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Original Article

Obesity and iron deficiency anemia as risk factors for asymptomatic bacteriuria

F. Cuttitta *, D. Torres, D. Vogiatzis, C. Buttà, M. Bellanca, D. Gueli, U. Lupo, C. Schimmenti, G. Virzì, R. Petrantoni, F. Balistreri, S. Paterna, G. Parrinello

Dipartimento Biomedico Medicina Interna e Specialistica, Azienda Ospedaliera Universitaria Policlinico "P. Giaccone", Università degli Studi di Palermo, Via del Vespro 129, 90127 Palermo, Italy

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ABSTRACT

Background: Few studies examined the risk factors of asymptomatic bacteriuria, showing contradictory results. Our study aimed to examine the association between different clinical and laboratory parameters and asymptomatic bacteriuria in internal medicine patients.
Materials and methods: 330 consecutive hospitalized subjects, asymptomatic for urinary tract infections (UTIs), underwent to microscopic examination of urine specimens. 100 subjects were positive for microscopic bacteriuria and were recruited into the study. At the quantitative urine culture 31 subjects of study population were positive while 69 subjects were negative for bacteriuria.
Results: The analysis of clinical characteristics showed that the two groups of subjects (positive and negative urine culture for bacteriuria) were significant different ($p < 0.05$) about obesity (76.7% vs 42% respectively), metabolic syndrome (80.6% vs 44,9%), cholelithiasis (35.5% vs 13,2%) and iron deficiency anemia (80.6% vs 53,6%). The univariate analysis showed that only obesity, cholelithiasis and iron deficiency anemia were positively associated with positive urine culture for bacteriuria (Odds Ratios [OR] = 3.79, p = 0.0003; OR = 2,65, p =0.0091; OR = 2.63, p = 0.0097; respectively). However, the multivariate analysis by logistic regression showed that only obesity and iron deficiency anemia, independently associated with positive urine culture for bacteriuria (OR = 3.9695, p = 0.0075; OR = 3.1569, p = 0.03420 respectively).
Conclusions: This study shows that obesity and iron deficiency anemia are independent risk factors for asymptomatic bacteriuria.

1. Introduction

Urinary tract infections (UTIs) are one of the most common infections for which antibiotics are prescribed. The presence of bacteria in the urine culture of an asymptomatic patient is known as asymptomatic bacteriuria. Asymptomatic bacteriuria is common, with varying prevalence by age, sex, sexual activity, and the presence of genitourinary abnormalities [1,2]. In this study we investigated the association between asymptomatic bacteriuria and further clinical and laboratory parameters.

2. Methods

330 consecutive subjects admitted to Department of Internal Medicine at the University Hospital of Palermo between January 2012 and December 2012, asymptomatic for UTIs, underwent to microscopic examination of urine specimens. 100 subjects were positive for microscopic bacteriuria and were recruited into the study. At the quantitative urine culture 31 subjects (19 females and 12 males) were positive while 69 subjects (46 females and 23 males) were negative for bacteriuria. Then two groups were individualized in the study population according to the positive or negative urine culture.

All the subjects underwent complete examination of urine. Microscopic analysis was performed on midstream urine and urine was cultured incase of positive microscopic analysis for bacteriuria. The cut-off for significant bacteriuria in our laboratory was 4000 or more microorganisms per microliter (μL) of urine.

The diagnosis of asymptomatic bacteriuria is based on the results of urine culture with specimen collected to minimize contamination. For asymptomatic women, two consecutive voided urine specimens with the same bacterial strain $\geq 10^5$ colony-forming units (CFUs) per milliliter (mL) of urine define bacteriuria. For asymptomatic men, a single voided specimen with $\geq 10^5$ CFUs/mL defines bacteriuria. For men or women, a single catheterized urine specimen with a single species $\geq 10^2$ CFUs/mL [1,2].

The metabolic syndrome (MetS) is defined as having a cluster of at least 3 of the following characteristics: elevated fasting glucose

Abbreviations: UTIs, urinary tract infections; OR, odds ratios; μL, microliter; mL, milliliter; dL, deciliter; μg, micrograms; mg, milligrams; CFUs, colony-forming units; BMI, body mass index; BPH, benign prostate hyperplasia.

