Metabolic syndrome and prostate abnormalities in male subjects of infertile couples

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INTRODUCTION

Metabolic syndrome (MetS) is a diagnostic category based on a cluster of abnormalities (abdominal obesity, impaired glucose metabolism, hypertriglyceridemia, reduced high-density lipoprotein (HDL) cholesterol and hypertension) that identifies subjects at high risk for diabetes and cardiovascular diseases.¹⁻³ Various diagnostic criteria for MetS have been proposed over recent years. Indeed, the parameters to be used for the diagnosis of MetS and their thresholds remains under debate.⁴⁻⁵ Nonetheless, insulin resistance has been recognized as the common feature underlying MetS,⁶ with visceral adiposity being the driving force.²⁻⁵ In addition to diabetes and cardiovascular diseases, several other pathologic conditions are associated with MetS including nonalcoholic fatty liver disease, polycystic ovarian syndrome, obstructive sleep apnea and lipodystrophy.² In addition, in the male, hypogonadism, erectile dysfunction and psychological disturbances are often associated with MetS.⁶⁻⁹

A possible association between MetS and male infertility has also been hypothesized.¹ Although several studies have evaluated the impact of being overweight and obesity on male reproductive health,¹⁰⁻¹³ only a few studies have assessed the influence of some MetS components on male fertility¹ and none have considered MetS to be a diagnostic category. We evaluated this topic specifically in a cohort of 351 males of infertile couples without known genetic abnormalities.⁷ Even after adjusting for confounders, we noted that an increase in the number of MetS components associated with hypogonadism, poor sperm morphology (but not other sperm parameters), testis ultrasound nonhomogeneity, erectile dysfunction, somatization (expression of physical symptoms in the absence of medically explained physical illness) and depressive traits.⁹

In addition, in this last decade, a growing body of evidence has also documented an independent association between benign prostatic hyperplasia (BPH)/lower urinary tract symptoms (LUTS) and obesity/MetS.¹⁴⁻¹⁸ In particular, we previously reported a positive correlation between MetS and BPH-related chronic inflammation in patients undergoing surgery for BPH.¹⁹,²⁰ A recently published epidemiological survey of the Boston area (BACH) confirmed an association between MetS and LUTS; however, when subjects were stratified by age, the association was confirmed only in the youngest individuals.²¹

Keywords: infertile men; interleukin-8; metabolic syndrome; prostate-related symptoms and signs; semen analysis; transrectal ultrasound
This study is aimed at investigating systematically the possible associations between MetS and prostate-related symptoms and signs in a cohort of young men in infertile unions and to establish whether these associations correlate with fertility.

**MATERIALS AND METHODS**

We retrospectively evaluated a consecutive series of 187 male patients (age: 36.5 ± 8.3 years) who attended our Outpatient Clinic initially between January 2010 and December 2011 seeking medical care for infertility. Based on guidelines of the World Health Organization, infertility was defined as the inability of a sexually active couple to achieve pregnancy despite unprotected intercourse over a period of greater than 12 months. Subjects with karyotypic abnormalities (n = 3), chromosome Y microdeletions (n = 2) or an absence of at least one vas deferens and/or one seminal vesicle (n = 11) were excluded from the analysis. Hence, a cohort of 171 selected patients was used for the analyses. The sociodemographic and clinical phenotype of the sample population is summarized in Table 1.

All patients were evaluated prior to any treatment. All enrolled patients underwent the typical diagnostic protocol used for infertility in newly referred subjects at the Andrology Outpatient Clinic. They underwent a complete andrological and physical examination and blood pressure (mean of three measurements taken 5 min apart in the sitting position using a standard sphygmomanometer), height, weight and waist circumference were measured. In addition, routine scrotal and transrectal ultrasounds were performed because our regional healthcare system does not allow any genetic analysis on infertile patients unless a suspected obstruction has been evaluated. All data were collected as part of the routine clinical procedure; therefore, based on Italian law, approval from the local Ethical Committee was not required. In addition, at the time of the initial visit, all patients provided written, informed consent to have their clinical records included in a dedicated database to be used, anonymously, for clinical research purposes.

**MetS assessment**

MetS was defined, based on the National Cholesterol Education Program Third Adult Treatment Panel, as the presence of three or more of the following five factors: central obesity (waist circumference >102 cm), elevated triglycerides (≥1.7 mmol l⁻¹ or treated for elevated triglycerides), elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or treated for hypertension), elevated fasting glucose (≥6.1 mmol l⁻¹ or treated for diabetes) and reduced HDL cholesterol (<1.03 mmol l⁻¹ or treated for dyslipidemia).

**Biochemical parameters**

Blood samples were drawn in the morning after an overnight fast to determine blood glucose (using the glucose oxidase method; Aeroset Abbott, Rome, Italy), HDL cholesterol and triglycerides (using the automated enzymatic colorimetric method; Aeroset Abbott, Rome, Italy), total testosterone (TT, using the electrochemiluminescent method; Modular Roche, Milan, Italy), insulin levels and sex hormone binding globulin (SHBG) using an electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). Free testosterone was calculated based on Vermeulen’s formula (available at http://www.issam.ch/freetesto.htm).²⁷

**Semen analyses and determination of seminal plasma interleukin 8 (sIL-8) levels**

On the same day as the ultrasound, all patients underwent semen analysis, which was performed based on World Health Organization analysis, which was performed based on World Health Organization.
criteria. In addition, routine urine and seminal cultures were assessed in all men. Furthermore, sIL-8, a reliable surrogate marker of prostatitis, was also quantified. Seminal plasma aliquots were frozen and stored for later quantification of sIL-8 levels using conventional two-site enzyme-linked immunosorbent assay (ELISA; human IL-8 ELISA set; BD Biosciences, San Diego, CA, USA) according to the manufacturer’s instructions. Each seminal plasma sample was diluted from 1:5 to 1:625. Assay sensitivity for sIL-8 was <1 pg ml⁻¹.

