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ARTICLE

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Men with spinal cord injury have a smaller prostate volume than age-matched able-bodied men: a meta-analysis of case-control studies

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STUDY DESIGN: Meta-analysis

OBJECTIVES: Denervation and androgen deficiency, peculiar to individuals with chronic spinal cord injury (SCI), could hinder, to some extent, both prostate growth and activity. To comprehensively assess the relationship between SCI and prostate volume, we carried out a meta-analysis of the available case-control studies.

METHODS: A thorough search of MEDLINE, Scopus and Web of Science was carried out to identify studies comparing prostate volume in men with and without SCI. Quality of the studies was assessed using the Newcastle–Ottawa Scale (NOS). Mean differences (MDs) in prostate volume were combined using a random effect model. Funnel plot was used to assess publication bias.

RESULTS: Four studies met the inclusion criteria and provided information on 278 men with SCI and 1385 able-bodied controls. The overall difference in prostate volume between the two groups reached the statistical significance (pooled MD: −14.85 ml, 95% CI: −27.10 to −2.61, $p = 0.02$). In a subgroup analysis including only the studies with the highest NOS score, the pooled MD remained significant (pooled MD: −18.56, 95% CI: −33.14 to −3.99, $p = 0.01$). The shape of funnel plot did not allow to rule out a possible publication bias.

CONCLUSIONS: This meta-analysis suggests that in men with SCI, prostate volume tends to be smaller than in age-matched able-bodied men. Longitudinal studies of men with long-lasting SCI in advanced age are warranted to clarify whether this condition is associated with a lower risk of age-related prostate proliferative diseases.

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INTRODUCTION

In the last decades, major advances in life support treatments and medical care of the acute post-injury phase resulted in a substantial improvement in life expectancy of people with spinal cord injury (SCI) [1]. While a larger number of patients survive now the acute life-threatening complications, in chronic SCI, clinical concerns related to the neurological damage largely overlap with those from different medical fields with a deep impact on quality of life, morbidity and mortality. Nowadays, many patients with SCI are likely to go through age-related health issues and age, specifically, represents a well-known risk factor for prostate diseases, including hyperplasia [2] and cancer [3].

Of note, men with SCI could be somehow susceptible to prostate disorders because of both gland chronic traumatism and inflammation associated to catheterization and recurrent urinary tract infections (UTIs). Therefore, one would expect a larger number of patients with SCI to develop prostate disorders later in their lives. Nevertheless, quite surprisingly, in a meta-analysis involving 35,293 men with SCI and 158,140 age-matched able-bodied controls, pooled estimates revealed a significant association of SCI with a lower risk of prostate cancer, which was more than halved in the age group over 55 years [4]. It has been hypothesized that a combination of factors peculiar to men with SCI, including androgen deficiency and the loss of neurotrophic influences of nerve projections to the gland might be somewhat protective against prostate proliferative disorders [5]. In this light, a significant smaller prostate size following SCI would be expected.

The present systematic review with meta-analysis of case-control studies aimed to comprehensively investigate the relationship between SCI and prostate volume, thus answering the following question: "Is SCI associated with a statistically significant lower prostate volume compared to that observed in age-matched able-bodied general population?"

MATERIALS AND METHODS

This meta-analysis was conducted according to the Cochrane Collaboration and to the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [6]. It also complies with the guidelines from Meta-analyses Of Observational Studies in Epidemiology (MOOSE) [7]. The PRISMA and MOOSE Checklists have been presented as

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Supplementary Tables 1 and 2, respectively. This study was registered on the International prospective register of systematic reviews (PROSPERO) with the number CRD42020176365.

Systematic search strategy

We performed an extensive search in Medline, Scopus, and Web of Science, including the following free and vocabulary terms: "spinal cord injur*", "spine injur*", paraplegia, tetraplegia, quadriplegia, prostate, using the Boolean functions AND/OR. The search was restricted to English-language case-control studies enrolling human participants, published up to March 1, 2021. If it was not clear from the abstract whether the study contained relevant data, the full text was retrieved. The identification of eligible studies was performed by four authors independently (MT, DT, SP and FDA), and disagreements resolved by the other investigators. No search software was employed. The reference lists of the identified studies were also manually checked to identify any additional pertinent reports.

