Reduced semen quality in chronic prostatitis patients that have cellular autoimmune response to prostate antigens

Rubén Darío Motrich¹, Mariana Maccioni¹, Rosa Molina², Andrea Tissera², José Olmedo³, Clelia Maria Riera and Virginia Elena Rivero¹,⁴

¹Immunología, CIBICI – CONICET, Departamento de Bioquímica Clínica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, ²CIGOR, Centro Integral de Ginecología, Obstetricia y Reproducción, Córdoba and ³FUCDIM, Fundación Urológica Córdoba para la Docencia e Investigación Médica, Córdoba, Argentina

⁴To whom correspondence should be addressed at: Inmunología, Departamento de Bioquímica Clínica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Haya de la Torre esquina Medina Allende, Ciudad Universitaria, Córdoba, 5000, Argentina. E-mail: vrivero@bioclin.fcq.unc.edu.ar

BACKGROUND: The relationship between chronic prostatitis and fertility has been controversial for many years. We have previously shown the presence of a cellular autoimmune response against prostate antigens in a group of chronic prostatitis patients. Our main goal was to investigate whether chronic prostatitis (either caused by an infection or an autoimmune response to the prostate gland) could have a deleterious effect on semen quality.

METHODS: Forty-four patients diagnosed as suffering from chronic prostatitis were included and divided into groups according to the presence of infection and/or cellular autoimmune response against prostate antigens. Healthy normal individuals were included as controls. Measurements for sperm concentration, motility, morphology, prostate and seminal vesicle markers, antisperm antibodies, white blood cells and pro-inflammatory cytokines were performed accordingly.

RESULTS: The most severe abnormalities were seen in patients with no evident infection and an autoimmune response against prostate antigens. Moreover, significantly increased levels of pro-inflammatory cytokines were detected in seminal plasma from these patients.

CONCLUSIONS: This study shows that chronic prostatitis patients with cellular autoimmune response to prostate antigens present important alterations in their semen quality parameters. We speculate that an autoimmune response against prostate antigens and the inflammatory process involved may affect male fertility.

Key words: autoimmunity/chronic prostatitis/cytokines/male infertility/semen quality

Introduction

Chronic prostatitis is a common diagnosis but very little is understood about the aetiology and the pathogenesis of the disease (Bierklund Johansen and Weidner, 2002; Krieger and Riley, 2002). Men with chronic prostatitis present an episodic and relapsing condition characterized by pelvic pain, irritative voiding symptoms and effects on sexual function (McNaughton et al., 2000). The symptoms of the disease are suggestive of an infection in the prostate gland and bacterial infections occur in ~5–10% of patients (Krieger, 2003). However, a large body of evidence accumulated over many years has failed to provide convincing proof that some fastidious organisms are responsible for symptoms in a significant proportion of men who present symptoms of chronic prostatitis (Domingue and Hellstrom, 1998). The National Institutes of Health proposed a classification of prostatitis syndromes in four categories (Krieger et al., 1999): acute and chronic bacterial prostatitis (categories I, II), chronic pelvic pain syndrome (CPPS) (category III) and asymptomatic inflammatory prostatitis (category IV). Regarding the last two categories, the use of this classification has not generated an improvement, neither in the therapeutic approaches nor in the clarification of their aetiologies.

Given the lack of a clear infectious aetiology for the majority of men diagnosed as chronic prostatitis patients, several groups including ours wondered whether men with this kind of condition might have an autoimmune component to their disease. Recently, we have reported that a significant proportion of men with chronic prostatitis have evidence of cellular response to prostate antigens (Motrich et al., 2005). We and others (Alexander et al., 1997; Ponniah et al., 2000; Batstone et al., 2002; Motrich et al., 2005) demonstrated the presence of lymphocytes able to proliferate in response to known prostate antigens such as prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP), together with elevated levels of interferon (INF)-γ in culture supernatants in a group of patients with non-infectious chronic prostatitis (Motrich et al., 2005).

