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Asymptomatic Bacteriuria (ASB), Renal Function and Hypertension

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1. Introduction

Chronic kidney disease is an increasing public health problem. In the United States, the prevalence is estimated to be approximately 11% of the adult population. Chronic kidney disease may progress to end-stage renal failure, a condition associated with high morbidity and mortality. Diabetes mellitus (DM) is one of the main causes of kidney disease and end-stage renal failure. In the United States, DM is the primary diagnosis in 44% of all new cases of renal replacement therapy. Vascular complications are the most common cause of diabetic nephropathy, but it is possible that urinary tract infections (UTIs) also contribute to renal insufficiency in patients with DM.

The urinary tract is normally sterile. However, asymptomatic bacteriuria (ASB), which is defined as the presence of a positive urine culture with at least 10e5 cfu/ml collected from a patient without symptoms of a UTI, is a common phenomenon, especially in women. Different studies report a prevalence of approximately 1-5% among healthy young women, increasing to over 20% in the elderly and 12-26% in women with DM. A Swedish study among 1,462 adult women showed that women with bacteriuria at study entry had an increased risk of having bacteriuria six and twelve years later, compared to women without bacteriuria (Odds Ratio (OR) 6.9 and 3.1, after six and twelve years, respectively). Another Swedish study among 116 schoolgirls with ASB showed that at baseline renal parenchymal reduction was found in 10.3%, while reflux was found in 20.7%, but only 30% of the 116 patients had a history referable to an earlier UTI. A 3-year follow-up of these 116 schoolgirls with ASB (treated or untreated) showed that the risk of developing renal damage as a result of ASB in a schoolgirl with a roentgenographically normal urinary tract seemed to be small.

Escherichia coli is the most prevalent causative microorganism in both symptomatic and asymptomatic bacteriuria, accounting for more than 80% of uncomplicated UTIs. Previous studies have demonstrated that patients with renal scarring due to pyelonephritis are at increased risk for the development of hypertension and chronic kidney disease. Results from previous in vitro and in vivo studies indicate that a UTI with *E. coli* can lead to renal damage, either by the microorganism itself or by the following host response. For instance, it has been shown that type 1 fimbriae (the adhesive organelles at the outer surface of the bacterial

membrane) can cause scarring in the renal parenchyma of rats, with large foci of inflammation. This might be due to the activation of polymorphonuclear leukocytes by type 1 fimbriated-strains, which leads to the release of tissue destroying enzymes. Mice models have shown that although neutrophils are important in bacterial clearance, they can also cause renal damage.

In a clinical study, renal scarring was detected in 29 of 63 adult women ten to twenty years after hospitalization for pyelonephritis. In contrast, no study has convincingly shown that ASB can lead to a clinically relevant decline in renal function in otherwise healthy women. Several authors in the first half of the twentieth century have suggested a role of bacteriuria in the etiology of hypertension, but the pathogenesis is not understood.

2. ASB and renal function decline in healthy women

2.1 Study population, baseline cohort

Between 1974 and 1986 all women, born between 1911 and 1945, who lived in the city of Utrecht and surroundings, the Netherlands, were invited for a breast-cancer-screening program, with a participation rate of 68 to 72%. A total number of 38,994 women, aged 39 to 68 years old at intake, participated (the baseline cohort). Baseline measurements, performed between 1974 and 1986, included extensive questionnaires, a short medical examination, and the collection of a midstream morning urine sample. Data obtained through the questionnaires included age, marital status, smoking habits, parity, menopausal age, diet and drug use. During the medical examination weight and height were measured. Approximately 200 ml urine was stored in plastic polypropylene jars, without preserving agents, and stored at –20°C for future analyses. All women gave oral consent to use their data and urine samples for future scientific research.