Inclusion and exclusion criteria

The outcome of interest was the relationship between prostate volume and SCI. The eligibility criteria used for the inclusion were: (i) observational case-control studies involving adult men with SCI (cases) and age-matched able-bodied men (controls) (ii) availability of mean values ± standard deviation (SD) of prostate volume (ml) in both groups, as assessed by ultrasonography. All case series, case reports, reviews and intervention trials were excluded. When the same population was used for multiple publications, the study with the largest number of cases was included. Two independent reviewers (SDA and AB) evaluated the full text of all selected studies for eligibility and, where disagreement occurred, a third reviewer (SF) took a decision after open discussion.

Data extraction

Data were extracted from the selected studies by three independent reviewers (AP, MT and CC) by including the first author, publication year, age of the participants, level and completeness of SCI, the years since injury, the mean values ± SD of prostate volume along with the total number of participants in cases and controls. When available, information about testosterone levels was also extracted. When summary statistics were not fully reported, these were calculated whenever possible [8]. Wherever quantitative data were missing or inconsistent, the authors were contacted to obtain the necessary information.

Quality assessment

The quality of each included study was evaluated by the Newcastle–Ottawa Quality Assessment Scale (NOS) [9]. The NOS used a "star system" to judge the quality of article by three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of the exposure. The number of stars was calculated between 0 and 9. Those getting scores ≥ 7 were regarded as high-quality studies. Three independent authors (MM, SDA and AB) carried out the quality assessment and when a disagreement occurred, a third author (SF) took a decision.

Statistical analysis

Data extracted from individual studies were pooled using the mean difference (MD) in a random effect model, which assumes that the studies included in the meta-analysis had varying effect sizes, thus providing a more conservative estimate of the overall effect. We used the Cochrane X^2 (Cochrane Q) and the I^2 test to analyze the between-study heterogeneity [10].

The funnel plot was used to graphically explore the publication bias: a symmetric inverted funnel shape arises from a "well-behaved" dataset, in which publication bias is unlikely [11].

Analyses were carried out using the package 'metafor' of R statistical software (version 3.0.3; The R Foundation for Statistical Computing) and the Review Manager (RevMan) of the Cochrane Library (version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

Study selection

We identified 890 published reports through electronic search. After duplicate removal, 632 studies were left, of which 585 were excluded based on titles and abstracts. Hence, as shown in Fig. 1, a total of 47 studies were identified, of which 4 meet the criteria for the inclusion in the quantitative analysis [12–15]. The main characteristics of the selected articles are reported in Table 1.

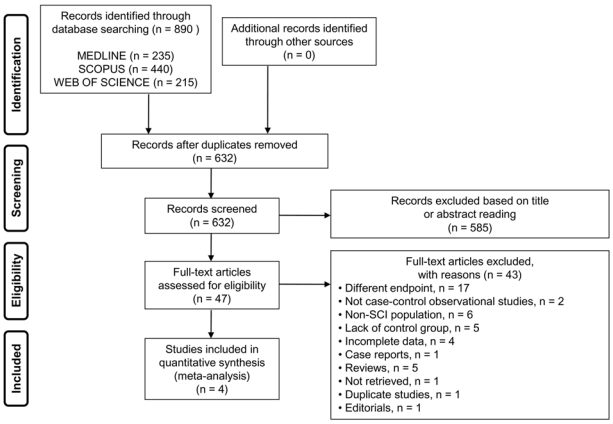

Fig. 1 Flow chart showing an overview of the study selection process. SCI spinal cord injury.