Male infertility is a multifactorial disease and diagnosis and therapy must be oriented as such. Although the relationship
between prostatitis and infertility remains unclear, bacteria, viruses, leukocytes, reactive oxygen species, cytokines, obstruction and immunological abnormalities must be seen as cofactors in the development of infertility in patients with male accessory glands infections and prostatitis (Weidner et al., 1999; Schoor, 2002; Everaert et al., 2003). Some reports have associated chronic prostatitis, mainly of infectious origin, with abnormalities in semen quality and function (Schoor, 2002). However, evidence supporting a correlation of an inflammatory state due to an autoimmune response against the prostate gland and the different seminal parameters does not exist.

In the present study, we analysed a group of patients with chronic prostatitis in order to investigate whether an autoimmune response to prostate antigens could have any effect on the seminal plasma quality of these patients.

**Materials and methods**

**Patients**

We included 44 patients (mean ± SD age: 40.41 ± 9.37 years, range 20–50) and 15 control volunteers (age: 32.18 ± 6.49 years, range 24–45) in our study. Normal individuals answered a questionnaire and had no history of any genitourinary symptoms, instrumentation or surgery. They underwent the same assessment as patients. Patients and controls agreed to donate blood samples and semen; they had not been taking antibiotics, non-steroidal anti-inflammatory drugs (NSAID) or steroids for 4 weeks prior to, or during, the study. Volunteers who had undergone vasectomy were specifically excluded.

A diagnosis of chronic symptomatic prostatitis was given in cases of a history of ≥3 months of pelvic or genital pain, or both, associated with voiding and/or sexual dysfunction and painful digital rectal examination of the prostate. All patients underwent a standard evaluation, including digital rectal examination, microscopic examination and culture of urine and semen. To discriminate between patients with infectious and non-infectious chronic prostatitis, conventional and non-conventional bacterial cultures were performed in their urine and semen. We could detect infection of known prostatic pathogens (e.g.: *E. coli; St. aureus; Klebsiella sp.; C. trachomatis; C. albicans; Trichomonas sp.*) in 15 out of 44 of these patients, and we therefore named this group as group A (patients with type II NIH prostatitis). Group B included patients with negative cultures and positive lymphoproliferative autoimmune response against prostate antigens (group B, n = 10) and group C included patients with negative cultures and negative lymphoproliferative response against prostate antigens (group C, n = 19) (both groups, B and C, included patients with type III NIH prostatitis). Group D age-matched volunteers with no history of genitourinary disease, who were used as control group, did not show any presence of an infectious agent either in semen or in urine (group D, n = 15). Neither the patients from group A nor individuals from group D showed positive proliferative responses against prostate antigens.

**Lymphoproliferation assay against prostate antigens**

The proliferation assay was performed as described previously (Rivero et al., 2002). Peripheral blood mononuclear cells from each patient and controls were divided into two aliquots to use as responder and as antigen-presenting cells (APC). Syngeneic peripheral blood mononuclear cells (PBMC) irradiated at 3000 cGy served as APC. The APC were pulsed for 2 h at 37°C with different prostatic antigen sources: human prostate extract (PE), seminal plasma obtained from pooled donor samples having a normal semen analysis (SP), PSA (Sigma) or PAP (Sigma). After 2 h of incubation, pulsed APC were washed twice and added to plates containing 1.5 × 10^5 responder cells (non-irradiated syngeneic PBMC). All cell combinations were set up in quadruplicate. Plates were incubated for 5 days at 37°C in water saturated with 7.5% CO_2_ atmosphere. Subsequently, as a positive control of proliferation, the PBMC were incubated with the mitogen Concanavalin A (Sigma) at 5 mg/ml. DNA synthesis was measured by adding 1 mCi of [methyl-^3_H]-thymidine (^	extsuperscript{3}H]TdR) per well 18 h before harvesting the cells onto glass fibre filters. Labelled material was automatically harvested and counted in a β-plate scanner (Pharmacia, France). The response was expressed as a stimulation index (SI) calculated from c.p.m. incorporated in antigen-pulsed cultures/c.p.m. incorporated in cultures with medium. Threshold value for positivity for each antigen assayed (SP, EP, PSA and PAP) was set above the mean SI + 3 SD of the SI observed in the healthy control individuals.