2.2 Study population, follow-up cohort

From 1993 to 1997, 50,313 women living in Utrecht and surroundings who were scheduled for breast cancer screening during this period received an invitation by mail to join an additional study to assess the relation between nutrition and cancer and other chronic diseases, the Prospect-EPIC study (the follow-up cohort). A total of 17,357 women (participation rate 34.5%) agreed to take part . Participants were between 49 and 70 years old at enrolment. Information was collected on the basis of two self-administered questionnaires and a medical examination including blood pressure. Non-fasting blood samples were successfully drawn from 97.5% of the women, and stored under liquid nitrogen at –196°C. Approximately 88% of the women signed a detailed informed consent, enabling the researchers to use their blood samples for future analysis, and to obtain information on future morbidity and mortality.

To address the relation between *E. coli* bacteriuria and renal function development, we performed a full cohort analysis for women who participated in both the baseline cohort and the follow-up cohort. *E. coli* bacteriuria was diagnosed by a real-time Polymerase Chain Reaction in this urine sample. Participants were between 49 and 70 years old at enrolment. The mean duration of follow-up was 11.5 ± 1.7 years, ranging from 8.1 to 18.6 years from baseline until participation in the follow-up study. Forty-eight of 490 women (10%) were classified with *E. coli* bacteriuria at baseline. At study endpoint, the mean creatinine clearance for women with baseline bacteriuria was 87 ± 21 ml and without baseline bacteriuria 85 ± 18 ml per minute, respectively (Figure 1). *E. coli* bacteriuria at baseline was not associated with creatinine levels at follow-up, adjusted for age and weight and the

distribution in stages of renal function was not different for women with bacteriuria compared to women without bacteriuria.

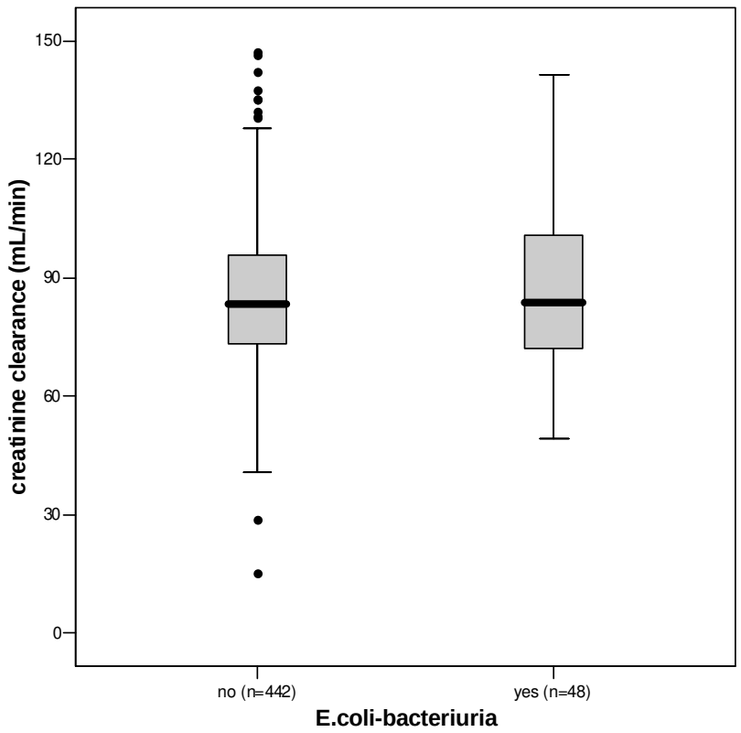


Fig. 1. Differences in creatinine clearance between women WITHOUT DM with and without ASB. (Meiland R, Stolk RP, Geerlings SE, Peeters PH, Grobbee DE, Coenjaerts FE, Brouwer EC, Hoepelman AI. Association between *Escherichia coli* bacteriuria and renal function in women: long-term follow-up. Arch Intern Med. 2007 Feb 12;167(3):253-7.)