Quality of the included studies

Results of quality assessment of selected reports are provided in Table 2. The NOS quality scores ranged from 5 to 8. Of the four studies, all but one [13] were considered to be of high quality, scoring ≥7. In particular, in the study by Hvarness et al. [13], a possible representativeness bias arose from the identification of non-consecutive cases from record registers of a SCI clinic; furthermore, in the same study, a selection bias of control group could not be ruled out, as it was drawn from a sample described elsewhere [16].

Synthesis of results and publication bias

The four studies included in the quantitative synthesis collectively provided information on 278 men with SCI and 1385 able-bodied controls. As shown in Fig. 2, the pooled estimate indicated a significantly lower prostate volume in the group with SCI (MD: −14.85 ml, 95% CI: −27.10 to −2.61, $p = 0.02$). The pooled MD remained significant in a subgroup analysis, where we excluded the study by Hvarness et al. [13], exhibiting both the lowest NOS score and the smallest sample size (MD: −18.56, 95% CI: −33.14 to −3.99, $p = 0.01$, Fig. 3).

The shape of the funnel plot with a wide scatter of effect estimates around the true effect (Fig. 4), did not allow to rule out a possible a possible publication bias.

DISCUSSION

The impact of SCI on prostate pathophysiology remains quite controversial, despite the great care devoted to the urological issues in this population. Overall, the present meta-analysis revealed a tendency of spinal-cord-injured men to exhibit a significantly smaller prostate volume compared to age-matched able-bodied controls. This would be inconsistent with the purported prostate hypertrophying effects exerted by some conditions peculiar to men with SCI, including traumatisms by bladder catheterization and chronic inflammation due to recurrent UTIs. In particular, it has been well documented that inflammation may activate the release of cytokines and growth factors promoting prostatic cell proliferation [17]. Accordingly, in tissue from benign prostatic hyperplasia (BPH), inflammation degree correlates with both prostate volume and weight [18]. Actually, in a series of 138 men with chronic SCI, we recently found that those with a larger prostate volume did not exhibit a significantly higher

Table 1. Main characteristics of the four studies included.

Study	Mean age of participants (years)	SCI group size (*n*)	Control group size (*n*)	Time since SCI (years)	Level of SCI (*n*, %)		Completeness of SCI (*n*, %)		TT levels in SCI group (ng/dL)	TT levels in control group (ng/dL)
					T12 and above	L1 and below	Motor complete (AIS A-B)	Motor incomplete (AIS C-D)		
Bartoletti et al. [14]	61.3	113	109	14.7	91 (80.5)	22 (19.5)	57 (50.4)	56 (49.6)	321.5	649.7
Hvarness et al. [13]	50.5	31	31	28.9	29 (93.5)	2 (6.5)	19 (61.3)	12 (38.7)	346.1	473.0
Pannek et al. [12]	53.7	100	575	13.7	62 (62.0)	38 (38.0)	41 (41.0)	59 (59.0)	NR	NR
Torricelli et al. [15]	54.0	34	670	NR	NR	NR	NR	NR	NR	NR

AIS ASIA (American Spinal Injury Association) impairment scale, *L1* first lumbar vertebra, *NR* not reported, *SCI* spinal cord injury, *T12* twelfth thoracic vertebra, *TT* total testosterone.

Table 2. Newcastle–Ottawa assessment scale for case-control studies.

Study	Selection				Comparability		End-point			
	Definition of cases	Representativeness of cases	Selection of controls	Definition of controls	On age	On other risk factors	Assessment of the end-point	Same method of ascertainment for cases and controls	Non-response rate	Score
Bartoletti et al. [14]	1	1	1	1	1	0	1	1	1	8
Hvarness et al. [13]	1	0	0	1	1	0	1	1	0	5
Pannek et al. [12]	1	1	1	1	1	0	1	1	0	7
Torricelli et al. [15]	1	0	1	1	1	0	1	1	1	7

