

Urinary tract infections in diabetic women during menopause: new basis for a multidisciplinary approach

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Postmenopausal estrogen withdrawal is the common basis for both vulvovaginal and urogenital atrophy. The concept of hormonal dependence of genital tract tissues explains the onset of female low urinary tract symptoms at the menopause. Withdrawal of estrogens during the menopausal transition results in changes in the vagina and external genitalia, which are collectively known as vulvovaginal atrophy (VVA). Menopause is also associated with significant changes in the low urinary tract and pelvic floor. The urethra and surrounding tissues, the bladder muscle and mucosa, and the pelvic floor muscles all express estrogen receptors and become to some extent dysfunctional in the absence of estrogens. Nearly 50% of postmenopausal women have clinical symptoms related to VVA; moreover, most of them report symptoms related to overactive bladder and a significant number also experience concomitant urge urinary incontinence. All these signs and symptoms characterize a new clinical disorder, the so called genitourinary syndrome of menopause (GSM).¹

In postmenopausal women, urinary tract infections (UTIs) often accompany the signs and symptoms of GSM. In particular, UTIs are the most common bacterial infections in women and increase in incidence at the climacteric. For this reason, it is important to identify the underlying abnormalities or modifiable risk factors. Several risk factors for recurrent UTIs have been reported, including the frequency of sexual intercourse, spermicide use, and abnormal pelvic anatomy.^{1,2}

Oral, transdermal, or vaginal use of estrogens is effective in improving GSM. Moreover, vaginal, but not systemic, estrogens are used to treat overactive bladder in postmenopausal women. A systematic review of the effects of estrogen on symptoms suggestive of overactive bladder, and more general, of GSM, concluded that estrogen therapy may be effective in alleviating urogenital

symptoms and that local administration may be the most beneficial.²⁻⁴

Concerning UTIs, antimicrobial prophylaxis has been demonstrated to be effective in reducing the risk of recurrent UTIs in women; particularly quinolone seems to be the first-line antibiotic therapy, but its use may lead to drug resistance of both the causative microorganisms and the indigenous flora. The increasing prevalence of *Escherichia coli* (the most prevalent uropathogen that is resistant to antimicrobial agents) has stimulated interest in novel nonantibiotic methods for the prevention of UTIs. Evidence shows that topical estrogen use normalizes vaginal flora and greatly reduces the risk of UTIs. The use of intravaginal estrogens may be reasonable in postmenopausal women not taking oral estrogens. A number of other strategies have been used to prevent recurrent UTIs, including probiotics, cranberry juice, and D-mannose.²⁻⁵

Parallel to genitourinary changes, early after menopause women begin to gain weight and their body fat is redistributed from a gynecoid to an android pattern. The increase in body mass index and proportion of visceral fat is strongly correlated with the development of hypertension, insulin resistance, and with a number of metabolic risk factors for cardiovascular disease. It is otherwise known that menopause is associated with an increase in the levels of triglycerides, total cholesterol, low-density lipoprotein cholesterol, and lipoprotein (a). The levels of high-density lipoprotein cholesterol were shown to gradually fall after menopause, although they always remained significantly higher in women than in men. This finding was considered a protective factor for women.⁶

Insulin resistance and type 2 diabetes have been associated with a greater cardiovascular risk among women in different clinical trials. Moreover, data from a meta-analysis suggested that the risk for fatal coronary artery disease

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associated with diabetes is 50% higher in women, whereas diabetes and hypertension represent the two most important cardiovascular risk factors in women, especially when they coexist.⁷ Estrogen seems to contribute to glucose homeostasis through increased glucose transport into the cell, whereas the lack of estrogens has been associated with a progressive decrease in glucose-stimulated insulin secretion and insulin sensitivity as well as an increase in insulin resistance. Hormone replacement therapy has been found to exert a beneficial effect on glycated hemoglobin levels in postmenopausal women, but reports of long-term complications of diabetes and risk profile must be accurately assessed.⁸

At present, there are limited data providing reliable evidence for clinical associations between the menopausal status, type 2 diabetes, and UTIs. The study by Borowczyk et al⁹ is one of the very few studies conducted on this topic to date. The authors performed an accurate and novel clinical analysis of UTIs in postmenopausal women affected by type 2 diabetes, encompassing all risk factors and providing clinical and metabolic implications for these complicated patients.

Remarkably, the authors demonstrated that microangiopathy, retinopathy, and nephropathy were the most significant risk factors for UTI and increased its risk 4.9-fold, 2.4-fold, and 3.5-fold, respectively, whereas they found no significant correlations between the duration of diabetes, type of antidiabetic treatment, serum glucose level, the level of diabetic control measured with glycated hemoglobin, and UTI occurrence. Interestingly, the other clinical correlates of UTI in this study were urinary incontinence, hyperlipidemia, and microalbuminuria.

As expected, the major implicated pathogens were *Escherichia coli* (66.7%) and enterococci. Most of the pathogens (93.8%) were susceptible to all tested quinolones, thus suggesting that a 7-day quinolone regimen may be considered the current standard treatment option for these patients.

