confidence interval.

**4. Discussion**

The definition of ASB is not consistent among different studies. Several studies used urine culture to define ASB, while one study used ASP (pyuria) as an indication of ASB. In the current study, ASP was used as an indication of ASB. Regardless of which criteria were used, misclassification of ASB status is possible. Most studies have shown prevalences of ASB that range from 6% to 10% using urine culture. The prevalence of ASP in 10.6% in the current population is comparable with that of previous studies. The prevalence of ASP among diabetic women was 23.4% in our study, which is also similar to two other studies. Nakano et al reported a prevalence of ASP of 27.9% (pyuria was defined as the presence of less than 10 leukocytes per high-power field) among diabetic women in Japan, and Geerlings et al documented 26.0% ASP (bacteriuria by urine culture) among 378 diabetic women.

Asymptomatic pyuria; CI = confidence interval.
virulent than those of nondiabetic individuals. Although a plausible pathogenesis as to why people with diabetes are predisposed to ASB is available as described above, those explanations cannot explain why the effects of glycemic disorders on ASB are only evident in women and not in men.

The clinical implications of ASB can be significant. Ribera et al demonstrated that ASB is a major risk factor for developing symptomatic UTIs. They followed 289 women and 168 men over a 12-month period. Among patients with ASB, 69.2% (67.6% of women and 76.5% of men) developed symptomatic UTIs, while only 9.8% without ASB (14.9% of women and 2.6% of men) developed symptomatic UTIs. Although some investigators disagree about treating asymptomatic UTIs in people with diabetes, we believe treating asymptomatic UTIs prevents symptomatic UTIs.

5. Conclusions

Our results suggest that patients with glycemic disorders have a higher prevalence of ASB, but this is true only for women, not for men. The reason why glycemic disorders are not associated with a higher risk of ASB among men remains unclear. Further research is required to determine how to protect women with diabetes from this diabetic complication.

References