Association of anti-sperm antibodies with chronic prostatitis: a systematic review and meta-analysis

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Abstract

Chronic prostatitis is a risk factor for impaired male fertility potential, and anti-sperm antibodies (ASAs) cause the autoimmune disease immune infertility, which has a negative effect on semen parameters. Current studies have investigated the ASA-positive relationship between chronic prostatitis versus normal controls, but have shown inconsistent results. Hence, we systematic searched the PubMed, EMBASE, Science Direct/Elsevier, Medline, and the Cochrane Library up to October 2015 for case-control studies that involved the ASA-positive relationship between chronic prostatitis patients versus normal controls. The meta-analysis was performed with Review Manager and Stata software. After literature search, six studies were identified, including 721 cases of chronic prostatitis and 160 normal controls. Our results illustrated a significant correlation of the ASA-positive relationship between chronic prostatitis patients versus normal controls. The combined odds ratio of the ASA-positive rate in chronic prostatitis patients and normal controls was 3.26 (1.86–5.71). There was also a significant correlation of the ASA-positive relationship between National Institutes of Health (NIH) III versus normal controls, and the combined OR was 2.46 (1.10–5.51). However, there was no significant correlation of the ASA-positive relationship between National Institutes of Health (NIH) II versus normal controls. The present study

illustrates that the positive rate of ASAs in chronic prostatitis patients was significantly higher than in the control group, suggesting that chronic prostatitis has a negative effect on male reproductive function. However, studies with larger samples are needed to better illuminate the correlation between ASAs and chronic prostatitis.

Key words: anti-sperm antibody, chronic prostatitis, male infertility

Introduction

Prostatitis is the most common urological disease in men under the age of 50 years, with prevalence ranging from 2.2% to 9.7% worldwide, with an overall rate of 8.2% (Krieger et al., 2008). It is defined as a heterogeneous mixture of syndromes, with broad diagnostic criteria but its etiology and pathophysiology are somewhat vague (Sharp et al., 2010; Pontari et al., 2008). The prostate is a male accessory sex organ that provides secretions vital for normal fertility. It secretes several major components of seminal plasma that nourish and protect spermatozoa following ejaculation. The current study considered the prostate to be an immunocompetent and not an immunoprivileged site as previously thought (Whitmore et al., 1977; Kramer et al., 2001). Given the intimate association of the prostate with male reproductive function, prostatitis has long been suspected of playing a role in male subfertility. But strong evidence for a direct impact of prostatitis on male fertility is lacking.

Research on anti-sperm antibodies (ASAs) began in 1899, when it was initially reported that sperm could be antigenic if injected into a foreign species (Landsteiner et al., 1899). The presence of ASAs in infertile men was first reported by Rumke et al. (1954) and Wilson

et al. (1954). Since then, ASAs have been considered by several authors as a possible causative factor in infertility, with significant levels being detected in the semen of 5–15% (Adeghe et al., 1993) of infertile men but in only 1–2% (Ayvaliotis et al., 1985; Bates et al., 1997) of fertile men. It is assumed that the development of ASAs is mainly a consequence of trauma to the blood–testis barrier, epididymis, or vas deferens (Gubin et al., 1998). ASAs is also associated with inflammation, and their appearance is often thought to be of idiopathic origin (Lenzi et al., 1997).

Current studies have investigated the correlation between the presence of ASAs and chronic prostatitis, but have shown contradictory results. Some studies have shown a significant ASA-positive relationship in patients with chronic prostatitis compared with healthy individuals (Hoover et al., 2012; Marcelo et al., 2009; Puxin et al., 2009), but not other studies (Chunhua et al., 1992; Su Qin et al., 2005; Jianguo et al., 2004). Therefore, we systematically reviewed the available literature and performed a meta-analysis to evaluate the correlation of ASAs and chronic prostatitis, which might shed valuable insights into the relationship between chronic prostatitis and male infertility.