2.3 Nested case-control study population

To obtain follow-up information on end-stage renal failure, we obtained data from the Renal Replacement Registry Netherlands (RENINE) that were available May 2002. RENINE is a foundation in which all Dutch nephrologists participate and where patients are registered who at one time have used kidney replacing therapy (hemodialysis or renal transplantation), with a coverage rate throughout the years of nearly 100%. Data from the baseline cohort and RENINE were matched on (maiden and married) name combined with date of birth to select the cases. A group consisting of four times the number of cases was randomly selected from the baseline cohort to form the control group. Four women participated in the follow-up cohort and were also selected as one of the cases who received kidney replacing therapy during follow-up; one woman underwent kidney transplantation before blood withdrawal (and was excluded for the cohort analysis), three women developed end-stage renal failure thereafter (and were included in both analyses). After excluding four individuals with a missing urine sample 49 cases and 206 controls were included. Among the cases, the mean duration until the date of kidney replacing therapy was 13.8 ± 7.4 years, with a minimum and maximum duration of 1.6 and 25.5 years, respectively. In the control group, the mean follow-up (i.e. the time from participation in the baseline cohort until study-endpoint in May 2002) was 27.0 ± 0.2 years.

No difference in duration until kidney replacing therapy was found between bacteriuric and non-bacteriuric individuals (14.6 versus 13.7 years, p = 0.80). Seven of 49 women who developed renal failure had *E. coli* bacteriuria at baseline, compared to 29 of 206 women in the control group (both 14%). The OR for the development of renal failure in the presence of *E. coli* bacteriuria, corrected for age, was 1.1 (95% CI 0.4–2.8, p = 0.86).

In a Swedish study the prevalence of ASB in women was 4%. After 15 years a reinvestigation was carried out, 40 cases (with ASB) and 40 age-matched healthy controls participated. Nobody had developed progressive renal disease. The age-dependent decrease after 15 years was the same in both groups.

The results of these longitudinal findings give strong support to the absence of an association between ASB and renal function decline in healthy women. As an explanation, Svanborg et al. found that certain *E. coli* strains stop expressing adherence factors like type 1 and P fimbriae once they have established bacteriuria. Therefore, these strains can remain present in the bladder without triggering an inflammatory response from the host and without side effects.

In conclusion, no relation between ASB and renal function decline has been demonstrated in healthy women. It has been recommended in American and European guidelines not to screen or to treat ASB in premenopausal non-pregnant women and older persons living in the community. The results of these studies confirm these recommendations.

3. ASB and hypertension in healthy women

Several authors in the first half of the twentieth century have suggested a role of bacteriuria in the etiology of hypertension. For instance, Kass showed small differences in blood pressure between bacteriuric and non-bacteriuric women aged 15 to 64 years old.

The association between ASB and hypertension was investigated in a cohort study of 444 women who were followed for the development of hypertension in relation to *E. coli* bacteriuria at baseline. Hypertension was defined as the (previous) use of antihypertensive medication and/or a measured systolic blood pressure of at least 160 mm Hg or a diastolic blood pressure of 95 mm Hg or higher. A history of having had a heart attack or stroke was assessed at follow-up by the two additional questions: "Have you ever had a heart attack / stroke?". Mean age at baseline was 45.0 ± 3.2 years and 48 women (10%) had *E. coli* bacteriuria. After 11.5 years women who had *E. coli* bacteriuria at baseline had a mean blood pressure at study endpoint of 133 ± 20 mmHg systolic and 78 ± 11 mmHg diastolic, and women without bacteriuria had values of 129 ± 20 and 78 ± 11 mmHg, respectively (p-value for difference 0.33 and 0.88). Interestingly, although *E. coli* bacteriuria was not associated with the blood pressure as a continuous variable, it was associated with the development of hypertension during follow-up (OR 2.8, 95% CI 1.4–5.5). This was mainly due to more bacteriuric women that started antihypertensive drugs when compared to non-bacteriuric participants. This association remained statistically significant after correction for age, weight and creatinine. Eight of the 45 women (18%) who had to be excluded because of the use of antihypertensive medication at baseline, had *E. coli* bacteriuria, which was higher than the percentage of 9% of the final study group without antihypertensive drugs at baseline (p = 0.06). However, no association between ASB and renal function decline was demonstrated. The incidence of heart attacks or strokes was not increased among women with bacteriuria at baseline. These results suggest that bacteriuria increase also the chance to develop hypertension.

