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ORIGINAL ARTICLE

Metabolic syndrome is the key determinant of impaired vaginal lubrication in women with chronic spinal cord injury

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Abstract

Purpose Spinal cord injury (SCI) affects sexual health of both male and female, but little attention has been given to sexuality of SCI women. Similar to penile erection, vaginal lubrication represents a neurovascular event and then both denervation and vascular damage might contribute to its impairment. Nevertheless, the relative weight of lesion location/degree and vascular risk factors in determining hypolubrication in women with SCI has not yet been investigated. The aim of this study was to recognize among putative determinants of poor sexual arousal in women with SCI, neurogenic and vascular/metabolic independent predictors of vaginal hypolubrication.

Methods Twenty-eight consecutive female patients admitted to a rehabilitation program because of chronic SCI (≥ 1 year) underwent clinical and biochemical evaluations, including assessment of vaginal lubrication by the Female Sexual Function Index (FSFI). As, in people with SCI, waist circumference overestimates visceral fat mass due to abdominal muscle paralysis, metabolic syndrome (MetS) was defined according to specific criteria proposed for SCI population: BMI ≥ 22 kg/m^2 and two or more of the following: triglycerides ≥ 150 mg/dL (or actual treatment), HDL < 50 mg/dL, hypertension (or actual treatment), fasting glucose ≥ 100 mg/dL or diabetes mellitus type 2.

Results A FSFI lubrication sub-score < 3.6, suggestive for impaired vaginal lubrication, was exhibited by 53.7% of the study population. When compared to the group with normal lubrication, a significantly higher proportion of these women had paraplegia (93.3% vs 38.5%, $p = 0.003$) and met the SCI-specific criteria for MetS (73.4% vs 7.6%, $p = 0.0006$), whereas, no significant differences were found between the two groups in the proportion of women exhibiting the single components of MetS. At the multiple logistic regression analysis, only the presence of MetS exhibited a significant independent association with impaired vaginal lubrication (OR = 3.1, 95% CI 1.2, 5.8, $p = 0.01$).

Conclusions In women with SCI, a clustering of modifiable vascular/metabolic risk factors, constituting the MetS, could contribute to sexual dysfunctions by affecting the vaginal lubrication, independently of the level of the spinal cord lesion.

Keywords Spinal cord injury · Vaginal lubrication · Metabolic syndrome · Female sexual dysfunction · Female sexual functioning

Introduction

Sexual dysfunction associated with spinal cord injury (SCI) may significantly impact the health and well-being of both men and women. Although several studies have investigated the sexual health in males with SCI, there exist relevant gaps in the understanding of pathophysiology and management of sexual dysfunction in females with SCI. It has been reported that although women with SCI have normal menses and fertility, female sexual dysfunctions (FSDs), and, in particular, impaired vaginal lubrication, are highly prevalent in this population as compared with able-bodied women [1].

Vaginal lubrication refers to the naturally produced fluid in the vagina. Its production increases significantly during sexual arousal owing to increased blood flow. Under normal conditions, activation of the sympathetic adrenergic nerve keeps the arteriolar component of the vaginal microcirculation contracted, resulting in the moderate passage

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of exudates, which is enough to humidify the vagina. During sexual arousal, the central sympathetic tone decreases, meanwhile intestinal vasoactive polypeptide (VIP) and nitric oxide (NO), released by the non-adrenergic non-cholinergic (NANC) fibers cause relaxation of the smooth vascular and non-vascular muscles of the clitoris and vagina, resulting in increased blood flow [2]. Therefore, vaginal lubrication is both a nervous and vascular process.

