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Benign prostatic hyperplasia and intraprostatic inflammation are associated with liver inflammation: it's time for prevention

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SUMMARY

Some evidences have supported the link between benign prostatic hyperplasia (BPH)/lower urinary tract symptoms (LUTS) and inflammation. In this study, we aimed to evaluate the association between prostatic inflammation (PI) and non-alcoholic steatohepatitis (NASH) evaluated by a non-invasive scores in a cohort of patients affected by BPH/LUTS. Between January 2012 and January 2016, we conducted a prospective study in a single academic outpatient clinic on 132 consecutive patients who underwent surgery for lower urinary tract symptoms (LUTS) due to bladder outlet obstruction (BOO). A non-invasive non-alcoholic steatohepatitis score (NASH score) was calculated, and PI was evaluated through the Irani score. Patients with a NASH score > 1.05 had an average larger prostate volume (55 vs. 45 cc, $p < 0.05$), a greater waist circumference (103 vs. 93.5 cm, $p < 0.01$), and high values of blood glucose, triglycerides, insulin, and BMI compared to patients without NASH; 36% of patients with an Irani score ≥ 4 had NASH compared to 16.1% of patients who had a NASH score < 1.05 ($p < 0.05$). We found that non-alcoholic steatohepatitis (NASH ≥ 1.05) was an independent risk factor for Irani score ≥4 (OR: 3.24; $p < 0.05$) and of prostate volume ≥ 40 cc (OR: 13.99; $p < 0.01$). LUTS/BPH and NASH can be closely related, underlying common triggers of induction. In particular, inflammation seems to be associated with both conditions and with prostate gland overgrowth. Early identification of this class of patients could play a key role in preventing complications related to disease progression.

INTRODUCTION

Lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH) and metabolic syndrome (MetS) are two of the most common diseases of the aging male, with a high impact on the world economy, due to their association with increased morbidity and mortality (Fenter *et al.*, 2006; Misra & Khurana, 2008; Parsons *et al.*, 2009; Vuichoud & Loughlin, 2015; Egan, 2016; La Vignera *et al.*, 2016). In particular, many clinical studies have demonstrated an association between MetS and prostatic disease, including LUTS and BPH (Moul & McVary, 2010; Parsons *et al.*, 2013; Russo *et al.*, 2017b). In two recent meta-analysis, authors found a close link between prostate volume and MetS, and in particular, they found that obesity, dyslipidemia, and age increased the risk of having MetS (Gacci *et al.*, 2015; Russo *et al.*, 2015a,b). Strengthening these multifactorial associations, in a recent meta-analysis Gacci *et al.* proved that the presence of moderate to severe LUTS significantly increased the risk of reported history of major adverse cardiac events (MACE) ($p < 0.001$) and that this risk was lower in older patients and higher in those with diabetes (Gacci *et al.*, 2016).

The relationship between these two widespread pathologies could be attributed to chronic inflammation; in fact, it has been recently demonstrated that MetS is related to prostate overgrowth and flogosis (Gacci *et al.*, 2013; Vignozzi *et al.*, 2014; De Nunzio *et al.*, 2016; Zhao *et al.*, 2016). Prostate inflammation (PI) is also associated with worse outcome like an increased risk of BPH progression and of medical therapy failure (Kwon *et al.*, 2010; Taoka & Kakehi, 2017). To this regard, MetS is a systemic inflammatory disease that is involved in the etiopathogenesis of different pathologies ranging from atherosclerosis to cancer, and for this reason, it was recently described as 'metaflammation': a chronic condition secondary to greater nutrients in adipose cells (Russo *et al.*, 2016b). All these findings have underlined the possible link about the coexistence of MetS and NAFLD and the coexistence with PI (Russo *et al.*, 2016a).

Herein, we aim to evaluate the association between PI, assessed by the Irani score (IS), and non-alcoholic steatohepatitis (NASH) evaluated by a non-invasive scores in a cohort of patients affected by BPH/LUTS.

MATERIALS AND METHODS

Between January 2012 and January 2016, we conducted a prospective study in a single academic outpatient clinic on 132 consecutive patients who underwent a transurethral resection of the prostate (TURP) for lower urinary tract symptoms (LUTS) due to bladder outlet obstruction (BOO) (ethics committee approval number 578/12).

Inclusion criteria were as follows: International Prostate Symptoms Score (IPSS) ≥ 12, prostate-specific antigen (PSA) < 4 ng/ml, Q_{max} < 15 ml/s, prostate volume greater than 30 cc but less than 80 cc, BOO refractory to alpha-blockers therapy. Table S1 lists the exclusion criteria for the study.