**Semen analysis**

Semen samples were collected directly into a sterile container by masturbation after 2–7 days of sexual abstinence. Semen samples and blood were obtained at the same visit. Standard clinical semen analysis was performed according to World Health Organization (1999) criteria. Semen analysis consisted of determination of sample volume, sperm density (concentration), progressive motility, vitality (eosin exclusion), morphology (World Health Organization (1992) classification and Kruger classification, pH, and concentrations of citrate and fructose. Citrate and fructose were measured as tests of function of the prostate and seminal vesicles respectively. Identification of leukocytes and other cells was done by a peroxidase cytochemical technique (Politch et al., 1993). Results were expressed as 1 × 10^6 leukocytes/ml. To assess the functional integrity of sperm membrane, hypo-osmotic swelling (HOS) test was used as previously described (World Health Organization, 1999). Semen samples were also tested for antisperm antibodies (IgA and IgG) by using the commercially available ImmunoSpheres anti-IgA kit (Bioscreen Inc., NY, USA) and MarScreen anti-IgG kit (Bioscreen Inc.).

**Cytokines in seminal plasma**

Tumour necrosis factor (TNF)-α and interleukin (IL)-1β were assayed in seminal plasma by the use of a commercially available chemiluminescence immunometric assay kit (Immulite; DPC, Los Angeles, CA, USA). The assay was performed according to the manufacturer’s instructions in an automatic analyser (Immulite). The cytokine contents were expressed in pg/ml, according to standard curves ranging from 1.7 to 1000 pg/ml for TNF-α, and from 1.5 to up to 1000 pg/ml for IL-1β.

**Statistics**

Statistical analysis was performed using Fisher’s least significant difference test or the Kruskall–Wallis test, as appropriate. P < 0.05 was considered statistically significant.

**Results**

**Autoimmune response against prostate antigens in patients with chronic prostatitis**

In order to investigate whether an autoimmune cause might be the reason for discomfort seen in all chronic prostatitis patients enrolled in our study, we performed PBMC
proliferation assays in response to different prostate antigens. As a source of human prostate antigens we chose seminal plasma proteins (SP), a normal prostate tissue extract (PE) and also purified prostate proteins such as PSA and PAP.

None of the patients from group A who were coursing with an infection at the time of the study showed positive lymphoproliferative response against the autoantigens assayed. In contrast, we detected a positive proliferative response against most of the antigens examined in 10 patients (group B) (Table I). These patients had no signs of infection. The rest of the patients examined, who also did not have signs of infection, showed negative proliferation against prostate antigens (group C) (Table I). When secretion of INF-γ and IL-10 in culture supernatants from PBMC stimulated with SP, PSA or PAP was assayed, only supernatants from antigen-stimulated PBMC from group B showed elevated levels of INF-γ (data not shown).

Semen quality and inflammatory cytokines in samples of patients with infectious and autoimmune chronic prostatitis

To examine whether there might be a correlation between an inflammatory state due to an autoimmune response against the prostate gland and the different seminal parameters, we performed semen analyses in the groups of patients under study. The results are presented in Table II and Figure 1. No significant differences were found in the pH and volume of the ejaculates of any of the groups under study (Table II). When prostate and seminal vesicle markers (citric acid and fructose respectively), were evaluated, no significant differences from the control levels were found. However, citric acid levels appeared to be reduced (although non-significantly) in all the patients with clinical symptoms of prostatitis, being more evident in group B patients. Significantly elevated levels of peroxidase-positive cells were only detected in patients bearing an infection at the time of the study (group A), which could be related to the low percentage of sperm viability observed in this group. It should be kept in mind that this test only detects macrophages and polymorphonuclear leukocytes, providing no information about the presence or absence of lymphocytes (Table II). When we analysed the levels of TNF-α and IL-1β in seminal plasma of these patients, only samples from group B showed a significant enhancement of these cytokines in seminal plasma (Table II). Sperm motility appeared to be diminished, although not significantly, in samples from groups A and B patients (Table II). Asthenozoospermia alone or in combination with other abnormalities was observed in 50% of patients of both groups (data not shown). As can be seen in Figure 1, striking abnormalities in some of the ejaculate parameters could be detected in patients of group B. The sperm count was significantly reduced (oligozoospermia) only in samples from group B patients (P < 0.05) when compared with the control group D (Figure 1A). HOS revealed that the sperm plasma membrane was severely and significantly affected only in sperm from group B patients (P < 0.05) when compared with values found in samples from control group D patients (Figure 1B). The morphology of the sperm was also altered in a high percentage of group B and also group A patients, when analysed by World Health Organization criteria (Figure 1C). The percentage of normal sperm was significantly diminished only in samples from group B patients when stricter criteria (Kruger) were used (Figure 1D).