### Screening of prostate-related symptoms and lower urinary tract symptoms

Patients were asked to complete the Italian translation of the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), which is a brief self-reported questionnaire for screening prostatitis symptoms and that scores for pain, voiding symptoms and quality of life. The NIH-CPSI total score was calculated as the sum of the scores of these domains. LUTS were evaluated using the Italian translation of the International Prostate Symptom Score (IPSS), which is a brief self-administered questionnaire for screening symptoms related to BPH and that comprises seven questions on symptoms and one question on quality of life. The NIH-CPSI total score was calculated as the sum of the scores of these domains. LUTS were evaluated using the Italian translation of the International Prostate Symptom Score (IPSS), which is a brief self-administered questionnaire for screening symptoms related to BPH.

### Transrectal color Doppler ultrasonography (CDU)

We previously reported an association between MetS and scrotal parameters in a larger cohort of subjects who attended our unit for infertility. The characteristics of that cohort were not different from the cohort in this study; thus, in this study, we focused on the possible associations between MetS and transrectal ultrasound features. All patients underwent scrotal and transrectal CDU; the latter before and after ejaculation. To prevent bias on the part of the examiner, scrotal and transrectal CDU was performed intermittently by two experienced physicians who were unaware of the clinical data and who used the same ultrasonographic console (Hitachi H21, Hitachi Medical System, Tokyo, Japan). Prostate and seminal vesicle CDU features were studied by scanning the organs at 5 mm intervals at various longitudinal, transverse and oblique scans with patients lying in a supine position. Testicular and epididymal CDU features were examined based on previous studies. Identical testicular and epididymal features are defined based on previous studies.

### Identification of case patients and controls

MetS was defined as described above. Subjects with ≥3 MetS components (n = 22) were compared with controls selected from the same cohort at a 1:2 ratio (n = 44). For each case, the first two patients following those with MetS within the same series who were the same age (±4 years) and who showed a similar TT level (± 4 nmol/l), smoking habit (current/nonsmoker) and moderate-severe alcohol consumption (current/no consumption of ≥4 drinks per day based on a previous publication) for statistical analyses that compared cases with age-1, TT-, smoking habit-, moderate-severe alcohol consumption-matched controls, associations with P < 0.05 were considered significant.

### Data analyses

Data were expressed as the mean ± s.d. when normally distributed, the median (quartiles) for parameters with non-normal distributions and as percentages when categorical. Correlations were assessed using Spearman’s or Pearson’s methods as appropriate. Differences between more than two groups were assessed using one-way analysis of variances. Unpaired two-sided Student’s t-test was used to compare means of normally distributed parameters. Relative risks and 95% confidence intervals were calculated for correlations of categorical parameters, and chi-squared tests were used for comparisons. Stepwise multiple linear, logistic binary or ordinal regressions were applied for multivariate analyses as appropriate. All statistical analyses were performed in SPSS (Statistical Package for Social Sciences, Chicago, USA) for Windows 20.0.

### RESULTS

Among the 171 patients studied (age: 36.6 ± 8.4 years), 44.4% (n = 76) showed no components of MetS, whereas one, two, three, four and five MetS factors were present in 47 (27.5%), 26 (15.2%), 16 (9.4%), three (1.75%) and three (1.75%) subjects, respectively. Twenty-two subjects (12.9%) fulfilled the criteria of National Cholesterol Education Program Third Adult Treatment Panel MetS. Subjects with MetS were older (43.8 ± 10.6 vs. 35.5 ± 7.5 years for MetS and no-MetS subjects, respectively; P < 0.0001). No difference in the percentage of subjects who smoked currently or consumed moderate-severe amounts of alcohol was found when MetS...
and no-MetS subjects were compared (21.1% vs 28.6%, P = 0.496; 16.7% vs 24.8%, P = 0.233; MetS vs no-MetS subjects, respectively). In addition, no difference in the prevalence of leukocytospermia or current positive urine and/or seminal cultures was observed when men with and without MetS were compared (5.3% vs 8.8%, P = 0.508; 5.6% vs 8.1%, P = 0.575; MetS vs non-MetS subjects, respectively).

**Correlations of MetS with hormonal, clinical and semen parameters**

Age-adjusted logistic ordinal models showed that insulin levels increased as a function of MetS components (Wald = 29.5 (0.09–0.18), P < 0.0001) (Figure 1a). Figure 1b–1d also showed the age-adjusted relationships between insulin and TT, SHBG and calculated free testosterone: all of these parameters decreased as a function of increasing insulin levels (adjusted r = -0.359, P < 0.0001; adjusted r = -0.200, P < 0.001; adjusted r = -0.320, P < 0.0001, respectively). In view of these associations, all the following analyses were adjusted for age, insulin and TT levels.

Digitorectal examinations revealed that an enlarged prostate was positively associated with the number of MetS components (hazard ratio (HR) = 1.47 (1.03–2.14)) for each increment in the number of MetS components, P < 0.05. Of the semen parameters, only normal semen morphology was negatively associated with an increasing number of MetS components (Wald = 5.59 (-0.15 to -0.01), P < 0.02).