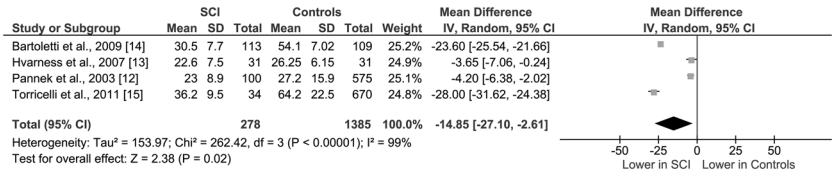

Fig. 2 Forest plot of the mean difference in prostate volume among men with and without spinal cord injury (SCI). Diamond indicates the overall summary estimates for the analysis (the width of the diamond represents the 95% CI); boxes indicate the weight of the individual studies in the pooled analysis. Prostate volume is reported in ml. CI confidence interval, df degrees of freedom, IV inverse variance, SCI spinal cord injury, s.d. standard deviation.

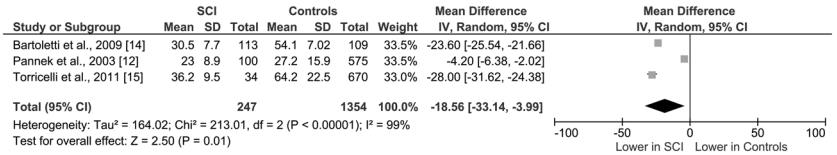

Fig. 3 Forest plots depicting the results of the subgroup analysis on the relationship of SCI with prostate volume. The study Hvarness et al. [13], exhibiting both the lowest quality score at the Newcastle–Ottawa scale and the smallest sample size, was excluded. Prostate volume is reported in ml. CI confidence interval, df degrees of freedom, IV inverse variance, SCI spinal cord injury, s.d. standard deviation.

incidence of UTIs, when compared to those with a smaller volume [5]. Furthermore, in the same study, among putative determinant of prostate volume, only a lower testosterone and a level of the lesion above T12, along with a younger age, were independently associated with a lower prostate volume [5]. In this scenario, the here revealed tendency to a smaller prostate size in men with SCI might suggest that, in this population, androgen deficiency and denervation play a preeminent role in influencing prostate pathophysiology, overcoming the possible "hypertrophying" impact of the chronic inflammation.

A decline in testosterone levels in spinal-cord-injured men has been repeatedly reported in the last decades [5, 19–28]. During the acute post-injury phase, the proportion of men with biochemical androgen deficiency reaches 83% [19], because of the impact of severe physical distress and systemic illness on testosterone biosynthesis. Nevertheless, a multifactorial, albeit not yet fully elucidated pathogenesis underlies the significantly higher prevalence rates of low testosterone even in men with chronic SCI when compared to age-matched able-bodied controls [21, 22]. A low-grade systemic inflammation related to obesity and recurrent infections results in increased levels of inflammatory cytokines suppressing the pituitary secretion of luteinizing hormone (LH). Moreover, adipose tissue is responsible for the aromatization of androgens into estrogens, which exert an inhibitory effect on LH secretion in males [29]. In people with chronic SCI, the excess of fat mass reflects a disrupted energy balance due to the loss of muscle trophism and performance ability that underlie a substantial decrease in overall energy expenditure [30]. However, low testosterone, in turn, can make obesity and muscle wasting worse, driving the pluripotent stem cell commitment into adipogenic rather than myogenic lineage [31], thus establishing a vicious cycle. The link between prostate hypotrophy and androgen deficiency is supported by the well-known role of the dihydrotestosterone (DHT), the metabolically active form of testosterone, in promoting prostatic cell proliferation. It is known that 5α-reductase inhibitors, blocking the conversion of testosterone into DHT, reduce the biological activity of the gland and improve the BPH symptoms [32–34].