It is important to emphasize that none of the patients under study presented antisperm IgG or IgA, excluding another autoimmune syndrome as a possible cause of the observed abnormalities (data not shown).

Taking all these data together, we can conclude that patients who had positive lymphoproliferative autoimmune responses against prostate components (group B; Table I) showed severe alterations in sperm quality (Table II). Furthermore, for some of the parameters under analysis, these alterations were more marked than those observed in patients bearing an infection (Table II).

Discussion

Chronic prostatitis is a very common disease in the male genitourinary system. However, the relationship between chronic prostatitis and fertility has been controversial for many years (Weidner et al., 1999; Schoor, 2002; Engeler et al., 2003; Everaert et al., 2003). Some reports have associated chronic prostatitis, mainly of infectious origin, with abnormalities in semen quality and function (Schoor, 2002). Leib et al. (1994) reported reduced semen quality caused by chronic non-bacterial prostatitis with sperm morphological and motility alterations. Menkveld et al. (2003) also demonstrated that chronic non-bacterial prostatitis patients have significant abnormalities on sperm morphology parameters, as evaluated by Kruger’s criteria. In contrast, Weidner et al. (1991) reported that mean values of sperm concentration, motility and morphology revealed no differences among patients with non-bacterial prostatitis, prostatodynia and control groups. Supporting these data, Pasqualotto et al. (2000) did not find differences in sperm concentration, percentage of motility or morphology among patients with chronic prostatitis, prostatodynia and a control group. Moreover, Ludwig et al. (2003)

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**Table I. Lymphoproliferative response expressed as stimulation index (SI)**

<table>
<thead>
<tr>
<th>Tested antigen</th>
<th>Group A (± SD)</th>
<th>Group B (± SD)</th>
<th>Group C (± SD)</th>
<th>Group D (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminal plasma</td>
<td>1.03 ± 0.37</td>
<td>2.34 ± 1.31a</td>
<td>0.92 ± 0.41</td>
<td>0.99 ± 0.32</td>
</tr>
<tr>
<td>Prostate extract</td>
<td>1.01 ± 0.43</td>
<td>1.37 ± 0.57</td>
<td>0.76 ± 0.36</td>
<td>0.72 ± 0.39</td>
</tr>
<tr>
<td>Prostate-specific antigen</td>
<td>1.22 ± 0.31</td>
<td>2.18 ± 0.99a</td>
<td>0.94 ± 0.36</td>
<td>1.00 ± 0.35</td>
</tr>
<tr>
<td>Prostatic acid phosphatase</td>
<td>1.09 ± 0.41</td>
<td>2.52 ± 1.09a</td>
<td>0.95 ± 0.38</td>
<td>1.09 ± 0.31</td>
</tr>
</tbody>
</table>

Values are mean values ± SD.

