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Asymptomatic Bacteriuria with *Escherichia coli* in Type 2 Diabetic Patients: An Unresolved Riddle

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Authors' contributions

This work was carried out in collaboration between all authors. Author AD designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors SS, BD and PA managed the literature searches and reviewed the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Asymptomatic bacteriuria (ASB) is a common finding, but there is a considerable controversy about the appropriate management of bacteriuria. ASB was found to be three times higher in patients with diabetes, especially in women when compared to non-diabetic counterpart. Asymptomatic bacteriuria is the presence of bacteria in the urine presenting without any clinical symptoms of UTI. The objective of this review is to highlight the studies done on ASB in diabetes patients with special reference to *Escherichia coli* (*E. coli)*, risk factors and its management. The review showed that increasing age, females, post-menopausal status, poor glycaemic control, long duration of diabetes, microalbuminuria, leukocyturia ,poor hygiene were associated with ASB. Available literature does not support the use of antibiotics, however short term trials have shown benefit with topical esteriol. Further clinical trials are needed.

Keywords: Asymptomatic bacteriuria; E. coli; type 2 diabetes mellitus; risk factor; management.

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1. INTRODUCTION

An estimated 150 million Urinary tract infection occurs annually worldwide [1]. It is known that diabetes increases the risk of infection especially that of genitourinary tract. Both symptomatic and asymptomatic urinary tract infections are reported to occur with increased frequency in patients with type 2 diabetes especially in women. A study has shown that ASB may lead to symptomatic urinary infection, as well as increase in the frequency of renal failure as one of the long term adverse effects [2]. Asymptomatic bacteriuria is the presence of bacteria in the bladder urine presenting without any clinical symptoms of UTI [2]. Studies have shown that age, sexual activities, duration of diabetes, metabolic control of the disease and the state of complications are known to be the predisposing factor for the development of ASB in diabetics [3,4,5]. ASB is usually caused by normal flora of the gut, which then ascends up the urethra into the bladder and potentially the kidneys [6]. Changes in the host defence mechanisms, presence of diabetic cystopathy and microvascular disease in kidney may play a role which increases the incidence of UTI in diabetic patients [7]. Several studies have shown *Escherichia coli* as the most common causative agent of UTI in both diabetic and non-diabetic patients, uropathogenic *E. coli* possesses variety of pathogenicity determinants that make colonization of Urinary tract possible [8,9,10]. This review aims to determine the best available evidence from original articles and randomised trials.

2. METHODOLOGY

2.1 Literature Survey

A literature search of Medline, PubMed was done using the term “Asymptomatic bacteriuria in diabetes mellitus” for the years 1986 to 2014 in order to find all the articles that considered epidemiology, risk factors, prognosis of ASB in patients with type 2 diabetes. On the basis of title and displayed abstract, articles were chosen for the selected topics. A total of 143 articles were found. Only studies in which ASB was defined as absence of symptoms of UTI and isolation of at least 10^5CFU/ml of the same bacteria in two consecutive urine cultures were included. Among the non-english articles, only those with abstract in english were reviewed and included. Of the published articles 47 original articles, 19 reviewed and 5 clinical articles were excluded in which studies were mainly focused on symptomatic UTI and type 1 diabetes mellitus.

2.2 Outcome Measures

Data on prevalence, risk factors, intervention used and efficacy of intervention were collected.