Although more recent studies also found a correlation, only one prospective study has shown that bacteriuria is associated with the development of hypertension. In the above mentioned cohort study, a higher prevalence of hypertension in the bacteriuric group after 12 years of follow-up was found. However, the underlying mechanism of this finding is not clear. Hypertension is a lasting increase in blood pressure with a heterogeneous etiology consisting of both genetic and environmental factors. Patients share the inability to excrete sodium at a normal arterial pressure. If bacteriuria would lead to hypertension, the most attractive explanation would be that hypertension arises secondary to renal scarring caused by the (type 1 fimbriae of the) uropathogens. In the multivariate analysis, correction for creatinine did not change the results, but hypertension can occur before the reduction in creatinine clearance becomes apparent. An alternative explanation is that both bacteriuria and hypertension are found more frequently among individuals with comorbidity or that they share a same (currently unknown) cause. This is supported by the higher prevalence of bacteriuria among women who used antihypertensive drugs at baseline. Given the importance of hypertension the nature of this correlation needs to be studied in future studies.

4. ASB and renal function decline and hypertension in patients with DM

Women with DM have an increased prevalence of ASB, but also an increased risk on symptomatic UTI's and developing complications of UTI's such as renal abscesses. It was also shown that at short term follow-up treatment of ASB in women with DM did not appear to reduce complications. *E. coli* is the leading uropathogen in non-diabetic as well as in diabetic patients. Ninety percent of *E. coli* possesses type 1 fimbriae, the adhesive organelles found at the outer bacterial membrane. We have shown in vitro that type 1-fimbriated *E. coli* have an increased adherence to uroepithelial cells voided by women with DM. Others demonstrated that UTI's with type 1-fimbriated *E. coli* can lead to scar formation in the renal parenchyma of infected rats.At present, conclusive and prospective data with a long follow-up period directly relating ASB (with *E. coli*) to long-term risk of renal failure in diabetic patients are lacking. Taken together, we hypothesized that ASB in women with DM could lead to a faster decline in renal function, and decided to enlarge our cohort of diabetic women and to prolong the follow-up period. Besides the effects on renal function, we also studied the influence of ASB on the development of hypertension.

The association between ASB and renal function decline (and hypertension) in patients with DM was investigated in a prospective study with women with DM type 1 (n=296) and type 2 (n=348). All patients were interviewed and their medical records were reviewed at baseline and at study closure to collect all relevant information. All patients were asked to provide 1 or 2 midstream urine specimens. The women were followed up for a mean (SD) duration of 6.1 (1.9) years. Women with DM type 1 were younger, but had a longer duration of DM, than women with DM type 2. At baseline, 201 women with DM type 2 (58%) were treated with insulin only, 97 (28%) with oral hypoglycemic medication only, 41 (12%) with a combination of both, and five women (2%) were on a diet only (data were incomplete for 4 women). Because the Cockcroft-Gault formula for the estimation of the creatinine clearance includes age, adjusting for age in a multivariate model is not possible. Therefore patients were stratified into 3 age strata to assess the impact of age on the association between ASB and the (relative increase in the) creatinine clearance (respectively 18 to 36, 37 to 55, and 56 to 75 years old). All analyses were performed on the entire study population and on women with DM type 1 and DM type 2 separately.The prevalence of ASB was 17% in the study population, lower in