* Corresponding author at: C. da Gallitano n. 1, CAP 90030, Godrano (PA) Italy. Tel.: +39 3282760680; fax: +39 091 6552140.
E-mail address: francesco_cuttitta@libero.it (F. Cuttitta).

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≥100 mg/dL or taking medications for elevated glucose; abdominal obesity, given as waist circumference: males > 102 cm, females > 88 cm; elevated triglycerides ≥150 mg/dL; reduced HDL-C (high-density lipoprotein cholesterol) < 40 mg/dL in males and < 50 mg/dL in females; elevated blood pressure systolic ≥130 mmHg and/or diastolic ≥85 mmHg or antihypertensive drug treatment in a patient with a history of hypertension [3].

History of atherosclerosis, in our study, is defined as documented presence of atherosclerotic plaques in aorta or in the supra-aortic, coronary or legs' arteries.

2.1. Other cut-off in our laboratory

Neutrophilic leukocytosis = 11000 or more leucocytes per μl of blood with neutrophils ≥ 75%; iron deficiency: serum iron < 50 micrograms (μg)/deciliter (dL); anemia: hemoglobin < 12 g/dL.

2.2. Statistical analysis

Categorical variables are presented as percentages and continuous variables as mean +/− 1 standard deviation. Group differences were assessed using Student's t-test for continuous variables and Chi-square test for categorical variables. The association between different clinical and laboratory parameters and asymptomatic bacteriuria was examined by univariate analysis and multivariate logistic regression analysis. A p value < 0.05 was considered to be statistically significant. Data was analyzed using MedCalc software version 11.3.0.0.

3. Results

The clinical and laboratory parameters of the study subjects are reported in Table 1. In the group with positive urine culture there was not statistically significant difference between males and females (38.7% vs 61.3%; p = 0.1271). Patients with positive urine culture, compared with those with negative urine culture, had a higher significant prevalence (p < 0.05) of obesity (76.7% vs 42%), metabolic syndrome (80.6% vs 44.9%), cholelithiasis (35.5% vs 13.2%) and iron deficiency anemia (80.6% vs 53.6%). Univariate analysis for asymptomatic bacteriuria was performed with all the variables listed in Table 1, but none of them showed a statistically significant association with positive urine culture for bacteriuria, except obesity, cholelithiasis and iron deficiency anemia, which were positively associated with positive urine culture for bacteriuria (Odds Ratios [OR] = 3.79, p = 0.0003; OR = 2.65, p =0.0091; OR = 2.63, p = 0.0097; respectively) (Table 2).

The multivariate logistic regression analysis (Table 3) showed that only obesity and iron deficiency anemia were positively and independently associated with positive urine culture for bacteriuria (OR = 3.9695, p = 0.0075; OR = 3.1569, p = 0.03420 respectively).

In the positive urine culture group (n = 31) isolated bacteria were as follows: *Escherichia coli* 17, *Enterococcus faecalis* 6, *Klebsiella* spp. 4, *Pseudomonas* spp. 2, *Proteus mirabilis* 2. Their antibiotic sensitivity was as follows: in *E. Coli* group, 5 pathogens were sensitive to ciprofloxacin, 4 to levofloxacin, 3 to norfloxacin, 2 to fosfomycin, 2 to ertapenem, and 1 to sulfamethoxazole/trimethoprim; in *E. faecalis* group, 2 pathogens were sensitive to piperacillin/tazobactam, 2 to ampicillin/sulbactam and 2 to levofloxacin; in *Klebsiella* spp. group, 3 pathogens were sensitive to ertapenem and 1 to ciprofloxacin; *Pseudomonas* spp. and *P. mirabilis* were sensitive to ciprofloxacin.