Methods

Literature search

This meta-analysis was restricted to published studies that investigated the ASA-positive relationship between chronic prostatitis versus normal controls. Two independent reviewers (Jiang YM and Cui D) searched PubMed, EMBASE, Science Direct/Elsevier, Medline, CNKI, and the Cochrane Library from inception to December

2014. The language or study type was not restricted. The search terms combined text words and MeSH terms. For example, the search terms for ASAs were: ‘antisperm antibodies’, ‘sperm antibodies’, ‘antibodies’, ‘ASAs’, and ‘semen antibodies’, while those for chronic prostatitis were: ‘prostatitis’, ‘prostatism’, ‘chronic prostatitis’, ‘chronic pelvic pain syndrome’, ‘abacterial prostatitis’, ‘bacterial prostatitis’, and ‘prostatodynia’. All related articles and abstracts were retrieved. In addition, references cited within relevant reviews were retrieved by hand, and only full articles were searched.

Eligibility criteria

Studies were included if patients met the diagnostic criteria of chronic prostatitis. The classification of prostatitis syndrome followed the consensus criteria of the National Institutes of Health (NIH). I: acute bacterial prostatitis; II: chronic bacterial prostatitis; III: chronic prostatitis/chronic pelvic pain syndrome; and IV: asymptomatic inflammatory prostatitis. The controls were healthy men with no history or evidence of andrologic or urologic disease. ASAs were detected by a sperm anti-sperm antibody test [mixed agglutination reaction (MAR), immunobead test (IBT), or enzyme-linked immunosorbent assay (ELISA)]. Available data were extracted from the article, including numbers of cases and controls, and the ASA-positive rate in all case–control groups.

Exclusion criteria

Studies were excluded if they were case reports or review articles. Studies involving patients with chronic prostatitis accompanied by other disorders of the urogenital system, and patients who had previously undergone surgery of the genital system were also

excluded.

Study selection and validity assessment

Two independent reviewers (Jiang YM and Du YF) screened titles and abstracts of all citations from the literature search. All relevant studies that appeared to meet eligibility criteria were retrieved. If an ambiguous decision was made based on the title and abstract, full texts were needed. The final decision about eligible studies was made by reviewing the articles. Disagreements were resolved by consensus or a third reviewer (Lu J). Two reviewers (Yang Lin and Li JM) completed the quality assessment according to the primary criteria for non-randomized and observational studies of the Newcastle–Ottawa Quality Assessment scale, a tool used for assessing the quality of non-randomized studies included. Using the tool, each study is judged on eight items, categorized into three groups: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. In meta-analysis, stars awarded for each quality item serve as a quick visual assessment. Stars are awarded such that the highest quality studies are awarded up to nine stars.

Data extraction and statistical analysis

Data, including demographic data (authors, year of publication, country, number and mean age of participants, and assay method) and outcome data of ASA-positive patients in all case–control studies, were extracted by two reviewers (Zhang J, and Li JM). Disagreements were resolved by consensus. Quantitative meta-analysis was performed by

three reviewers (Jiang YM, Cui D and Bai XJ) with Review Manager (RevMan) version 5.2 (Nordic Cochrane Centre, Cochrane Collaboration, 2012, Copenhagen, Denmark) and Stata version 12.0 (College Station, TX, USA). Available data were analyzed by meta-analysis. To understand better the ASA-positive relationship between chronic prostatitis patients versus normal controls, sub-analysis was performed simultaneously.

In order to calculate combined OR and its 95% confidence interval (CI). Heterogeneity was assessed by P value and I^2 statistics in the pooled analyses, which represents the percentage of total variation across studies. If P was <0.1 or I^2 was $>50\%$, the summary estimate was analyzed in a random-effects model. Otherwise, a fixed-effects model was applied. In addition, publication bias was detected by visual symmetry of funnel plots, with asymmetry suggesting possible publication bias. It was also assessed by the Begg's and Egger's tests in the meta-analysis. The Begg adjusted rank correlation test is a direct statistical analogue of the visual funnel graph. The Begg procedure tests for publication bias by determining if there is a significant correlation between the effect estimates and their variances. Asymmetry on the right of the graph (where studies with high standard error are plotted) may give evidence of publication bias. The Egger test detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the standardized effect estimates against their precision. If P was <0.05 , publication bias existed.