women with type 1 DM (12%) compared to women with type 2 DM (21%), but multivariate analysis revealed that this was due to the difference in age. *E. coli* was cultured in 74 (67%) of the 110 women with ASB. Other isolated microorganisms included *enterococci (9%), group B streptococci (8%), Klebsiella pneumoniae (6%), Staphylococcus aureus (3%), Proteus mirabilis (2%), Enterobacter* species (2%). The prevalence of leukocyturia (5 or more leukocytes per high-power field) was 15% in women with ASB, suggesting that bacteria were present without resulting into an inflammatory response. The creatinine clearance decreased from 87 at baseline to 76 mL/min at study endpoint in diabetic women with ASB, and from 97 mL/min to 88 mL/min in those without ASB (Figure 2). In the univariate analysis, ASB was associated with a higher relative decrease in creatinine clearance (14 ± 22% and 9 ± 23% in women with versus women without ASB, respectively, p = 0.03), but not with the absolute decrease in creatinine clearance (12 ± 19 and 9 ± 20 mL/min, respectively, p = 0.12). Using univariate analysis, age, the length of follow-up, the duration of DM and microalbuminuria were identified as possible confounding factors when studying the influence of ASB on renal function development. Therefore, a multivariate analysis was done, according to age strata, and including the length of follow-up, duration of DM, and microalbuminuria at baseline. In the multivariate analysis no association was found between ASB and the relative or the absolute decrease in creatinine clearance. Also when women with DM type 1 and those with DM type 2 were analyzed separately, no association was found (data not shown). Finally, also no association with a faster decline in renal function was found when only the urines with *E. coli* as the cultured microorganism were included in the analysis

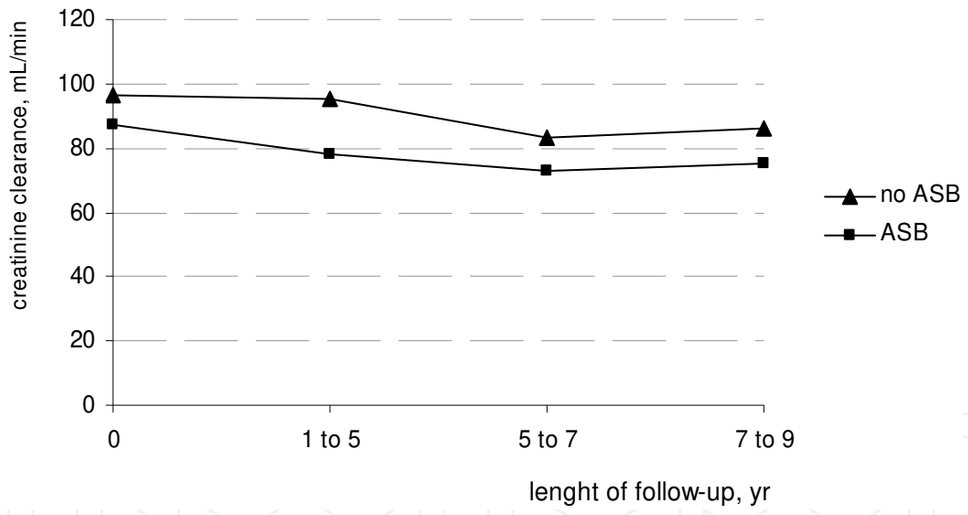


Fig. 2. Differences in creatinine clearance between women WITH DM with and without ASB. (Meiland R, Geerlings SE, Stolk RP, Netten PM, Schneeberger PM, Hoepelman AIM. Asymptomatic bacteriuria in women with diabetes mellitus. Arch Intern Med 2006; 166: 2222-7.)

Diabetic women with ASB developed hypertension more often than women without ASB (54% vs 37%; p=.045). However, in the multivariate analysis, including age, duration of DM, and length of follow-up, the association between ASB and hypertension disappeared (p>.20); a higher age was the strongest predictor for hypertension. In conclusion, in this prospective study after 6 years of follow-up, no association was found between ASB and a decline in renal function or the development of hypertension in women with type 1 DM or

type 2 DM. As shown, women with ASB at baseline had a lower creatinine clearance at study end point, a faster relative decrease in creatinine clearance, and hypertension more often when compared univariately with women without ASB. However, the differences were mainly explained by differences in age and duration of DM, and all differences disappeared in the multivariate analyses.

Comparable results were found in a small Polish study (25 patients with DM, including both men and women), in which no differences in the incidence of hypertension and renal function decline were demonstrated between patients with and those without ASB after 14 years.