4. Discussions

UTIs are not only a major health issue but also an economic cost [4,5] and, for this reason, a better characterization of their risk factors is important. It is well established that diabetes per se is associated with increased prevalence of asymptomatic bacteriuria, but this wasn't confirmed in our study. The two groups (positive and negative urine culture) were homogeneous about the diabetes and the components of the metabolic syndrome, except obesity (Table 1). Sure enough, they were significantly different about obesity and metabolic syndrome but at the univariate analysis only obesity showed a positive and statistically significant association with positive urine culture. This, probably, was due to the following reason: in the group with metabolic syndrome and positive urine culture (n. 25), 12 subjects had impaired fasting glucose (48%) while 22 subjects were obese (88%). Also univariate and multivariate analysis showed that other pathological conditions in addition to those metabolic were involved in the development of asymptomatic bacteriuria and that these conditions found their highest expression in obesity.

At present, the relationship between obesity and asymptomatic bacteriuria is poorly clear and few studies have investigated this issue. What literature that does exist, though, is consistent with our findings. Geerlings et al. have demonstrated that asymptomatic bacteriuria was independently associated with body mass index (BMI) [6]. Bamgbade

Table 1
Baseline characteristics of patients.

	Urineculture positive n. 31	Urineculture negative n. 69	p Value
Females n(%)	19(61.3%)	46(66.6%)	0.7740
Males n(%)	12(38.7%)	23(33.4%)	0.7740
Mean age	67.9 +/− 15	72.5 +/− 17	0.2133
Atherosclerosis n(%)	19(61.3%)	43(62.3%)	0.89
Hypertension n(%)	28(90.3%)	52(75.4%)	0.1462
Diabetes n(%)	16(51.6%)	29(42.0%)	0.4996
Central obesity* n(%)	23(76.7%)	29(42.0%)	0.0027
MetS n(%)	25(80.6%)	31(44.9%)	0.0019
Cirrhosis n(%)	2(6.5%)	10(14.4%)	0.4206
Cholelithiasis n(%)	11(35.5%)	9(13.2%)	0.0205
ARF n(%)	6(19.4%)	5(7.2%)	0.1446
CRF n(%)	17(54.8%)	41(59.4%)	0.8321
Nephrolithiasis n(%)	14(45.2%)	31(44.9%)	0.84
Urinary catheter n(%)	21(67.7%)	49(71.1%)	0.922
Iron deficiency n(%) anemia	25(80.6%)	37(53.6%)	0.018
Neutrophilic n(%) leukocytosis	12(38.7%)	32(46.4%)	0.6173
CRP (mg/dL)	6.9 +/− 9	6.3 +/− 8	0.7930
TG (mg/dL)	137 +/− 60	113 +/− 61	0.0826
HDL-C (mg/dL)	40 +/− 16	44 +/− 18	0.2604
LDL-C (mg/dL)	89 +/− 30	101 +/− 42	0.1485
T-C (mg/dL)	156 +/− 35	169 +/− 49	0.2204

Abbreviations
ARF = acute renal failure; CRF = chronic renal failure; CRP = C reactive protein; HDL-C = high density lipoprotein-cholesterol; LDL-C = low density lipoprotein-cholesterol; MetS = Metabolic Syndrome; T-C = Total-cholesterol; TG = triglycerides; and Central obesity* = (M ≥ 102, F ≥ 88 cm).

Table 2
Univariate regression for asymptomatic bacteriuria.

Risk factor	Coefficients	Standard error	Confidence intervals (95%CI)	Odds ratios	p Value
Obesity	0.3325	0.0875	0.1589 to 0.5062	3.7998	0.0003
Cholelithiasis	0.3000	0.1128	0.0761 to 0.5238	2.6596	0.0091
Iron deficiency anemia	0.2453	0.0930	0.0607 to 0.4299	2.6378	0.0097