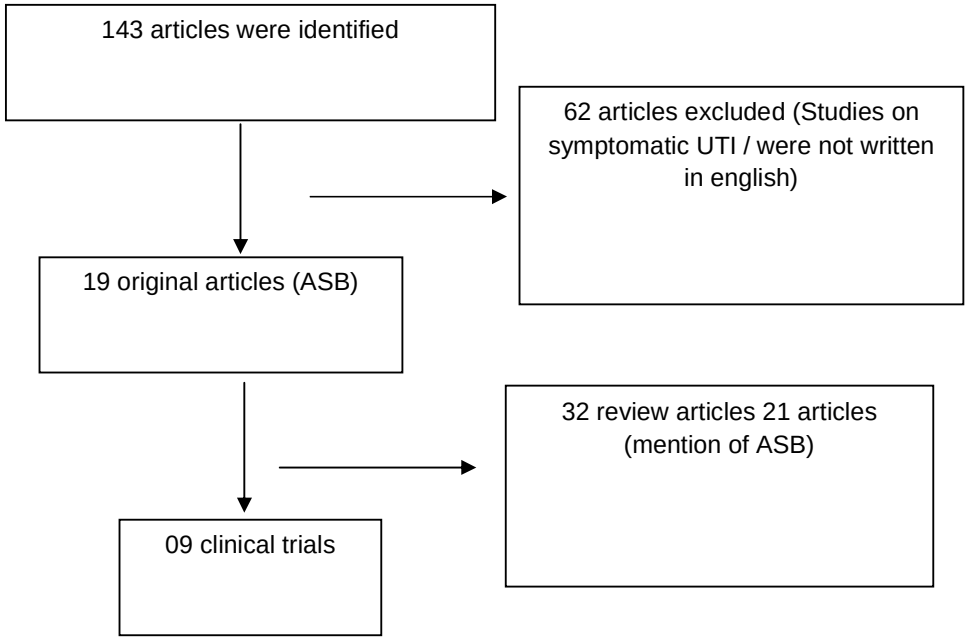

Table 1. Summary of characteristic finding of original articles (cross-sectional and cohort studies)

Year study site [References]	Total no of patients / No of patients with type 2 DM	Pre valence of ASB among DM	Risk factor	Antimicrobial pattern	Treatment
2013; Cameroon [11]	265/154	38.3%	Diabetes mellitus	Ciprofloxacin was most effective	Not recommended
2013; Moscow [12]	414/414	22.7%	Post menopausal	Na	Usage of local form of esteriol
2012; Ethiopia [13]	413/306	10.4%	Female	S-Aminoglycosides, Qinolones, Cephalosporins	Recommended
2008 ; Nigeria [14]	192/135	16%	Diabetes old age poor glycaemic control	S- Nitrofurans	Follow up recommended
2007; Iran [15]	100/100	72.3%	Uncontrolled diabetes	S-Aminoglycosides	NA
2006; Pisa [16]	1321/346	12.76%-M 14.97%-F	Old age female	Multidrug resistant	NA
2005; Australia [17]	496/496	7.3%	Female	NA	Not recommended
2004; Cuba [18]	113/30	27.3%	Old age	S- Cephalosporins Cefibuten	Vaginal topical estrogen was effective
2004 Spain [19]	289/289	25.6%	Increased levels of CRP, microalbuminuria leukocyturia,	NA	NA
2003; Turkey [20]	124/124	26%	Old age duration of diabetes	S- Quinolones Nitrofurans	Continuous surveillance In hospital and community
2002; Chile [21]	100/50	32%	Leukocyturia, longer duration of DM	NA	NA
2002; Zimbabwe [22]	176/Na	32%	Glucosuria, leuckocyturia	S- Aminoglycosides Nicene	Not recommended
2001; Italy [23]	148/Na	46.62%	Hygiene	NA	Careful hygiene habits recommended
1998; Cuba [24]	735/Na	8%	DM, old age, female	NA	Urine culture in case of leukocyturia Recommended
1997; Netherlands [25]	63/63	32%	Female	NA	NA
1996; Kenya [26]	135/135	11%	NA	S- Augmentin, Quinolones, Gentamycin	Not recommended
1988; Colorado [27]	624/206	5.8%	Old age, duration of DM	NA	NA
1986; Nigeria [28]	380/190	6.3%	Female, old age	NA	NA.
1986; California [29]	341/341	9%	Female, duration of DM	NA	NA

Note: Na: Not available; DM: Diabetes mellitus; M: Male; F: Female; S: Sensitive; R: Resistance; Multidrug resistant: Resistant to quinolones and Cephalosporins

Table 2. Summary of characteristics of findings of clinical trials (observational and clinical trials)