Results

Characteristics of the included studies

Figure 1 shows the detailed review process. A total of 1173 unduplicated studies were identified. Six studies were ultimately selected according to the eligibility criteria; three studies investigated a relationship between the ASAs and NIH II, and three investigated a relationship between the ASAs and NIH III. After group discussion, all reviewers were in agreement to include all six papers.

Table 1 summarizes the data from the six studies. All retrieved studies involved 721 cases and 160 controls. The mean ages of patient and control groups were in the ranges of 29.5–36.5 and 29.7–39.6 years, respectively. The mean ages of the patient and control groups were unavailable for two studies. All of these studies reported exclusion/inclusion criteria (Hoover et al., 2012; Marcelo et al., 2009; Chunhua et al., 1992; Su Qin et al., 2005; Jianguo et al., 2004; Puxin et al., 2009). Three of these studies (Marcelo et al., 2009; Su Qin et al., 2005; Puxin et al., 2009) detected ASAs by MAR, and included 578 patients with chronic prostatitis and 109 normal controls. Two studies (Chunhua et al., 1992; Jianguo et al., 2004) detected ASAs by ELISA, including 123 cases and 31 normal controls. One study (Hoover et al., 2012) detected ASAs by IBT test, including 20 cases and 20 controls.

Meta-analysis

The test of heterogeneity suggested a fixed-effect model and the meta-analysis revealed a significant correlation of the ASA-positive relationship between chronic prostatitis patients versus normal controls, with an overall combined OR of 3.26 (95% CI: 1.86–5.71) (Figure 2). Sub-analysis was performed simultaneously. There was also a significant correlation of the ASA-positive relationship between NIH III versus normal

controls, with a combined OR of 2.46 (95% CI: 1.10–5.51) (Figure 3). However, there was no significant correlation of the ASA-positive relationship between NIH II versus normal controls, with a combined OR of 1.46 (95% CI: 0.50–4.22) (Figure 3). There was no evidence of significant heterogeneity among these studies ($P>0.1$, $I^2<50\%$). The six studies analyzed in this systematic review were heterogeneous in terms of ASAs test type (IBT, MAR, and ELISA). Although the World Health Organization recommends MAR and IBT, two studies detected ASAs by ELISA. Therefore, we conducted sub-analysis (Figure 4) getting rid of ELISA test or getting rid of IBT test, but the final conclusion were not changed (the ASA-positive rate in chronic prostatitis patients was higher than in healthy individuals). Begg's funnel plot were largely symmetric (Figure 5), suggesting that there were no publication biases in the meta-analysis. Egger's regression test also indicated little evidence of publication bias ($P=0.683$). We also conducted a sensitivity analysis of the meta-analysis. We omitted one study sequentially, and the calculated combined ORs for the remaining studies yielded consistent results. In the overall meta-analysis, no single study significantly changed the combined results, which indicated that the results were statistically stable and reliable (Figure 6).

Discussion

Six studies investigated the ASA-positive relationship between chronic prostatitis patients versus normal controls. Only three studies (Chunhua et al., 1992; Su Qin et al., 2005; Jianguo et al., 2004) reported a significant correlation. In our meta-analysis, there was a significant correlation of the ASA-positive relationship between chronic prostatitis

versus normal controls (Figure 2). To understand better the correlation of the ASA-positive relationship between chronic prostatitis versus healthy male, we performed a sub-analysis simultaneously. Three out of six studies investigated the correlation of ASAs and NIH III, but only one study clearly reported a significant correlation. Our results suggest a significant ASA-positive rate between NIH III versus normal controls (Figure 3); however, the other three studies investigated the correlation of ASAs and NIH II. All these studies showed no significant correlation, which is identical with our meta-analysis.