et al. in a retrospective study, in which they evaluated postoperative complications, found relationship between obesity and UTIs [7]. Semins et al. evaluated 95,598 subjects in a national private claims database and demonstrated that an increasingly obese BMI is associated with UTIs [8]. Also Saliba et al. demonstrated that obesity is independently associated with UTIs particularly in males [9]. A plausible explanation is the direct association of obesity with benign prostate hyperplasia (BPH) [10], which in turn is associated with increased risk of UTIs in males [11]. Sure enough obesity may contribute to the development of BPH, because it is associated with elevated estrogen/testosterone ratio and with increase sympathetic activity [10]. However, in our study there was no statistically significant difference between males and females with positive urine culture, then also obese women are plagued by frequent UTIs. Overall women are more at risk of UTIs because of their short urethra and proximity of the urethra to the bowel [12,13]. But structural or functional abnormality of the genitourinary tract may make them more prone to infection. Sure enough obese women frequently have pelvic organ prolapse, urinary incontinence and residual urinary volume. These abnormalities in their urinary tract predispose them to infection. A case–control study of post-menopausal women found that mechanical and physiologic factors affecting bladder emptying (incontinence, cystocele, and postvoiding residual urine) were strongly associated with recurrent UTIs [14]. An increased postvoid residual urinary volume is an independent risk factor for recurrent UTIs in post-menopausal women [15]. Besides obese women may have an increased risk of asymptomatic bacteriuria for the presence of vaginal and uroepithelial cells of 2 unique non-secretor-associated glycolipids that serve as binding sites for specific *E. coli* adhesions [16]. We found, also, that iron deficiency anemia is a significant risk factor for asymptomatic bacteriuria. The literature on the relationship between iron deficiency and infection contains conflicting data and divergent results. Tansarli et al. aimed to systematically review the available evidence to examine whether iron deficiency, compared with normal iron status, is associated with susceptibility to infections. They concluded that the limited available evidence suggests that iron-deficient individuals might be more susceptible to the acquisition of different types of infections compared with those with normal iron status [17]. Musher et al. have reported a strong association between anemia and infections due to gram-positive bacteria [18,19]. In another study, Myers et al. found that post-operative UTIs were more common in anemic patients after total hip replacement than in non-anemic patients [20]. Many studies have suggested that both cell-mediated and humoral immunity can be impaired in iron deficiency anemia [21,22]. For example, the phagocytic activity of the monocytes has been found to be decreased in patients with iron deficiency anemia [21]. An impaired response of T lymphocytes to mitogens and a decreased bactericidal activity of neutrophils and macrophages have been documented in humans with iron deficiency anemia [23]. On the other hand, iron is required for the normal proliferation of tissues with a rapid turnover such as the uroepithelial cells, which constitute a physical barrier to infection. It is also a component of the biological systems that mediate the biosynthesis of peroxide-generating enzymes and nitrous oxide-generating enzymes or the regulation of cytokine production [24]. But what is the connection between obesity, infection and iron deficiency anemia? We hypothesized that obesity increases the risk of asymptomatic bacteriuria and later obesity with asymptomatic bacteriuria favor the occurrence of iron deficiency anemia. Sure, a growing body of evidence suggests that obesity is a chronic inflammatory state and this condition associated with recurrent infections would generate anemia (the anemia of chronic inflammation/infection) [25–30]. On the other hand, recurrent infections may be complicated by asymptomatic microscopic hematuria and also iron constitutes an essential nutrient for most of the human pathogens, then these pathological conditions increases iron deficiency [30–33]. Finally, when iron deficiency anemia is developed, obesity and anemia increase the risk of asymptomatic bacteriuria (Fig. 1). In addition to the abovementioned pathological conditions, obesity and anemia would increase the risk of infections through endothelial dysfunction, oxidative stress, reduced oxygen saturation at potentially infected sites [34]. Sure enough, pathological conditions may also contribute to the development of infections because these factors can lead to disturbances in monocyte migration and cytokine and chemoattractant production [35]. Then the available data suggest a clear association between obesity, iron deficiency anemia and risk of asymptomatic bacteriuria, independently of gender. However more clinical studies are necessary to elucidate the pathophysiology of this association. In conclusion, according to the study of Cai T et al. [36], the two most commonly isolated pathogens, in our study population, were *E. coli* (54, 8%) and *E. faecalis* (19, 35%), while the most commonly used antibiotics in our study population were ciprofloxacin (32%), levofloxacin (19%), ertapenem (16%) and norfloxacin (9,6%). UTIs are one of the most common infections for which antibiotics are prescribed. However recent studies have shown that treating asymptomatic bacteriuria may be counterproductive. The study of Cai T et al. [36] shows that asymptomatic bacteriuria should not be treated in young women affected by UTIs, suggesting it may play a protective role in preventing symptomatic recurrence. This study suggests that asymptomatic bacteriuria need be treated in high-risk groups like pregnant women. Thus, we propose that obese pregnant women with iron deficiency anemia might be screened more frequently for asymptomatic bacteriuria.