No association between MetS components and other physical or seminal parameters including leukocytospermia was observed (data not shown). Finally, no association between MetS components and current positive urine and/or seminal cultures was detected (data not shown).

**Correlations of MetS with prostate-related symptoms and signs (sIL-8)**

No association was found between MetS and prostate-related symptoms as captured by both NIH-CPSI and IPSS (not shown). A stepwise, positive correlation between the number of MetS components and sIL-8 levels was observed (Wald = 4.32 (0.04–1.48), P < 0.05) (Figure 2a). In particular, among the MetS components, only waist circumference was positively associated with sIL-8 (Figure 2b).

**Correlations of MetS with transrectal ultrasound parameters**

A progressively higher prostate volume was detected by ultrasound as a function of an increasing number of MetS components (Wald = 17.6 (0.05–0.13), P < 0.0001) (Figure 2c). In a logistic iterative analysis, of the MetS factors, waist size and reduced HDL cholesterol were significantly associated with prostate volume (Figure 2d). Interestingly, TZV was positively correlated with total prostate volume even after adjusting for the aforementioned confounders (adjusted r = 0.757, P < 0.0001). Thus, TZV also increased as a function of an increasing number of MetS components (Wald = 12.5 (0.07–0.24), P < 0.0001). In addition, TZV of MetS subjects was significantly higher than other subjects (10.7 ± 10.8 vs 3.9 ± 2.6 ml; P < 0.0001; subjects with MetS vs those without MetS, respectively). Finally, similarly to total prostate volume results, TZV was significantly associated with reduced HDL cholesterol levels (HR = 1.15 (1.01–1.31), P < 0.05). Conversely, only a trend towards statistical significance was observed for increased waist (HR = 1.11 (0.99–1.24), P = 0.08).

A positive association between an increasing number of MetS components was also observed for some ultrasonographic prostate features, such as arterial peak systolic velocity (APPSV, Wald = 9.57 (0.05–0.24), P = 0.002) (Figure 3a) and diameter of the major calcification (Wald = 3.11 (0.01–0.13), P < 0.05) (Figure 3c). Using a binary logistic model, moderate-severe prostate texture nonhomogeneity was also associated with an increase in the number of MetS components (HR = 1.87 (1.05–3.33) for each increment in the number of MetS components, P < 0.05) (Figure 3c). Of the MetS components, only increased waist circumference was significantly associated with APPSV (Figure 3b) and with moderate-severe texture nonhomogeneity (Figure 3d). After adjusting for confounders, no associations between MetS related-prostate CDU abnormalities and standard semen parameters were observed (Table 2). Finally, no associations between the number of MetS components and seminal vesicle features or the mean diameter of the deferential ampulla were observed (data not shown).

**Case-control analyses**

Correlations between MetS and seminal or ultrasound parameters showing statistical significance were further assessed by comparing subjects with MetS with matched controls (matched for age, TT, smoking habit and moderate-severe alcohol consumption) (Table 3) at a 1:2 ratio. Even in the case-controlled analyses, subjects with three or more MetS components showed a lower percentage of normal sperm morphology, higher sIL8 levels and more frequent prostate abnormalities, such as greater volume, higher arterial peak systolic velocity, greater calcification size and prevalence of moderate-severe nonhomogeneity (Table 3). No difference in the prevalence of leukocytospermia or current positive urine and/or seminal cultures was observed when MetS subjects were compared with controls (Table 3).

**Correlations of insulin levels with clinical, seminal and transrectal ultrasound parameters**

Univariate analyses revealed positive associations between insulin levels and increased prostate volume detected by either digitorectal examination (RR = 1.08 (1.03–1.14), P = 0.002 for each insulin mU1 increment) or ultrasound (r = 0.294, P < 0.0001), moderate-severe texture nonhomogeneity (RR = 1.08 (1.00–1.17), P = 0.05 for each insulin mU1 increment), hyperemia (RR = 1.05 (1.00–1.11), P < 0.05 for each insulin mU1 increment) and arterial peak systolic velocity (r = 0.286, P < 0.0001) and a negative correlation with the
prostatic venous plexus diameter ($r = -0.180, P < 0.02$). When a multivariate regression model was applied that included age and TT, the significant associations between insulin levels and prostate volume detected both by digitorectal examination (HR = 1.07 (1.01–1.13), $P < 0.05$ for each insulin mU l$^{-1}$ increment) and ultrasound (adjusted $r = 0.327, P < 0.0001$) (Figure 4a) and arterial peak systolic velocity (adjusted $r = 0.229, P = 0.002$) (Figure 4b) were confirmed. However, when the number of MetS components was introduced into the same model, only prostate volume detected by ultrasound was significantly associated with insulin levels (adjusted $r = 0.171, P < 0.05$).

Even after adjusting for the aforementioned confounders, no associations between insulin levels and semen parameters, sIL-8 levels, seminal vesicle features or diameters of the deferential ampulla were observed (data not shown).