During the week preceding surgery, blood samples were taken to collect serum. Blood pressure and anthropometric measurements, including height and weight for calculating body mass index (BMI) and waist circumference (CV), were determined. LUTS were evaluated by the International Prostate Symptom Score (IPSS) (Barry *et al.*, 1992) and prostate volume (TPV) by transrectal ultrasound. International Index of Erectile Function (IIEF-5) questionnaire was used to evaluate erectile function (Rosen *et al.*, 1997), while metabolic syndrome (MetS) was defined according to the 2006 International Diabetes Federation (IDF) criteria (Alberti *et al.*, 2006).

A non-invasive non-alcoholic steatohepatitis score (NASH score) was developed based on the Finnish and Italian cohort as described by Hyysalo *et al.* through the formula: 1.18 × MetS (yes = 1/no = 0) + 0.45 × type 2 diabetes (yes = 2/no = 0) + 0.15 × fasting serum insulin (mU/L) + 0.04 × AST (IU/L) − 0.94 × AST/ALT − 2.89. Using this model, a cutoff of 1.05 predicted NASH with a sensitivity of 65.2% and specificity of 72.9% (ROC = 0.774) (Hyysalo *et al.*, 2014).

Prostatic Inflammation (PI) was evaluated through all surgical specimens by two independent pathologists and scaled using the Irani score as previous reported (Irani *et al.*, 1997).

Statistical analysis

Continuous variables were summarized as median (interquartile range) due to their non-normal distribution (Kolmogorov–Smirnov test) and categorical variables as percentages. Differences between groups were tested by Mann–Whitney *U*-test. According to NASH score ≥ 1.05, patients were divided into two groups. Age-adjusted linear regression models have been performed to verify factors correlated with prostate inflammation. Multivariate logistic regression models have been constructed to identify predictive factors of high prostate

Table 1 Baseline characteristics of the patients

Patients, *n*	132
Age (years), median (IQR)	69.8 (64.6–74.1)
IPSS, median (IQR)	24.0 (20.0–25.0)
IIEF-5, median (IQR)	15.0 (7.0–19.0)
PSA (ng/dl), median (IQR)	2.3 (1.1–4.0)
TPV (cc), median (IQR)	51.0 (40.0–73.0)
WC (cm), median (IQR)	100.0 (93.0–106.0)
Serum glucose (mg/dl), median (IQR)	95.0 (84.0–116.0)
Cholesterol (mg/dl), median (IQR)	176.0 (154.0–200.0)
HDL, median (IQR)	39.0 (32.0–46.0)
LDL, median (IQR)	112.0 (93.0–143.0)
Triglycerides (mg/dl), median (IQR)	110.0 (72.0–153.0)
BMI (kg/m^2), median (IQR)	27.3 (23.4–25.6)
Insulin (ng/ml), median (IQR)	6.8 (3.8–12.1)
NASH score, median (IQR)	−0.8 (−1.7 to −0.1)
Irani grade, median (IQR)	2.0 (1.0–2.0)
Irani aggressiveness, median (IQR)	1.00
Irani score, median (IQR)	3.0 (2.0–4.0)
Metabolic Syndrome (MetS), *n* (%)	75/132 (56.8%)
NASH ≥1.05, *n* (%)	75/132 (56.8%)
Irani score ≥4, *n* (%)	36/132 (27.3%)
IPSS> 20, *n* (%)	102/132 (77.3%)
No MetS. No NASH, *n* (%)	40/132 (30.3%)
MetS or NASH, *n* (%)	35/132 (26.5%)
MetS + NASH, *n* (%)	57/132 (43.2%)

IPSS, international prostate symptoms score; PSA, prostate-specific antigen; IIEF-5, international index of erection function; TPV, prostate volume; WC, waist circumference; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index; NASH score, 1.18 × MetS (yes = 1) + 0.45 × diabetes (yes = 2) + 0.15 × fasting serum insulin + 0.04 × serum AST − 0.94 × (AST/ALT) − 2.89.