Male infertility is a complex clinical syndrome, and its incidence has shown an increasing trend in recent years (Liu et al., 1992). Prostate fluid is one of the nutritional components for sperm, and it provides primary energy for sperm activity (Jianning et al., 1992), and prostate disease inevitably affects the quality of semen. Prostatitis and male infertility have been disputed for many years, but strong evidence for a direct impact of prostatitis on male fertility is lacking.

Many studies have confirmed that ASAs has a negative effect on sperm parameters. It can reduce sperm concentration and motility and prolong semen liquefaction (Rossato et al., 2005; Armand et al., 2010; Armand et al., 2011; Dona et al., 1987; Patricia et al., 2007). ASAs has been used to explain unexplained infertility. Sperm ASAs are believed to have an adverse impact on male reproduction function, ASAs production is directed against spermatid surface antigens (Steen et al., 1994; Mazumdar et al., 1998), interfering with sperm motility and transport through the female reproductive tract and inhibiting capacitation and acrosome reactions (Bronson et al., 1990; Steen et al., 1994). On the other hand, ASAs have an indirect mechanism of action to mediate the release of cytokines which

affect sperm function and impair sperm-cervical mucus interaction (Sinisi et al., 1993; Mazumdar et al., 1998; Lombardo et al., 2001), induce sperm cytotoxicity, increase sperm phagocytosis or inhibit embryo development and implantation. As result, natural pregnancies rates decrease. (Marshburn et al., 1994; Vivas et al., 2007; Oliveros et al., 2000; Jaimes et al., 1984).

In humans, ASAs production is due to auto-antigenic and iso-antigenic properties of spermatozoa. The blood–testis barrier and integrity of the genitourinary tract isolate spermatogenesis from the immune system. Therefore, the ASA-positive rate is lower. When the genitourinary tract is damaged, such as by inflammation induced through genital infection or other disease, the integrity of the genitourinary tract is breached, and the immune system may produce ASAs. Batstone et al. (2002) have found lymphocyte infiltration in the semen of patients with autoimmune prostatitis. In humans, there is a phenomenon of semen prostate liquid reflux. In healthy male, the quality of semen parameters may not change, but in chronic prostatitis patients there may be a negative effect upon the sperm parameters (Weidner et al., 1991; Engeler et al., 2003; Ausmees et al., 2013; Motrich et al., 2006; Motrich et al., 2005; Leib et al., 1994; Henkel et al., 2006). This suggests that the integrity of the genitourinary tract is damaged in chronic prostatitis.

Several risk factors are involved in pathogenesis of infertility, and ASAs are just one of them. The current studies have confirmed that ASAs (Rossato et al., 2005; Armand et al., 2010; Armand et al., 2011; Dona et al., 1987; Patricia et al., 2007) and chronic prostatitis (Engeler et al., 2003; Ausmees et al., 2013; Motrich et al., 2006; Motrich et al., 2005; Leib et al., 1994; Henkel et al., 2006; Menkveld et al., 2003; Pasqualotto et al., 2000) influence

a negative effect **upon** semen parameters. In our study, the ASA-positive rate in chronic prostatitis patients was significantly higher than in the control group, which suggests that chronic prostatitis may have an effect on semen parameters through ASAs, but further studies are required. For evaluation of the risk of infertility in NIH III patients, detection of ASAs in seminal fluid may be important.

There were some limitations to our study that need to be taken into consideration when interpreting the results of this meta-analysis. First, the inherent limitations of the studies included in this analysis are the different ASAs assaying methods (IBT, MAR, and ELISA). However, our sub-analysis suggested that the different methods applied did not change the final conclusion. The Sensitivity and specificity of the different assays are lacking in the related studies. And it is unclear which proportion of ASAs binds to clinically relevant antigens and leads to infertility (Bohring et al., 2003; Ohl et al., 1995). IBT, MAR, and ELISA tests may provide a crude assessment of the correlation of ASAs in chronic prostatitis patients, and this may influence how one interprets correlation studies with chronic prostatitis and male immunological infertility. Second, the sample size of each study was relatively small, and a total of 721 chronic prostatitis patients and 160 normal controls were investigated in all six studies. Furthermore, several studies related to the topic were excluded owing to a lack of control data. As such, it is hard to make definitive conclusions about the clinical value of chronic prostatitis and immunological infertility.