**DISCUSSION**

This study demonstrates that in a cohort of relatively young male subjects examined for infertility, a stepwise, component-dependent association was observed between an increase in MetS severity and prostate enlargement and/or inflammatory signs (including sIL-8 levels and CDU abnormalities), but not with current infection of the male genital tract. No association between MetS-related prostate CDU abnormalities and semen parameters was detected. However, in this cohort, MetS was associated with poor sperm morphology. Reduced HDL levels and increased abdominal adiposity were the
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Metabolic syndrome and prostate

Figure 3: Association between metabolic syndrome (MetS) and arterial prostatic peak systolic velocity (APPSV), texture nonhomogeneity and major calcification size of the prostate as evaluated using color Doppler ultrasound (CDU). Association between the number of metabolic syndrome (MetS) components (NCEP-ATPIII classification) and APPSV (a), moderate-severe nonhomogeneity prevalence (c) or major calcification size (c, inset) of the prostate as evaluated using CDU. The number of subjects with no, one or more MetS components is indicated. Hazard ratio (95% confidence interval) for APPSV (b) and prostate moderate-severe nonhomogeneity (d) as detected by iterative logistic regression analysis considering MetS components as putative predictors. MetS components are defined by abnormal parameters or by specific therapy (t) based on NCEP-ATPIII groupings. m-s, moderate-severe.

Figure 4: Associations between insulin levels and prostate volume (a) or arterial prostatic peak systolic velocity (b) evaluated using color Doppler ultrasound (CDU). Subjects with or without metabolic syndrome are shown as filled or empty dots, respectively.

Main correlates of prostate enlargement in this young, asymptomatic cohort.

The association between MetS and prostate enlargement is consistent with several previous reports.\textsuperscript{20,42–49} Thus far, only a few studies have examined relatively young adults, and they offer conflicting results.\textsuperscript{20,51} Here, we report a novel association in a relatively young population (mean age 36.6 ± 8.4 years) of males of infertile couples. Increased central obesity and reduced HDL cholesterol were the parameters that most closely correlated with prostate enlargement. A potential relationship between BPH/prostate enlargement and obesity or increased waist circumference has been widely reported in several\textsuperscript{14,52} but not all previous studies.\textsuperscript{20} Moreover, low HDL cholesterol has been previously reported as a risk factor for the development of BPH.\textsuperscript{20,42–48} Our data suggest that MetS, and particularly high waist circumference and reduced HDL cholesterol, may play an important role in prostate growth onset at a young age.

We also noted a significant, stepwise correlation between the number of MetS components and seminal IL-8 (sIL-8), which has been proposed as a surrogate marker of prostate inflammation.\textsuperscript{29,53–55} IL-8 is a proinflammatory chemokine that is secreted by several cell types and that contributes to inflammation by acting in concert with IL-1β and IL-6.\textsuperscript{56–58} Moreover, low HDL cholesterol has been previously reported as a risk factor for the development of BPH.\textsuperscript{20,42–48} IL-8 in seminal plasma is considerably higher when compared with serum levels,\textsuperscript{62,63} local (within the male genital tract) production has been suggested.\textsuperscript{55,59,63} Of different cytokines and chemokines, sIL-8 appears to be the most reliable and predictive surrogate marker of prostatitis,\textsuperscript{29,54} and it is associated with CDU features suggestive of prostate inflammation in patients with male accessory gland infection (MAGI).\textsuperscript{23} Because IL-8 in seminal plasma is considerably higher when compared with serum levels,\textsuperscript{62,63} local (within the male genital tract) production has been suggested.\textsuperscript{55,59,63} Of different cytokines and chemokines, sIL-8 appears to be the most reliable and predictive surrogate marker of prostatitis,\textsuperscript{29,54} and it is associated with CDU features suggestive of prostate inflammation in patients with male accessory gland infection (MAGI).\textsuperscript{23} IL-8 is actively involved in BPH-associated chronic inflammation and mediates epithelial and stromal cell proliferation.\textsuperscript{54} In BPH tissues, epithelial and stromal cells secrete IL-8 actively,\textsuperscript{29,64} in response to varying stimuli including the proinflammatory cytokines interferon (IFN) γ and IL-17 that are produced by...
Table 3: Comparisons between subjects with metabolic syndrome and 1:2 ratio-matched controls (matched for age, total testosterone, smoking habits and moderate-severe alcohol consumption)

| Case patients (≥ 3 MetS factors, n=22) | Controls (matched 1:2, n=44) | P value |
|--------------------------------------|-------------------------------|---------|
| Age (years)                          |                               |         |
| 43.8±10.6                            | 41.0±6.6                      | 0.269   |
| Total testosterone (nmol l⁻¹)        |                               |         |
| 12.2±5.3                             | 13.0±4.5                      | 0.523   |
| Current smoker (%)                   |                               |         |
| 22.8                                 | 23.0                           | 0.532   |
| Current moderate-severe alcohol consumption (≥4 drinks per day, %) | | |
| 18.2                                 | 16.1                           | 0.574   |
| Semen volume (ml)                    |                               |         |
| 3.3±2.5                              | 3.5±1.7                        | 0.733   |
| Sperm concentration (10⁶ ml⁻¹)       |                               |         |
| 29.6±40.6                            | 32.0±45.7                      | 0.839   |
| Spermatozoa per ejaculate (10⁶ ml⁻¹) |                               |         |
| 89.6±134.2                           | 89.6±134.2                     | 0.628   |
| Sperm progressive motility (%)       |                               |         |
| 34.3±19.3                            | 34.8±22.5                      | 0.929   |
| Sperm morphology (normal forms, %)   |                               |         |
| 3.1±2.3                              | 5.8±6.1                        | 0.025   |
| Leukocytospermia (%)                 |                               |         |
| 4.6                                  | 4.6                            | 0.674   |
| Current positive urine and/or seminal culture (%) | | |
| 4.6                                  | 6.9                            | 0.625   |
| Log₈(sIL-8) (ng ml⁻¹)                |                               |         |
| 3.8±0.4                              | 3.5±0.4                        | 0.035   |
| Prostate volume at CDU (ml)          |                               |         |
| 35.0±14.6                            | 24.9±8.4                       | 0.006   |
| Prostate transitional zone volume at CDU (ml) | | |
| 10.7±10.8                            | 5.1±4.3                        | 0.004   |
| Arterial prostatic peak systolic velocity at CDU (cm s⁻¹) | | |
| 13.3±2.7                             | 9.6±2.7                        | 0.014   |
| Prostate moderate-severe inhomogeneity at CDU (%) | | |
| 95.6                                 | 46.0                           | 0.009   |
| Prostate calcification size at CDU (mm) |                               |         |
| 6.7±3.5                              | 2.5±4.1                        | 0.022   |