Table 2 Baseline characteristics of the patient population according to NASH score cutoff of 1.05

Variables	NASH score < 1.05	NASH score ≥ 1.05	*p*-value
Patients, *n* (%)	57 (43.2%)	75 (56.8%)	0.220
Age (years), median (IQR)	71.3 (66.4–74.4)	67.1 (63.2–72.8)	0.045
IPSS, median (IQR)	24.0 (19.0–25.0)	12.0 (8.0–19.0)	0.989
IIEF-5, median (IQR)	16.5 (6.0–19.0)	15.0 (7.0–19.0)	0.278
PSA (ng/dl), median (IQR)	2.65 (1.1–4.0)	2.2 (1.2–3.6)	0.038
TPV (cc), median (IQR)	45.0 (40.0–57.1)	55.0 (47.0–77.0)	0.001
WC (cm), median (IQR)	93.5 (86.0–100.0)	103.0 (97.0–107.0)	0.001
Serum glucose (mg/dl), median (IQR)	86.0 (81.0–106.0)	111.0 (92.0–128.0)	0.001
Cholesterol (mg/dl), median (IQR)	179.5 (154.0–199.0)	172.0 (158.0–201.0)	0.840
HDL, median (IQR)	41.0 (35.0–45.0)	38.0 (31.0–46.0)	0.252
LDL, median (IQR)	119.0 (93.0–144.0)	111.0 (89.0–132.0)	0.206
Triglycerides (mg/dl), median (IQR)	79.5.0 (57.0–129.0)	130.0 (91.0–175.0)	0.001
BMI (Kg/m^2), median (IQR)	24.6 (23.0–27.8)	28.1 (25.8–30.)	0.006
Insulin (ng/ml), median (IQR)	3.9 (3.0–4.5)	11.4 (8.1–13.9)	0.001
Irani grade, median (IQR)	1.5 (1.0–2.0)	2.0 (1.0–2.0)	0.065
Irani aggressiveness, median (IQR)	1.00 (1.0–1.0)	1.00 (1.0–2.0)	0.001
Irani score, median (IQR)	2.0 (2.0–3.0)	3.0 (2.0–4.0)	0.004
Metabolic syndrome (MetS), *n* (%)	17 (30.4%)	57 (76%)	0.001
IR, *n* (%)	2 (3.6%)	39 (52%)	0.001
Irani score ≥4, *n* (%)	9 (16.1%)	27 (36%)	0.011
IPSS> 20, *n* (%)	41 (73.2%)	60 (80%)	0.361
No MetS. No NASH, *n* (%)	39 (69.6%)	0 (0%)	0.001
MetS or NASH, *n* (%)	17 (30.4%)	18 (24%)	0.001
MetS + NASH, *n* (%)	0 (0%)	57 (76%)	0.001

IPSS, international prostate symptoms score; PSA, prostate-specific antigen; IIEF-5, international index of erection function; TPV, prostate volume; WC, waist circumference; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index; IR, insulin resistance; NASH score, 1.18 × MetS (yes = 1) + 0.45 × diabetes (yes = 2) + 0.15 × fasting serum insulin + 0.04 × serum AST − 0.94 × (AST/ALT) − 2.89.

inflammation (Irani score ≥ 4) and prostate volume ≥40 cc. For all statistical comparisons, significance was considered as $p < 0.05$ using SPSS v. 19 software (SPSS Inc, IBM Corp, Somers, NY, USA).

RESULTS

Table 1 lists the baseline characteristics of the patients' cohort. The prevalence of patients affected by MetS alone was 56.8% (75/132), by NASH was 56.8% (75/132), and by severe intraprostatic inflammation (Irani ≥4) with both diseases was 27.3% (36/132); 77.3% of the patients included in the study had a IPSS score >20.

Patients with a NASH score >1.05 had an average larger prostate volume (55 vs. 45 cc, $p < 0.05$), a greater waist circumference (103 vs. 93.5 cm, $p < 0.01$), and high values of blood glucose, triglycerides, insulin, and BMI compared to patients who did not have NASH. Seventy-seven percent of patients with MetS had a NASH score ≥1.05. Prostatic inflammation was also present in patients with NASH: 36% of patients with an Irani score ≥4 had steatohepatitis compared to 16.1% of patients who had a NASH score <1.05 (Table 2).

The age-adjusted linear regression analysis demonstrated that fasting glucose, LDL, insulin, and NASH were associated with increase in Irani score and therefore with intraprostatic inflammation. In particular, NASH was associated with increase in Irani grade ($r = 0.81$; $p < 0.01$), Irani aggressiveness ($r = 0.44$; $p < 0.05$), and Irani score ($r = 0.72$; $p < 0.01$).

The logistic regression analysis adjusted for age, PSA, prostate volume revealed that the presence of NASH ≥ 1.05 was an independent risk factor for Irani score ≥4 (OR: 3.26; $p < 0.05$) and of prostate volume ≥40 cc (OR: 13.99; $p < 0.01$) (Fig. 1).