In a recent Canadian study it was investigated whether successive isolates of urinary *E. coli* from the same diabetic woman were genetically similar. It was shown that untreated diabetic women with ASB may carry a genetically unique *E. coli* strain for up to 13 months. Women who received treatment for ASB had bacteriuria for a shorter duration and carried a single strain of *E. coli* for a shorter period compared with women who did not receive treatment. However, treatment was followed by recurrent infections for most women, usually with a new strain of *E. coli*. The ASB-causing *E. coli* from diabetic women did not have virulence characteristics typical of UTI-causing strains. This non-virulent microorganism might be an explanation of the low number of patients who have also leukocyturia, as a result of the absence of a host response to this.

Because in the above mentioned prospective study no evidence was found that ASB in itself can lead to a decline in renal function, either in women with type 1 DM or in women with type 2 DM, it is not likely that treatment of ASB will lead to a decrease in the incidence of diabetic nephropathy. This is in accordance with a recent study of women with DM with ASB in which a comparison was made between women who received antibiotic therapy and women who received placebo. In that study, no difference was seen in serum creatinine levels after a mean follow-up of 2 years.

In conclusion, the hypothesis that ASB will lead to renal function deterioration in women with DM can be rejected because no difference in renal function development, in either women with type 1 DM or those with type 2 DM were found. Also, the incidence of hypertension was not increased when comparing women with ASB versus women without ASB. Therefore, at this time, screening and subsequent treatment for ASB are not indicated in patients with DM.

5. ASB in renal transplant recipients

It has been found that up to 50% of renal transplant recipients have ASB and UTIs. Many risk factors contribute to the high incidence of UTIs and ASB, which can undermine graft function and survival. In a retrospective study the impact of ASB on renal transplant outcome was analysed in 189 renal transplant recipients. Screening resulted into 298 episodes of ASB in 96 recipients (follow-up 36 months). Significant risk factors included female gender, glomerulonephritis as the disease that led to transplantation, and double renal transplant. There were no differences in serum creatinine, creatinine clearance, or proteinuria between patients with and without bacteriuria. The incidence of pyelonephritis in these patients was 7.6 episodes per 100 patient-years compared with 1.1 in those without ASB. A total of 2-5 ASB episodes were independent factors associated with pyelonephritis whereas more than 5 episodes was a factor associated with rejection. Studies show contradictory results whether antibiotic treatment results into a lower prevalence of ASB in these patients.

6. Conclusions

E. coli bacteriuria is not associated with a decline in renal function or the development of end-stage renal failure in a population of generally healthy adult women. However, *E. coli* bacteriuria may increase the risk of future hypertension, but the pathogenesis is not understood.

Women with DM (type 1 or type 2) with ASB do not have an increased risk for a faster decline in renal function or the development of hypertension. Therefore, screening and treatment of ASB in diabetic women is not warranted.

Since nearly all studies are performed in women, it is not possible to make conclusions about the association between ASB, renal function and hypertension in men.

No differences in renal function prognosis between patients with and without ASB following kidney transplantation were demonstrated. However, the incidence of pyelonephritis was much higher in the group of patients with ASB. Therefore, screening protocols may be beneficial in this group of patients.

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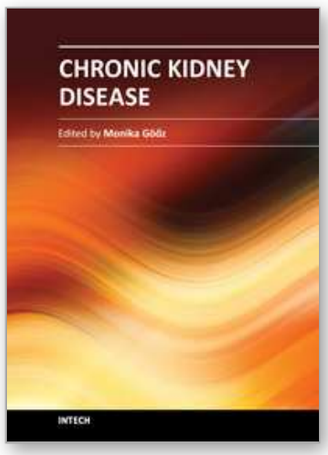
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Chronic kidney disease is an increasing health and economical problem in our world. Obesity and diabetes mellitus, the two most common cause of CKD, are becoming epidemic in our societies. Education on healthy lifestyle and diet is becoming more and more important for reducing the number of type 2 diabetics and patients with hypertension. Education of our patients is also crucial for successful maintenance therapy. There are, however, certain other factors leading to CKD, for instance the genetic predisposition in the case of polycystic kidney disease or type 1 diabetes, where education alone is not enough.

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