CDU: color-Doppler ultrasound; sIL8: seminal interleukin 8. The data are expressed as the mean±s.d. and as percentages when categorical.

prostate-infiltrating Th1 and Th17 cells, respectively.53,65–67 In particular, human stromal prostatic cells actively contribute to the organ-specific inflammatory process by acting as targets of bacterial or viral toll-like receptors agonists and as antigen-presenting cells capable of activating antigen-specific CD4 + T cells.68 In BPH cells, toll-like receptor activation leads to the production of proinflammatory cytokines (IL-6) and chemokines (IL-8 and CXCL10) capable of recruiting CXCR1 and CXCR2-positive leukocytes and CD15 + neutrophils.69 Finally, IL-8 stimulates overgrowth of prostate stromal and epithelial cells by directly promoting the proliferation of senescent epithelial cells,70 stromal transdifferentiation of myofibroblasts71 and by increasing secretion of fibroblast growth factor 2.72 Hence, IL-8 appears to be the link between T cell-mediated inflammatory responses and cell proliferation in the pathogenesis of BPH.73,74

A higher prevalence of MetS components was also associated with other CDU features of prostate inflammation including texture nonhomogeneity, major calcification size and elevated APPSV. Increased waist size is the common determinant of all of these CDU abnormalities. Prostate nonhomogeneity is typically considered a CDU abnormality related to inflammation28 and has been previously associated with elevated sIL-8 levels in infertile subjects with MAGI.13 Moreover, prostatic hyperechogenicity, which is associated with areas of calcification, has been previously proposed to be a CDU feature suggestive of MAGI.13 In particular, prostatic high-density echoes are considered the sonographic correlates of prostatic calculi and corpora amylacea, which as confirmed by histology performed on ultrasound-guided biopsies of the prostate.72 A recent report indicated that prostatic calculi and corpora amylacea comprised acute inflammatory proteins including lactoferrin, calprotectin, myeloperoxidase and α-defensins, all of which are in neutrophil granules.73 Prostatic calcifications are common in patients with CP and have been associated with the maintenance or enhancement of prostate inflammation, bacterial colonization and duration of symptoms.74,75 A positive correlation between sIL-8 levels and calcification size has also been previously reported by our group.23 Finally, we noted that APPSV correlated with MetS severity. Arterial PSV reflects tissue inflammation at various sites including the thyroid,76,77 exocrine glands3,78 and synovial membrane/joints.80,81 Thus far, APPSV has been studied for varying purposes including evaluation of BPH,20 prostate cancer,21 varicocele-related prostate CDU changes24 and premature ejaculation.25 More recently, elevated APPSV has been proposed as a CDU parameter that correlates with prostate inflammation,22,24,25 and in the prostate, APPSV is closely related to sIL-8.23

No correlation was found between the number of MetS components and current positive urine and/or seminal cultures suggesting that MetS is not associated with current infection of the male genital tract but is rather associated with chronic inflammation.

The relationship between central obesity and dyslipidemia with prostate overgrowth and inflammation, even in young subjects, is the main finding of this study. We previously reported a clear-cut association between MetS severity and prostate size28 and inflammation72,82 in cohorts of aged subjects. In the study of Gacci et al.,20 reduced HDL cholesterol and increased triglyceride levels were also noted to be the main determinants of MetS-related prostate alterations. However, these studies were performed in old individuals undergoing surgery for BPH.19,83 By culturing BPH stromal cells obtained from those patients, we demonstrated that in addition to tumor necrosis factor-α and lipopolysaccharide, oxidized LDL was capable of increasing IL-8, IL-6 and basic fibroblast growth factor secretion.25 In addition, tumor necrosis factor-α sensitized BPH cells to oxidized LDL by inducing its receptor (LOX-1)26. In a rabbit model of MetS we recently demonstrated that a 3-month high-cholesterol diet (HFD) induced severe prostatic inflammation characterized by increased corpora amylacea, fibrosis and hypoxia.28 In addition, the mRNA expression of several proinflammatory cytokines including IL-8 and T lymphocyte, macrophage, neutrophil and fibrosis/myofibroblast activation markers were significantly increased in the prostate of HFD animals.29 Together, all of these data suggest that BPH may be viewed as a complex disorder that also involves a metabolic component that may begin early in the life of the male, and although asymptomatic, it is likely detectable even in the early stages of the disease as suggested by this study. The mechanisms underpinning the relationship between MetS and prostate inflammation are likely to be similar in young and old men, but chronic exposure to elevated inflammation may contribute to BPH in the long-term.