In summary, the results of this meta-analysis suggest that the ASA-positive rate (as measured by MAR, IBT, and ELISA) was higher in chronic prostatitis patients than in healthy individuals. Our study did not indicate that ASAs or chronic prostatitis always

results in immunological infertility. ASAs alone have a poor correlation with *in vitro* fertilization or intracytoplasmic sperm injection pregnancy rates (Nagy et al., 1995; Esteves et al., 2007; Vujisic et al., 2005; Clarke et al., 2006), but in current studies the ASAs negative effect on semen parameters has been confirmed. The negative effect of chronic prostatitis on male reproductive function may be mediated by its toxic influence on semen, as well as through ASAs. Our results add new evidence to the correlation between chronic prostatitis and male reproductive function. And this field was in interest of many investigators. However well-designed studies with larger sample sizes and more appropriate ASAs assays are required to further address this issue.

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Table 1.Characteristics of included studies investigating the ASAs in chronic prostatitis patients

Study	Country	Mean age(case/control)	Assay	Control	Case (CAP)	II	III	IIIa	IIIb	OR (95% CI)
Mie PX. 2009	China	36.5/39.6	MAR	34	114	42		34	38	1.00[0.31,3.18]
P.Hoover. 2012	America	NI/NI	IBT	20	20	6	14			5.54[0.25,123.08]
Marcoin M. 2009	Germany	NI/NI	MAR	45	310	38		59	213	2.87[0.38,22.00]
Zhang JG. 2004	China	27.5/NI	ELISA	20	86		86			5.67[1.55,20.75]
Deng CH .1992	China	30.5/29.7	ELISA	11	37					5.91[1.12,31.20]
Qin S. 2005	China	29.5/NI	MAR	30	154	28		83	42	3.90[1.51,10.06]

Abbreviations: NI not indicated in studies.

Figure legends

Figure 1. Flow diagram of selection of eligible studies. After Literature search, a total of 1173 unduplicated studies were identified. Six studies were ultimately selected according to the eligibility criteria.

Figure 2. Forest plot showing the meta-analysis outcomes of the ASA-positive relationship between chronic prostatitis patients and normal controls. The results show that the positive rates of ASAs in chronic prostatitis patients were significant higher than normal controls ($P < 0.0001$).

Figure 3 Forest plot of sub-analysis showing the meta-analysis outcomes of the ASA-positive relationship between chronic prostatitis patients versus normal controls. There was also a significant correlation of the ASA-positive relationship between NIH III versus normal controls ($P = 0.03$). However, there was no significant correlation of the ASA-positive relationship between NIH II versus normal controls ($P = 0.49$).

Figure 4 Forest plot of sub-analysis showing the influence of different assay methods on meta-analysis. Sub-analysis results show that gets rid of ELISA test ($P = 0.007$) or gets rid of IBT test ($P < 0.0001$), but the final conclusion were not changed (the ASA-positive rate in chronic prostatitis patients was higher than in healthy individuals).

Figure 5 Begg's publication bias plot of included studies. The funnel plot of include studies indicates little evidence of publication bias.

Figure 6 Sensitivity analysis plot of association of antisperm antibodies with chronic

prostatitis. Omitting one study sequentially, no single study significantly changed the combined results.

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Excluded (n=823)

Potentially eligible studies for full-text
evaluation (n=87)

Full-text evaluation excluded (n=81)
Review article (n=2)
Case report (n=8)
No control case (n=18)
Study was assay serum AsA (n=5)
Accompanied by other disorders (n=32)
Chronic prostatitis accompanied
infertility (n=16)

Study include in systematic
review (n=6)

Studies included in
meta-analysis (n=6)

NIH II case n=104

NIH III case n=430

Begg's funnel plot with pseudo 95% confidence limits

Meta-analysis fixed-effects estimates (linear form)

Study omitted