As recently reported, androgen deficiency would work synergistically with denervation in hindering prostate gland enlargement [5]. In particular, sympathetic nervous system seems to play a role in the prostate trophism as in the rat, unilateral sympathectomy results in decreased ventral prostate weight, DNA, and protein content in the lesioned side [35]. Unfortunately,

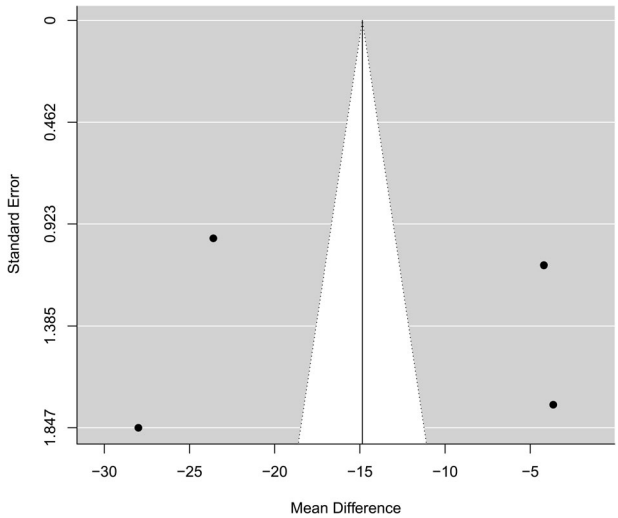

Fig. 4 Funnel plot for the analysis of the mean difference in prostate volume between men with spinal cord injury and able-bodied controls. The asymmetrical shape of the distribution suggests a possible pubblication bias.

only two of the four studies included in the present meta-analysis provided complete information about testosterone and level of the lesion [13, 14]. Interestingly, in these studies, both reporting a smaller prostate volume following SCI, most participants had a spinal lesion above the T12 level and SCI group exhibited testosterone levels significantly lower than age-matched able-bodied controls. It could be speculated that the "hypotrophying" impact of SCI-related factors on the prostate gland pathophysiology could result in a lower risk of developing BPH with age. Intriguingly, the greatest difference in prostate volume between men with SCI and controls was found in the study by Bartoletti et al. [14], where the mean age of the participants was older than in other studies. Hence, the difference in prostate volume would become more pronounced with aging, when BPH can get more prevalent in the able-bodied population but not in men with SCI.

As a major limitation of this meta-analysis, only four articles were included in the quantitative synthesis. This restricted number of studies resulted from a careful screening and selection of the literature, nevertheless, the quantitative synthesis provided an

overall MD with a very large 95% CI, albeit statistically significant (Fig. 2). As the pooled estimate was burdened by a not negligible degree of imprecision, caution should be used when interpreting its clinical relevance and reflections. Moreover, the dearth of studies and their details about the series under investigation did not allow us to carry out meta-regressions followed by subgroup analyses to investigate the possible source(s) of the significant between-study heterogeneity. However, of note, all studies were along the same lines in reporting a smaller prostate volume in SCI group than in controls. Therefore, heterogeneity did not reflect a disagreement among the studies in documenting an association between SCI and smaller prostate size, but rather a variability in the reported degree of SCI-related gland hypotrophy. Finally, although the shape of the funnel plot did not allow to rule out a possible publication bias, the inclusion of four studies only prevented us from performing tests for funnel plot asymmetry.

In conclusion, men with SCI tend to exhibit a smaller prostate volume when compared to age-matched able-bodied men. Longitudinal studies of men with long-lasting SCI in advanced age could ascertain whether and to what extent the purported "hypotrophying" impact of SCI on the prostate gland can result in a lower risk of developing BPH.

DATA AVAILABILITY

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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AUTHOR CONTRIBUTIONS

AP, MT and CC were responsible for acquisition of data, analysis, interpretation of data and drafting the article. SD was responsible for acquisition of data, statistical analysis and interpretation of data. DT, SP and FD were responsible for acquisition of data. MM was responsible for statistical analysis and interpretation of data. SF was responsible for critical revision of the paper for important intellectual content. AB was responsible for conception and design, analysis and interpretation of data, critical revision of the paper for important intellectual content, drafting the article, final approval of the version to be published. All authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

This study did not directly involve human participants.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41393-021-00712-7.

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