DISCUSSION

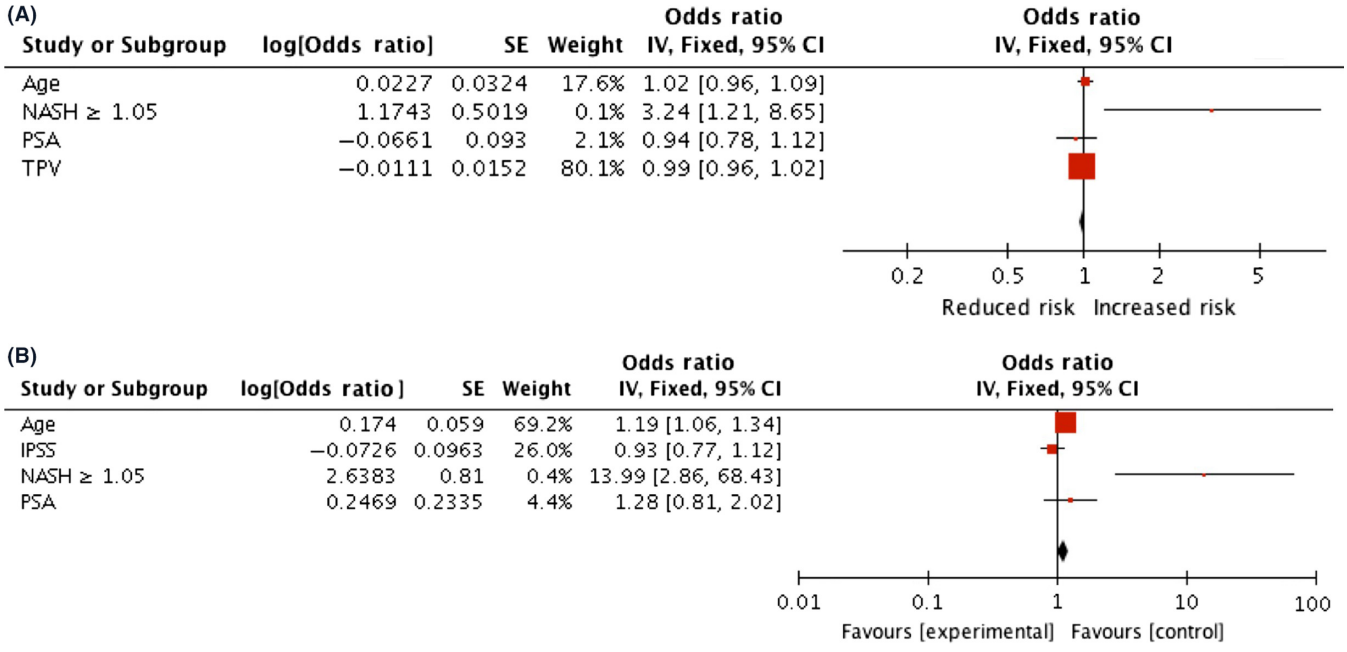
Non-alcoholic fatty liver disease (NAFLD) is a multifactorial disease, and it is the most prevalent form of chronic liver disease in Western countries. Furthermore, NAFLD is strongly associated with both hepatic and cardiometabolic mortality. In line with the increase in obesity due to changes in lifestyles, NAFLD has become increasingly common during the last decades. Central obesity, MetS, diabetes mellitus, and dyslipidemia are the most common risk factors (Karim *et al.*, 2015) of NAFLD. Based on this premises, many evidences have suggested the role of systemic inflammation in the context of NAFLD, referred as non-alcoholic steatohepatitis (NASH).

Although liver biopsy is currently the gold standard for diagnosing progressive steatohepatitis, it has many drawbacks, such as sampling error, cost, risk of complications, and is not possible for all NAFLD patients (Kleiner *et al.*, 2005).