Because hyperinsulinemia and insulin resistance represent the cornerstone of all definitions of MetS,24 all of the data reported here were adjusted for insulin levels. When the specific contribution of hyperinsulinemia was considered, after adjusting for MetS components and TT levels and age, we observed a specific effect of increased insulin levels on prostate volume and not on prostate inflammation. This finding is in apparent contrast with results published recently by our group that showed that insulin increased IL-8 release from myofibroblastic bBPH cells.19 However, in that study, the effect of insulin was negligible when compared with oxidized LDL (sixfold lower).19 The growth-promoting activity of insulin on the prostate gland is well-documented in several experimental and epidemiological studies.87

In this study, no association between an increase in the number of MetS components and prostate-related symptoms was observed, using either NIH-CPSI or IPSS scores. The lack of correlation between MetS...
and LUTS is consistent with some studies, but contrasts with most previous studies.\textsuperscript{15,16,18} However, all previous studies were performed in aged cohorts; whereas, our data were obtained from young subjects with relatively small prostates as assessed by ultrasound.

Finally, even after adjusting for confounders including the hypogonadal status, we observed an association between the number of MetS components and poor sperm morphology. These results confirmed previous findings obtained using a larger cohort of males of infertile couples where we assessed the possible correlations of MetS with scrotal parameters.\textsuperscript{3} The possible impact of MetS on sperm morphology was discussed in detail in that study. Here, we extend our investigation to possible associations between MetS-related prostate CDU features and semen parameters and note no correlation. This finding suggests that the effect of MetS on sperm quality is independent of MetS-related prostate abnormalities. Although a possible association between CP or MAGI and sperm quality has been proposed and some prostate CDU features have been proposed as suggestive of MAGI,\textsuperscript{19,88–90} a specific association between prostate CDU features and sperm parameters alterations has not been demonstrated. Here, we report that a number of MetS components, but not related prostate CDU abnormalities, are associated with poor sperm morphology.

This study has several limitations. First, the results were derived from patients consulting an Italian Andrology Clinic for infertility, and our population could have different characteristics from the general male population or those males consulting general practitioners for reasons other than infertility. Second, a true control group comprising age-matched, apparently healthy, fertile men is lacking and therefore true normative data on sonographic parameters cannot be inferred. Third, the data cannot distinguish between men who are clinically fertile and those who are not, and whether this feature confounds the results is unknown. Fourth, this study relies on a relatively small and young sample. Fifth, markers of prostate inflammation other than sIL-8 are lacking. Furthermore, parallel mechanistic studies to determine the consequences of IL-8 secretion on prostate growth and differentiation are warranted. Finally, the link between MetS or insulin levels and prostate enlargement in this study are correlative only. Statistically significant associations in a cross-sectional study do not infer causality.

However, this study also has several strengths. First, this study systematically evaluates several hormonal, seminal, laboratory and ultrasound parameters in a consecutive series of males of infertile couples. Second, during the same sonographic session, this study examined both scrotal and transrectal ultrasound features before and after ejaculation. Third, this study was performed on a sample of relatively young, infertile men and investigated a population that is poorly studied in the scientific literature. Fourth, this study considers several possible confounders, such as age, testosterone and insulin levels, smoking habits, alcohol consumption, leukocytospermia and positive semen and urine cultures of the patients. Fifth, a statistical analysis comparing patients with MetS with age-, TT-, smoking habits- and alcohol consumption-matched controls was performed. Finally, the study examined several end points simultaneously within the same population, which enabled a valid comparison of the coprevalence of the examined parameters and supported their possible association with the number of MetS components.

CONCLUSIONS
This study demonstrates that in a cohort of men with infertility, a component-dependent, stepwise association was observed between an increase in the number of MetS components and the total and transitional zone prostate enlargement and prostate related-inflammatory signs, but not symptoms or current infection of the male genital tract, which suggests a subclinical inflammation of the prostate. Relative prostate overgrowth may also correlate with MetS-related hyperinsulinemic state. In addition, MetS but not MetS's related prostate CDU abnormalities was associated with poor sperm morphology.

AUTHOR CONTRIBUTIONS
FL, GC and MM conceived and designed the study, performed the statistical analysis and drafted the manuscript. LV, MG and GF participated in the design of the study. FL, EM, MR and SC participated in data collection and management. All authors read and approved the final manuscript.

COMPETING INTERESTS
The authors declare no competing interests.