*aSignificant difference versus group D (control group) (P < 0.05).*
Table II. Semen analysis variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A (n = 15)</th>
<th>Group B (n = 10)</th>
<th>Group C (n = 19)</th>
<th>Group D (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminal plasma</td>
<td></td>
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<tr>
<td>pH</td>
<td>7.70 ± 0.13</td>
<td>7.58 ± 0.15</td>
<td>7.82 ± 0.36</td>
<td>7.57 ± 0.14</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>3.15 ± 1.67</td>
<td>3.08 ± 1.35</td>
<td>3.72 ± 3.01</td>
<td>2.57 ± 1.01</td>
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<tr>
<td>Prostate</td>
<td></td>
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<tr>
<td>Citric acid (mg%)</td>
<td>386.22 ± 136.29</td>
<td>324.86 ± 134.11</td>
<td>377.95 ± 171.70</td>
<td>434.30 ± 138.77</td>
</tr>
<tr>
<td>Seminal vesicle</td>
<td></td>
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<tr>
<td>Fructose (mg%)</td>
<td>239.45 ± 100.92</td>
<td>322.62 ± 189.16</td>
<td>279.25 ± 104.04</td>
<td>345.59 ± 178.08</td>
</tr>
<tr>
<td>Non-sperm cells</td>
<td></td>
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<tr>
<td>Peroxidase (+) cells (x10³/ml)</td>
<td>6.26 ± 12.48a</td>
<td>0.50 ± 0.58</td>
<td>3.08 ± 8.44</td>
<td>0.93 ± 0.96</td>
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<tr>
<td>Pro-inflammatory cytokines</td>
<td></td>
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<tr>
<td>Tumour necrosis factor-α (pg/ml)</td>
<td>12.47 ± 2.37</td>
<td>53.67 ± 28.59a</td>
<td>16.82 ± 4.08</td>
<td>24.51 ± 4.82</td>
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<tr>
<td>Interleukin-1β (pg/ml)</td>
<td>9.16 ± 1.46</td>
<td>59.65 ± 31.83a</td>
<td>9.05 ± 2.43</td>
<td>17.6 ± 6.61</td>
</tr>
<tr>
<td>Sperm cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viability (%)</td>
<td>70.8 ± 15.4a</td>
<td>81.2 ± 6.9</td>
<td>84.2 ± 7.8</td>
<td>83.7 ± 7.7</td>
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<tr>
<td>Spem cells motility</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Motile sperm cells (%)</td>
<td>45.75 ± 26.21</td>
<td>44.00 ± 17.82</td>
<td>60.26 ± 19.43</td>
<td>61.92 ± 12.83</td>
</tr>
<tr>
<td>Normal spermatozoa (%)</td>
<td>40.66 ± 26.73</td>
<td>37.00 ± 16.81</td>
<td>53.97 ± 19.47</td>
<td>52.54 ± 14.93</td>
</tr>
</tbody>
</table>

Values are mean values ± SD.
aSignificant difference versus group D (control group) (P < 0.05).

Figure 1. Semen abnormalities in samples of patients with chronic prostatitis. Sperm concentration (A), hypo-osmotic swelling (HOS) test (B), sperm morphology analysed by World Health Organization criteria (C) and analysed by Kruger’s criteria (D) were carried out in semen samples from patients with infectious chronic prostatitis (group A), non-infectious chronic prostatitis who showed positive stimulation indexes (SI) against the prostate antigens tested (group B), non-infectious chronic prostatitis patients who showed negative SI against the prostate antigens tested (group C) and age-matched control volunteers (group D). Results are expressed as mean values ± SD. Statistical analysis was performed using Fisher’s least significant difference test or the Kruskall–Wallis test, as appropriate. *P < 0.05 versus control group.
showed that elevated leukocyte counts in prostate secretions and in ejaculate, as indicators of inflammation, have no negative impact on total sperm count, sperm concentration, motility, morphology, and sperm vitality in patients with chronic non-bacterial prostatitis.

One possible explanation for the contradictory findings could be that chronic non-bacterial prostatitis comprises a heterogeneous group of patients. Recently, we have demonstrated the presence of lymphocytes able to proliferate in response to known prostate antigens such as PSA, PAP and others only in 34% of the patients with non-infectious chronic prostatitis enrolled in our study (Motrich et al., 2005). These results are in accordance with data reported by Alexander et al. (1997) and Batstone et al. (2002), who also found an autoimmune lymphoproliferative response to prostate antigens in 30 and 65% of the patients studied respectively. Interestingly, in the present work, the major abnormalities in some of the ejaculate parameters could be detected in patients with chronic non-bacterial prostatitis who presented signs of an autoimmune response against the prostate gland (group B). When the comparative analysis of sperm parameters was performed with patients from groups B and C grouped together, no significant differences were found. We can hypothesize that, in the same way, these significant differences could have been masked in the other studies mentioned. We observed that when patients had positive lymphoproliferative responses against prostate components, important alterations in sperm quality could be observed. Certainly, for some of the parameters under analysis, such as sperm concentration, HOS test and sperm morphology evaluated by Kruger’s criteria, these alterations were even more marked than those observed in patients with an infection.

Existing data on the relationship between sperm parameters and hormonal profile have been derived from infertile men, men with andrological problems, men exposed to environmental toxins (Uhler et al., 2003) or men who present autoantibodies to sperm antigens (Chiu and Chamley, 2004). Neither antisperm IgG nor IgA antibodies nor alterations in the endocrine status of the hypothalamic–testicular axis were present in the patients in our study (data not shown), excluding the hormonal factor and the presence of antisperm antibodies as a possible cause of the observed seminal alterations.