NAFLD and NASH are etiologically associated with systemic and hepatic insulin resistance (Marchesini *et al.*, 2003); insulin-like growth factor (IGF) and high serum concentrations of insulin and IGF-1 are considered central mediators of the stromal–epithelial interactions. High glucose concentration, moreover, increase oxidative stress, leading to a higher risk of insulin resistance (IR) that is the one of major aberration of MetS. A link between hyperinsulinemia and prostatic hyperplasia was first suggested in 1998 by Hammarsten *et al.*; this study showed that diabetes, arterial hypertension, obesity, high fast insulin levels, and low HDL-cholesterol levels were all risk factors for prostatic enlargement (Hammarsten *et al.*, 1998). Insulin resistance is believed a key point that leads to excessive fat accumulation also in the liver (Asrih & Jornayvaz, 2015). The association between non-alcoholic fatty liver disease and benign prostatic hyperplasia/lower urinary tract symptoms has emerged in the last few years in literature (Russo *et al.*, 2015c). To this regard, we have recently demonstrated that patients affected by NAFLD showed greater risk of having moderate–severe LUTS and high fatty liver index (FLI) can be used to predict subjects at high risk of lower urinary tract symptoms (Russo *et al.*, 2015c).

We would point out that inflammation plays a central role in the pathophysiology of MetS and NAFLD and it has a key role in

Figure 1 Multivariate logistic regression for significant predictors of Irani score ≥4 (A) and prostate total volume ≥40 cc (B), adjusted for age, PSA, TPV, IPSS. [Colour figure can be viewed at wileyonlinelibrary.com]



the severity and progression of BPH-related symptoms; insulin resistance and metabolic syndrome are the common risks factors for BPH and NAFLD, and similar common etiopathogenic factors may have similar trophic effects on hepatic tissue and prostate.

The role of erectile dysfunction as an early indicator of a possible concurrent cardiovascular disease has been widely discussed in the literature; with this in mind, andrologists, cardiologists, and diabetologists (and general practitioners) have the great opportunity to collaborate and find shared clinical workup for the benefit of a large number of men (Foresta *et al.*, 2017). Similarly, with our study and our results on the association between NASH score and prostate inflammation and hyperplasia, we would like to underline the importance of a more accurate (and possibly hepatological) glicometabolic evaluation in patients with prostatic inflammation and BPH so as to recognize and eventually treat patients who have NAFLD by preventing their dangerous complications that could lead to at cirrhosis and hepatocellular carcinoma.

Taking into account that obesity represents a key factor for these multifactorial disease, lifestyle and diet changes should be considered and suggested to the patients in order to prevent the disease and progression. However, research evaluating the role of any single dietary component and LUTS prevention is difficult to interpret given the potential influence of other nutrients in relation to the total dietary exposure (Vargas *et al.*, 2016; Russo *et al.*, 2017a). In this context, the traditional Mediterranean diet is characterized by high intakes of fruits, vegetables, legumes, nuts, breads, and other largely unrefined cereals; olive oil as the main fat; moderately high fish; moderate alcohol, mainly wine; low consumption of milk and dairy products, mainly from yogurt and cheeses; and low consumption of poultry, red meat, and eggs (deKoning & Anand, 2004). Although there is a lack of literature data about the role of Mediterranean diet and LUTS, Liu *et al.* have demonstrated that fruit and vegetable consumption significantly reduced the risk of LUTS progression by 37.2% (OR: 0.628) or risk of symptomatic BPH by 34.3% (OR: 0.657) after 4 years compared with the moderate group consumption (Liu *et al.*, 2016). For all these reasons, diet and lifestyle changes may represent an important issue for prevention and mitigate severity of BPH/LUTS and NAFLD.

However, our study has several limitations. First, we did not perform the liver biopsy that remains the gold standard for the diagnosis of steatohepatitis, but we used a score that, although good, does not have an excellent accuracy and can overestimate the true prevalence of NASH. Second, we did not evaluate the impact of NAFLD/NASH persistence of symptoms after surgery neither how many years patients were previously suffering from metabolic syndrome (key aspect in the onset of the intraprostatic inflammation). Another limitation of this study is that the study was not a prospective longitudinal study, which could result in an incomplete explanation of causal relationships; however, considering that is not easy to perform a prospective longitudinal study for assessing this topic, it may be useful to extend the study to more patients.

CONCLUSION

LUTS/BPH and NASH can be closely related, underlying common triggers of induction. In particular, inflammation seems to be associated with both conditions and with prostate gland overgrowth. Early identification of this class of patients could play a key role in preventing complications related to disease progression.

CONFLICT OF INTEREST

Each author declares no conflict of interest.

AUTHORS' CONTRIBUTION

S. Privitera, S. La Vignera, and R.A. Condorelli drafted the manuscript. G.I. Russo participated in the project development, collecting data, and statistical analysis. A.E. Calogero, S. Cimino, and G. Morgia involved in the supervision. V. Favilla collected the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Exclusion criteria for the study.