REFERENCES
1. Kasturi SS, Tannir J, Brannigan RE. The metabolic syndrome and male infertility. J Androl 2008; 29: 251–9.
2. Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, et al. The metabolic syndrome. Endocr Rev 2008; 29: 777–822.
3. Eckel RH, Alberti KG, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2010; 375: 183–1.
4. Corona G, Rastrelli G, Vignozzi L, Mannucci E, Maggi M. Testosterone, cardiovascular disease and the metabolic syndrome. Best Pract Res Clin Endocrinol Metab 2011; 25: 337–53.
5. Corona G, Mannucci E, Forti G, Maggi M. Hypogonadism, ED, metabolic syndrome and obesity: a pathologic link supporting cardiovascular diseases. Int J Androl 2009; 32: 587–98.
6. Reaven P. Metabolic syndrome. J Insur Med 2004; 36: 132–42.
7. Corona G, Mannucci E, Schulman C, Petrone L, Mansani R, et al. Psychobiologic correlates of the metabolic syndrome and associated sexual dysfunction. Eur Urol 2006; 50: 595–604.
8. Corona G, Rastrelli G, Morelli A, Vignozzi L, Mannucci E, et al. Hypogonadism and metabolic syndrome. J Endocrinol Invest 2011; 34: 557–67.
9. Lotti F, Corona G, Degli Innocenti S, Filiberti E, Scognamiglio V, et al. Seminal, ultrason and psychobiological parameters correlate with metabolic syndrome in male members of infertile couples. Andrology 2013; 1: 229–39.
10. Hammoud AO, Gibson M, Peterson CM, Meikle AW, Carroll DT. Impact of male obesity on infertility: a critical review of the current literature. Fertil Steril 2008; 90: 897–904.
11. MacDonald AA, Herbsprung GP, Showell M, Farquhar CM. The impact of body mass index on semen parameters and reproductive hormones in human males: a systematic review with meta-analysis. Hum Reprod Update 2010; 16: 293–311.
12. Sermondade N, Faure C, Feuex L, Levy R, Czernichow S, et al. Obesity and increased risk for oligozoospermia and azoospermia. Arch Intern Med 2012; 172: 440–2.
13. Sermondade N, Faure C, Feuze L, Shayeg AB, Bonpe JP, et al. BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis. Hum Reprod Update 2013; 19: 221–31.
14. Mngiu AK, McVary KT. Lower urinary tract symptoms, benign prostate hyperplasia, and obesity. Curr Urol Rep 2009; 10: 247–53.
15. Moul S, McVary KT. Lower urinary tract symptoms, obesity and the metabolic syndrome. Curr Opin Urol 2010; 20: 7–12.
16. Gorbachinsky I, Akpinar H, Assimos DG. Metabolic syndrome and urologic diseases. Rev Urol 2010; 12: 157–80.
17. Parsons JK. Lifestyle factors, benign prostate hyperplasia, and lower urinary tract symptoms. Curr Opin Urol 2011; 21: 1–4.
18. De Nunzio C, Aronson W, Freedland SJ, Giovannucci E, Parsons JK. The correlation between metabolic syndrome and prostatic diseases. Eur Urol 2012; 61: 560–70.
19. Vignozzi L, Gacci M, Cellai I, Santi R, Corona G, et al. Fat boosts, while androgen receptor activation counteracts, BPH-associated prostate inflammation. Prostate 2013; 73: 799–800.
20. Gacci M, Vignozzi L, Sebastianelli A, Salvi M, Giannessi C, et al. Metabolic syndrome and lower urinary tract symptoms: the role of inflammation. Prostate Cancer Prostatic Dis 2013; 16: 101–6.
21. Kupelian V, McVary KT, Kaplan SA, Hall SA, Link CL, et al. Association of lower urinary tract symptoms and the metabolic syndrome: results from the Boston area community health survey. J Urol 2013; 189: S107–14.
22. World Health Organization. WHO manual for the standardized investigation and diagnosis of the infertile couple. Cambridge: Cambridge University Press; 2000.
23. Lotti F, Corona G, Mancini M, Filiberti E, Degli Innocenti S, et al. Ultrasonographic and clinical correlates of seminal plasma interleukin-8 levels in patients attending an andrology clinic for infertility. Int J Androl 2011; 34: 600–13.
Correlation between metabolic syndrome and prostate volume.
Sohn JC, Chang HS, Kim CI. The correlation between metabolic syndrome-risk factors for the development of benign prostatic hyperplasia. J Urology 2011; 85: 330–4.

Parsons JK, Sarma AV, McVary K, Wei JT. Obesity and benign prostatic hyperplasia: clinical connections, emerging etiological paradigms and future directions. J Urology 2013; 189: S102–6.

Penna G, Fibbi B, Amuchastegui S, Corsiero E, Lavagny G, et al. The vitamin D receptor agonist elocalcitil inhibits I\(\beta\)-dependent benign prostatic hyperplasia stromal cell proliferation and inflammatory response by targeting the RhoA/Rho kinase and NF-kappaB pathways. Prostate 2009; 69: 480–93.

Fibbi B, Penna G, Morelli A, Adorini L, Maggi M. Chronic inflammation in the pathogenesis of benign prostatic hyperplasia. Int J Androl 2009; 32: 1–15.

Lotti F, Maggi M. Interleukin 8 and the male genital tract. J Reprod Immunol 2013; 93: 54–65.

Steiner GE, Djavan B, Kramer G, Handisius A, Newman M, et al. The picture of the prostatic lymphokinome network is becoming increasingly complex. Rev Urol 2002; 4: 171–7.

Baggiolini M, Loetscher P, Moser B. Interleukin-8 and the chemokine family. Int J Immunopharmacol 1995; 17: 103–8.

Feldmann M, Saklavala J. Proinflammatory cytokines. In: Oppenheim JJ, Feldmann M, editors. Cytokine Reference. New York: academic Press; 2001. p. 291–305.

Hoedrher WW, Nadler RB, Koch AE, Campbell PL, Ludwig M, et al. Evaluation of the cytokines interleukin 8 and epithelial neutrophil activating peptide 78 as indicators of inflammation in prostatic secretions. Urology 2000; 56: 1025–9.

Lotti F, Maggi M, Adorini L, et al. Cytokine expression pattern in benign prostatic hyperplasia infiltrating T cells and impact of lymphocytic infiltration on cytokine mRNA profile in prostatic tissue. Lab Invest 2003; 83: 1131–46.

Kramer G, Mitteregger D, Marberger M. Is benign prostatic hypertrophy (BPH) an immune inflammatory disease? Eur Urology 2007; 51: 1202–16.