Year study site	Patients profile case / control	Intervention	Results	Conclusion
2013; Moscow [37]	87 , Follow up- 12 months	Group 1- treated with esteriol group 2- No therapy	Group 1- ASB in 19.4% Group 2 – ASB in 68.4%	Esteriol prevents UTI in postmenopausal women
2009; Canada [38]	70, Follow up- 3 months to 3 years	36 women – treated 34 women - Not treated	ASB- 36% Antibiotic group 76% had recurrent infection	Treatment does not resolve ASB
2006; Spain [39]	457, Follow up- 12 months	NA	With ASB- 67.6% women Without ASB- 14.9% women	ASB can lead to symptomatic UTI
2006; Canada [40]	50 Type 1 DM-9 Type 2 DM-41 Follow up- 36 months	50- Placebo. Antibiotics after 3 months for symptomatic UTI	Persistent ASB at year 1,2 and 3 36%, 23%, 23%	Treatment not recommended
2004; Netherlands [41]	229	NA	ASB- 19%	Urine culture not recommended
2004; Seattle [42]	218-DM 799-Non DM 2 years follow-up	NA	ASB with DM- 10.6% ASB without DM- 5.5%	ASB is considered complication in postmenopausal women.
2002; Canada [43]	50-placebo 55-treated 36 months follow up	Treatment- Co, orally twice a day	Therapy - 66 episodes of ASB Placebo 23 episodes of ASB	Treatment not recommended
2001; Netherlands [44]	258-type 1 378-type 2, 153- Without DM (control) 18 month follow up	NA	ASB in type 1-21% ASB in type 2- 29% Control -6%	ASB is considered complication of diabetes in women.
1995; Canada [45]	Type 1- 264 Type 2 - 676	NA	ASB- 7.9% (85) out of 85, ASB in type 2- 75.3%, type 1- 22.4%	Origin and duration of diabetes increases ASB

Note: NA: Not available; DM: Diabetes mellitus; Co: Cotrimaxozole

2.3 Epidemiology

From the literature survey the prevalence of ASB is higher in diabetic patients especially in diabetic women, in whom it is three times higher when compared to non-diabetics [8]. Studies from different countries like USA, Canada, Australia, Cuba, Moscow, Italy and many Asian and African countries have shown 5.8% to 53% diabetic patients have ASB [11-29]. The most common aetiological agents causing ASB is found to be *Escherichia coli* (*E. coli*) followed by *Klebsiella* specie, *Proteus* specie, *Pseudomonas* specie, *Enterobacter* specie and gram positive organisms include *Staphylococcus aureus*, group B *Streptococcus*, *Enterococcus* specie [30]. However there are some studies which report *Klebsiella* specie as the common organism isolated [31,32,33]. One of the factor for the increase pathogenicity of uropathogenic *E. coli* is adhesins which promote attachment to the human urogenital tract causing inflammatory response [34].

2.4 Findings

There are very limited numbers of molecular studies especially on asymptomatic bacteriuria in diabetes. Geerling et al. [35] showed that type 1 fimbriae is the most prevalent virulence factor of *E. coli* isolated from urine of diabetic women with ASB. These studies also found an association of decline in renal function and presence of *E. coli* that can code for Cnf or Sfa or express type 1 fimbriae. An animal study by Mizunoe et al. [36], showed that *E. coli* with type 1 fimbriae caused severe scarring, whereas strains without type 1 or with pfimbriae did not. Table 1 shows the prevalence, risk factors, anti-microbial profile and recommendations of the original articles. Table 2 shows the observations, interventions, results and conclusion of various clinical trials which were referred in preparing this article.

3. RISK FACTORS ASSOCIATED WITH ASB

Several studies have shown many factors associated with ASB.

3.1 Age as Risk Factor

Elderly population both male and female have higher prevalence of ASB [46,47]. Dementia generally seen in elderly may be associated with ASB because the affected patients may be unable to recognise symptoms or not able to report symptoms. ASB is also prevalent in elderly long term care residents who are prone to cognitive deficits which may be considered as a risk factor. Poor hygiene and incomplete bladder emptying can also be a potential contributor for ASB [48].

3.2 Gender as Risk Factor

It is evident from the various observational and cross-sectional studies; females are more prone to urinary tract infection both symptomatic and asymptomatic, which is attributed due to short urethra that is in proximity to the areas that are colonised with enteric bacteria [49,13,17]. Geerlings et al. [31] found that prevalence of ASB is higher in women with diabetes mellitus than in women without diabetes: (26% versus 6%). Increased frequency of ASB is seen in postmenopausal women due to significant atrophic changes of the vaginal mucosa and urethra with estrogen deficiency and changes of the vaginal flora leading to high pH and low VHI (vaginal health index) [37]. Studies have also shown that sexually active female can also develop ASB [43].