5. Limitations

Factors other than obesity and iron deficiency anemia, which were not evaluated, such as underlying diseases associated with these pathological conditions, could be responsible for the higher incidence of asymptomatic bacteriuria in the obese patients with iron deficiency anemia.

This study may also be affected by detection bias, as obese subjects with iron deficiency anemia are more likely to be under medical care, and hence, may be more likely to be diagnosed with asymptomatic bacteriuria leading to differentially overestimation of asymptomatic bacteriuria in this group of subjects. More studies are needed to confirm our findings.

Table 3
Multivariate logistic regression for asymptomatic bacteriuria.

Risk factor	Coefficients	Standard error	Confidence intervals(95%CI)	Odds ratios	p Value
Obesity	1.3787	0.5157	1.4447 to 10.9071	3.9695	0.0075
Cholelithiasis	0.7657	0.5473	0.7356 to 6.2868	2.1504	0.1618
Iron deficiency anemia	1.1496	0.5428	1.0896 to 9.1466	3.1569	0.0342

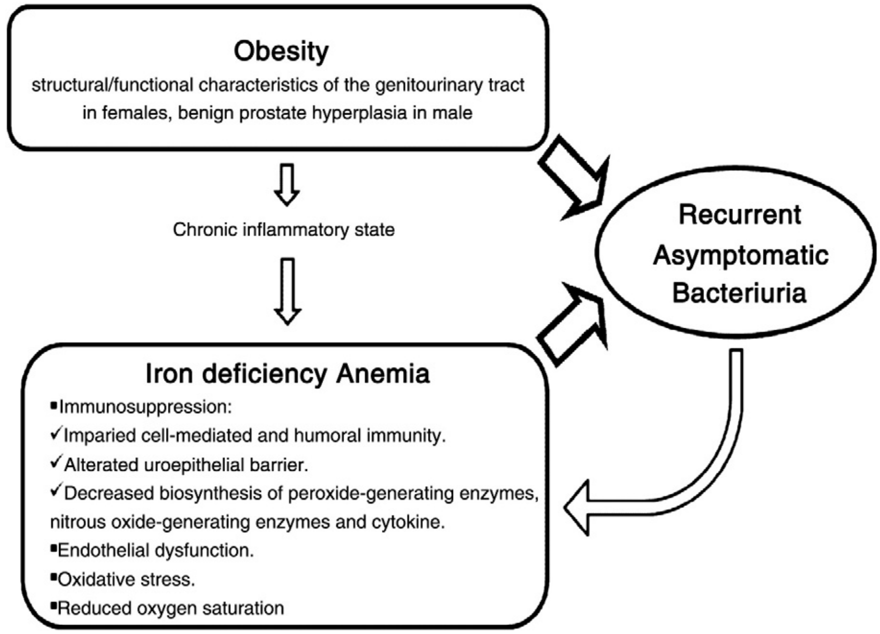

Fig. 1. Pathophysiology of association between obesity, infection and iron deficiency anemia. Obesity increases the risk of asymptomatic bacteriuria and later obesity with asymptomatic bacteriuria favor the occurrence of iron deficiency anemia. Finally, when iron deficiency anemia is developed, increase the risk of asymptomatic bacteriuria.

Learning points

- Obesity increases the risk of anemia and asymptomatic bacteriuria.
- Asymptomatic bacteriuria increases the risk iron deficiency anemia.
- Obesity and anemia increase the risk of asymptomatic bacteriuria.

Conflict of interests

The authors state that they have no conflicts of interest.

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