The results suggest a possible role for low glomerular filtration rate and microalbuminuria in the development of UTI. According to the authors, albuminuria, which mirrors kidney damage, might increase vulnerability to bacterial infections; therefore, they speculated that if impaired renal function increases the risk of UTI, a vicious cycle forms whereby a growing renal insufficiency and recurrent UTIs reciprocally contribute to one another. However, in this study, glucosuria, although considered to contribute to the growth of pathogenic microorganisms, was not demonstrated to be a real risk factor for UTI.

The question remains whether the risk factors for UTI such as urinary incontinence, lower glomerular filtration rate, or microalbuminuria are the causes for UTI and not its results or sequelae of past disease; however, it is difficult to design a methodology that could assess this clearly. Another clinical correlate of UTI found in this innovative work is hyperlipidemia; however, this

phenomenon was not reported in previous studies and remains to be elucidated. The authors suggested that the risk of UTI may be therefore assessed on the basis of a few other markers, which may improve the diagnosis and clinical management of postmenopausal women with diabetes, thus providing an interesting new perspective for this complex group of patients. According to this approach, the dose, delivery system, and duration of treatment should be individualized to relieve symptoms in this patient group. Definitely, the present study is the first to suggest an individualized approach to prognosis and management of diabetes complications. According to these novel hypotheses, the risk of diabetes-related complications may be reflected not only in diabetes duration and metabolic control themselves but rather in their long-term pathophysiological consequences on the urogenital system, thus suggesting a modern, innovative, and more accurate clinical assessment of postmenopausal diabetic patients suffering from UTIs.

The number of patients enrolled to the study may be small, but the authors used very precise exclusion criteria to analyze a group of 40 postmenopausal women with type 2 diabetes. Those criteria included antibiotic therapy in the last 3 months, asymptomatic bacteriuria, renal insufficiency, anatomic genitourinary abnormalities, and catheterization. The use of such strict criteria minimized the effect of potential confounding factors and made the sample size acceptable and the obtained data accurate. The limitation of this observational study was the lack of the control group of postmenopausal women without diabetes.

Whether there is any association between UTIs and menopause in patients with type 2 diabetes is the subject of debate, partly due to the fact that it is difficult to assess the difference between the effects of menopause and those of diabetes in UTIs in aging women. It was demonstrated that UTIs, urinary urgency, frequency, and urgency incontinence are symptoms of GSM in older postmenopausal women, but it will be interesting to understand the real independent impact of menopause and type 2 diabetes on the aging process in women. The genuine improvement of this study is the development of a novel approach to the problem of UTIs in postmenopausal women with type 2 diabetes. An innovative approach should be integrated, focused on prophylaxis, and take into account the many possibilities on 3 levels: risk stratification, vigilance, and early treatment; prevention of diabetes-related risk factors; and adequate control of risk factors resulting from anatomic and hormonal postmenopausal changes.

Though the study by Borowczyk et al⁹ lays the basis for a novel clinical multidisciplinary approach to postmenopausal diabetic patients suffering from UTIs, future studies should help understand the hormonal setting of these study populations in order to better characterize individual menopausal conditions for a tailored

approach. The knowledge of the hormonal changes occurring during menopausal transition and in the postmenopausal period is the first mandatory step for tailoring different treatments to individual needs and symptoms, promoting healthy aging of women.

REFERENCES

- 1 Calleja-Agius J, Brincat MP. The urogenital system and the menopause. *Climacteric*. 2015; 18 Suppl 1: 18-22.
- 2 Palacios S, Mejía A, Neyro JL. Treatment of the genitourinary syndrome of menopause. *Climacteric*. 2015; 18 Suppl 1: 23-29.
- 3 Palacios S, Castelo-Branco C, Currie H, et al. Update on management of genitourinary syndrome of menopause: a practical guide. *Maturitas*. 2015; 82: 308-313.
- 4 Neves-E-Castro M, Birkhauser M, Samsioe G, et al. EMAS position statement: the ten-point guide to the integral management of menopausal health. *Maturitas*. 2015; 81: 88-92.
- 5 Caretto M, Giannini A, Russo E, Simoncini T. Preventing urinary tract infections after menopause without antibiotics. *Maturitas*. 2017; 99: 43-46.
- 6 Matthews KA, Crawford SL, Chae CU, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? *J Am Coll Cardiol*. 2009; 54: 2366-2373.
- 7 Hu G, Tuomilehto J, Silventoinen K, et al. Joint effects of physical activity, body mass index, waist circumference and waist-to-hip ratio with the risk of cardiovascular disease among middle-aged Finnish men and women. *Eur Heart J*. 2004; 25: 2212-2219.
- 8 Steinberg HO, Paradisi G, Cronin J, et al. Type II diabetes abrogates sex differences in endothelial function in premenopausal women. *Circulation*. 2000; 101: 2040-2046.
- 9 Borowczyk M, Chmielarz-Czarnocińska A, Faner-Szczepeńska P, et al. Urinary tract infections in postmenopausal women with type 2 diabetes: clinical correlates and quinolone susceptibility. *Pol Arch Intern Med*. 2017; 127: 336-342.