3.3 Glycosuria, Macroalbumunuria, Glycated Haemoglobin (HbA1c) and Pyuria as Risk Factor

Glycosuria, macroalbumunuria and pyuria was considered as a risk factor for ASB [50,51]. The presence of pyuria in cases of ASB has shown not to be significant however some studies show that presence of pyuria in ASB can be a risk factor for developing symptomatic UTI. Nakano et al. [50] suggest that asymptomatic pyuria is more prevalent in diabetic women than in non-diabetic women: (27% vs 15.8%). The findings of their study indicate degree of neuropathy, nephropathy and retinopathy increases the prevalence of asymptomatic pyuria in women with type 2 diabetes. Papazafiropolou et al. [51] suggest that diabetic subjects with macroalbuminuria showed increased prevalence of ASB compared to diabetic subjects without macroalbuminuria which has showed to be statistically significant with $p<0.001$. The presence of macroalbuminuria has shown to be a marker for endothelial dysfunction leading to structural damages to the kidneys, which in turn makes them susceptible for bacterial colonization resulting in an elevated risk for developing ASB. Kasian et al. [37] and collaborators found no correlation between ASB

and glycosylated haemoglobin A1C whereas Aswani et al. [52] and associates suggest that increased A1C predisposes diabetics to UTI [46], Hale Turan et al. [20] showed significant association of A1C and ASB, Their findings also suggest that high level of A1c in diabetic patients can be defined as a risk factor for ASB. A possible explanation for this could be likely that hyperglycaemia may impair the host defence response to microorganisms by affecting the polymorphonuclear leukocyte functions [53,54]. But their significance has not yet been confirmed through clinical studies. However, other studies found no correlation between glycaemic controls and ASB. Geerlings et al. [31] and Hale turan et al. [20] found significant association between duration of diabetes and ASB, it was considered as a predisposing risk factor. Moreover a trial study showed that the risk factor for the development of symptomatic UTI in women with type 2 diabetes was the presence of ASB [37].

4. MANAGEMENT OF ASB

There has been considerable controversy about the appropriate management of bacteriuria and especially ASB in diabetic patients. The necessity to treat or not to treat ASB in type 2 diabetic patients is matter of controversy, as per IDSA (Infectious diseases Society of America) guidelines, treatment of ASB is recommended only for pregnant women or for those undergoing invasive genitourinary procedures [55]. Several studies have been done in the past to assess whether treatment is required in management of ASB. Although it is recommended that ASB need not be treated, we see high prevalence of *E. coli* sepsis in diabetes patients leading to high mortality [56], treating becomes mandatory when develop active infection for such patients. Papazafiropolou et al. [51] suggests that bacteriological screening of ASB is warranted in diabetic patients especially if pyuria is detected in urine analysis .There is a current opinion that prescription of antibiotics to diabetic patients with ASB is necessary only to those patients who need catheterization or have urinary tract structural abnormalities [48]. Antimicrobial therapy clears bacteriuria in short term, but does not decrease the number of symptomatic episode and hospitalization during long-term follow up [38]. Large number of studies shows that an antimicrobial treatment in ASB does not lead to decreasing of frequency of recurrences and re-infection [11,18,22]. Treatment of ASB in women with diabetes does not appear to reduce complication and that screening and treatment are not needed [38]. In case of postmenopausal diabetic women with ASB the local forms of estriol are found to be effective [57,12,37], safety needs to be established for long term use. In a one year study Cranberry juice was shown to reduce incidence of bacteriuria, however longer trial are needed to confirm their efficacy [58]. This literature reviewed, does not support the antibiotic use for ASB in diabetic patients, however these patients are at high risk of developing urinary tract infection and hence they need to be actively monitored for sign and symptoms of urinary tract infection and early antibiotic use is recommended if they become symptomatic.

5. CONCLUSION

Asymptomatic bacteriuria is common in diabetic patients especially in women and elderly population. This review shows that poor glycaemic control, macroalbuminuria, pyuria, longer duration of diabetes and hygiene can be considered as the risk factor for developing ASB. In most of the developing countries, where health related spending is a major limiting factor to access better healthcare, it is important that a physician in the primary healthcare setup to have a certain level of awareness with regard to diagnosis, prevention and treatment of ASB in the high risk group.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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