Koumantakis E, Mataliotakis I, Kyriakou D, Fragouli E, Relakis K. Increased levels of interleukin-8 in human seminal plasma. Andrologia 1998; 30: 339–43.

Konig JE, Senge T, Alhoff EP, Konig W. Analysis of the inflammatory network in benign prostatic hyperplasia and prostate cancer. Prostate 2004; 58: 121–9.

Steiner GE, Stix U, Handisius A, Wilhelms M, Hafler A, et al. Cytokine expression pattern in benign prostatic hyperplasia infiltrating T cells and impact of lymphocytic infiltration on cytokine mRNA profile in prostatic tissue. Lab Invest 2003; 83: 1131–46.

Kramer G, Mitteregger D, Marberger M. Is benign prostatic hypertrophy (BPH) an immune inflammatory disease? Eur Urology 2007; 51: 1202–16.

Marberger M, Lotti F, Maggi M, Adorini L, et al. Cytokine expression pattern in benign prostatic hyperplasia infiltrating T cells and impact of lymphocytic infiltration on cytokine mRNA profile in prostatic tissue. Lab Invest 2003; 83: 1131–46.

Kramer G, Mitteregger D, Marberger M. Is benign prostatic hypertrophy (BPH) an immune inflammatory disease? Eur Urology 2007; 51: 1202–16.

Marberger M, Lotti F, Maggi M, Adorini L, et al. Cytokine expression pattern in benign prostatic hyperplasia infiltrating T cells and impact of lymphocytic infiltration on cytokine mRNA profile in prostatic tissue. Lab Invest 2003; 83: 1131–46.

Kramer G, Mitteregger D, Marberger M. Is benign prostatic hypertrophy (BPH) an immune inflammatory disease? Eur Urology 2007; 51: 1202–16.

Marberger M, Lotti F, Maggi M, Adorini L, et al. Cytokine expression pattern in benign prostatic hyperplasia infiltrating T cells and impact of lymphocytic infiltration on cytokine mRNA profile in prostatic tissue. Lab Invest 2003; 83: 1131–46.

Kramer G, Mitteregger D, Marberger M. Is benign prostatic hypertrophy (BPH) an immune inflammatory disease? Eur Urology 2007; 51: 1202–16.

Marberger M, Lotti F, Maggi M, Adorini L, et al. Cytokine expression pattern in benign prostatic hyperplasia infiltrating T cells and impact of lymphocytic infiltration on cytokine mRNA profile in prostatic tissue. Lab Invest 2003; 83: 1131–46.

Kramer G, Mitteregger D, Marberger M. Is benign prostatic hypertrophy (BPH) an immune inflammatory disease? Eur Urology 2007; 51: 1202–16.
80. Varsamidis K, Varsamidou E, Tjetjis V, Mavropoulos G. Doppler sonography in assessing disease activity in rheumatoid arthritis. *Ultrasound Med Biol* 2005; 31: 739–43.

81. Carotti M, Salaffi F, Morbiducci J, Ciapetti A, Bartolucci L, et al. Colour Doppler ultrasonography evaluation of vascularization in the wrist and finger joints in rheumatoid arthritis patients and healthy subjects. *Eur J Radiol* 2012; 81: 1834–8.

82. Berger AP, Hominger W, Bektic J, Pelzer A, Spranger R, et al. Vascular resistance in the prostate evaluated by colour Doppler ultrasonography: is benign prostatic hyperplasia a vascular disease? *BJU Int* 2006; 98: 587–90.

83. Turgut AT, Olcucuoğlu E, Koşar P, Geyik PO, Koşar U, et al. Power Doppler ultrasonography of the feeding arteries of the prostate gland: a novel approach to the diagnosis of prostate cancer? *J Ultrasound Med* 2007; 26: 875–83.

84. Lotti F, Corona G, Mancini M, Biagini C, Colpi GM, et al. The association between varicocele, premature ejaculation and prostatitis symptoms: possible mechanisms. *J Sex Med* 2009; 6: 2878–87.

85. Vignozzi L, Cellai I, Santi R, Lombardelli L, Morelli A, et al. Antiinflammatory effect of androgen receptor activation in human benign prostatic hyperplasia cells. *J Endocrinol* 2012; 214: 31–43.

86. Vignozzi L, Morelli A, Sarchielli E, Comeglio P, Filippi S, et al. Testosterone protects from metabolic syndrome-associated prostate inflammation: an experimental study in rabbit. *J Endocrinol* 2012; 212: 71–84.

87. Vikram A, Jena G, Ramana P. Insulin-resistance and benign prostatic hyperplasia: the connection. *Eur J Pharmacol* 2010; 641: 75–81.

88. Weidner W, Krause W, Ludwig M. Relevance of male accessory gland infection for subsequent fertility with special focus on prostatitis. *Hum Reprod Update* 1999; 5: 421–32.

89. Krause W. Male accessory gland infection. *Androlgia* 2008; 40: 113–6.

90. Rusz A, Pilatz A, Wagenlehner F, Linn T, Diemer T, et al. Influence of urogenital infections and inflammation on semen quality and male fertility. *World J Urol* 2012; 30: 23–30.

How to cite this article: Lotti F, Corona G, Vignozzi L, Rossi M, Maseroli E, Cipriani S, Gacci M, Forti G, Maggi M. Metabolic syndrome and prostate abnormalities in male subjects of infertile couples. *Asian J Androl* 20 January 2014. doi: 10.4103/1008-682X.122341. [Epub ahead of print]