Three hypotheses could be postulated to explain the alterations observed in sperm. Prostate secretion meets sperm cells during ejaculation, thus one possibility would be that the damage occurs in the short time during ejaculation. The second possibility would include a direct effect of inflammation on the testis and epididymis. The third possibility would be a combination of both of them. Previous studies have shown the presence of cytokines such as TNF-α and IFN-γ in the semen of infertile men (Gruschwitz et al., 1996). Furthermore, it has been reported that some men with chronic prostatitis have elevated levels of inflammatory cytokines in seminal plasma (Alexander et al., 1998; Paulis et al., 2003). We found that patients who showed a proliferative response to prostate antigens presented significantly elevated levels of TNF-α and IL-1 in seminal plasma. It has been reported that negative effects on sperm motion are evident as soon as 30 min after incubation of sperm cells with TNF-α (Estrada et al., 1997). Indeed, Estrada et al. studied the in vitro effects of TNF-α and IFN-γ on human sperm motion, viability and the HOS test, demonstrating that there was a time-dependent negative effect of TNF-α plus IFN-γ on sperm motility, viability, HOS test, and lateral-head displacement (Estrada et al., 1997). Moreover, the prostate secretes components that are involved in the total antioxidant capacity (TAC) of the seminal plasma, and the balance between reactive oxygen species (ROS) present in seminal plasma and TAC is important for the survival of sperm (Sikka, 2002). Pasqualotto et al. (2000) reported that TAC was significantly lower in patients with chronic non-infectious prostatitis (with or without leukocytospermia) when compared to control individuals. Moreover, chronic prostatitis has been proved to cause scarring of the prostatic and ejaculatory ducts with inflammatory-associated obstructions of the male reproductive tract (Dohle, 2003). These data may explain the oligozoospermia and asthenozoospermia found in our patients. On the other hand the deleterious effect of ROS on semen quality has been documented (Sharma and Agarwal, 1996) and a diminished prostate secretory function could be associated with enhancement of sperm apoptosis.

On the other hand, a possible direct testicular or epididymal effect of inflammation could be responsible for the alterations observed in semen from these patients with an autoimmune response against prostate antigens. Moreover, an increase of sperm alterations during longstanding inflammation could be expected. Although we cannot rule out this hypothesis, findings in our animal model of experimental autoimmune prostatitis demonstrate that the inflammation due to an autoimmune response against prostate has detrimental effects on the quality of seminal sperm but not on epididymal sperm (unpublished data).

In this work, we demonstrate for the first time that a proliferative response against prostate antigens is associated with a marked alteration of semen quality in patients with chronic prostatitis. These results argue in favour of the importance of prostate functionality in the quality of the semen. It is possible that the autoimmune response against prostate antigens and the associated inflammation could be involved in the seminal alteration observed. As a secretory organ, the prostate produces large amounts of soluble proteins which are secreted into the ejaculate and optimizes the conditions for successful fertilization, giving an adequate medium for the survival of sperm, and enhances their motility in the female reproductive tract (Chow and O, 1998). For example, PSA, the best-known product of the prostate gland, is needed for degradation of the seminal plasma inhibitor precursor/semenogelin I, which is the predominant protein of the human semen coagulum, having a positive impact on sperm motility. Some researchers found that seminal PSA levels were diminished in patients with low sperm motility (Yoshida et al., 2003). Zinc, which to a high degree also originates from the prostate, also plays an important role in sperm function mainly via its effect on chromatin stability (Richthoff et al., 2002). The ecto-5-nucleotidase, another prostatic enzyme,
has a significant role in the regulation of sperm motility in vitro (Aumuller et al., 1997). It is possible that the autoimmune response against prostate antigens and the associated inflammation observed could modify the prostate function and be the cause of the seminal alterations and infertility associated with some cases of prostatitis (Ahlgren et al., 1995).

We speculate that an autoimmune response against prostate antigens in some patients with non-infectious prostatitis, and the involved inflammatory process, may seriously compromise the quality of their semen, and therefore affect fertility.

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