Similar to erectile dysfunction in men, it has been hypothesized that altered vaginal lubrication in women can be due to conditions that cause vascular damage (e.g., cardiovascular or metabolic diseases) or nervous damage. In this context, although the relationship between vaginal lubrication (and more generally FSD) and cardiovascular diseases or vascular/metabolic risk factors has been investigated in the general population, conflicting results have been produced regarding the association between impaired lubrication and obesity or metabolic syndrome (MetS) [3, 4]. Interestingly, patients with chronic SCI (lasting more than 1 year) undergo changes in body composition owing to denervation of sublesional somatic districts. This results in significant muscle hypotrophy, leading to reduced energy expenditure, exacerbated by the state of global immobility. The result is a substantial increase in fat mass, which is also underestimated by the simple calculation of the body mass index (BMI) owing to the loss of lean mass. Indeed, in a study on adults with chronic SCI, a BMI value still within the normal range for the general population, was associated with a percentage of body fat content (as evaluated by bioelectric impedance) already compatible with a state of obesity in able-bodied people [5]. In spite of its pathophysiological plausibility, no data exist about the relationship between impaired vaginal lubrication and the clustering of vascular/metabolic risk factors constituting the MetS in women with SCI, where, mainly according to the level and completeness of the neurological damage, even the reported prevalence of poor lubrication is largely variable, ranging from 6.0 to 23.2% [6–8].

On this basis, we performed a cross-sectional analysis in women with chronic SCI to define the relative weight of the MetS as a possible independent predictor of vaginal hypolubrication among the putative determinants of sexual dysfunction.

Materials and methods

Study population and design

Fifty-two female patients were consecutively admitted to a rehabilitation program at the "San Raffaele Scientific Institute" of Sulmona, Italy, because of SCI over a period of 2 years. We excluded 10 of them as they did not meet the inclusion criteria, that is, documented history of neurologically stable SCI for more than 1 year and sexual intercourses in the last year. Exclusion criteria were menopausal status and current treatments by systemic route with preparations based on estrogens, PDE5-inhibitors or ospemifene. Accordingly, 8 patients were excluded because of menopause. None of the patients had a history of any urologic or gynecologic surgery. At the admission, no patient had acute or chronic coexisting illnesses that could hinder the rehabilitative program. Moreover, none of the patients had a history of communication or cognitive disorders that could affect the validity of their responses to the questionnaires. Among the 34 enrolled women, 6 of them did not provide informed consent to answers related to their sexual life; therefore, our study population included 28 women, aged 42.4 ± 10.6 years.

Clinical and neurologic examination

Two experienced physicians (SD and GF) performed a detail clinic and neurologic examination as previously reported [9]. Briefly, based on the International Standards for Neurological Classification of SCI from the American Spinal Injury Association (ASIA) and ASIA Impairment Scale (AIS) [10, 11], patients with complete lack of motor and sensory functions in the lowest sacral segment (anal area) were categorized as grade A, whereas those with incomplete lesions were categorized as grades B through D. Grade B indicated motor complete lesion with some sensation below the level of the lesion. Grade C also indicated some preservation of motor function; however, 50% of the muscles below the level of the lesion were unable to move against gravity. Grade D indicated that more than 50% of the muscles below the level of the lesion were spared and able to move against gravity.

Bodyweight was recorded with patients wearing light clothing using a professional mechanical chair scale Mod. DM2 (Wunder Sa. bi. S.r.l; Monza, Italy). After resting the patient on a bed, legs were straightened, the head was positioned in the Frankfurt plane, and the feet were placed in a dorsally flexed position. The height was determined by an elastic tape, measuring in segments the distance between the heel to knee, the knee to hip, and the hip to head. Body mass index (BMI) was also calculated (kg/m^2).

A functional independence degree in ADL was assessed by the Spinal Cord Independence Measure (SCIM), a 19-item instrument to measure the degree of functional independence attained in ADL [12]. The SCIM weighs each function separately to provide a final score that ranges from 0 (totally dependent) to 100 (totally independent). The 6th and 7th items of SCIM explore, respectively, the bladder and bowel dysfunction, and they represent the bowel/bladder SCIM sub-score.

The Numerical Rating Scale (NRS) was used to assess the presence and intensity of SCI-related pain, based on the

National Institute on Disability and Rehabilitation Research recommendations [13]. Patients were asked to rate their pain verbally on a scale from 0 to 10, with 0 signifying no pain, while 10 depicting the worst possible pain.

We evaluated muscle tone and spasticity degree at the lower extremities by the Ashworth Scale [14], scoring from 0 (no increase in muscle tone) to 4 (rigidity). The overall score was calculated by the mean of the scores obtained on the principal joints of the inferior limbs.

Female Sexual Function Index

The Female Sexual Function Index (FSFI) is a self-administered questionnaire that assesses a female's sexuality in both clinical and general populations [15]. This multidimensional tool consists of 19 items that are divided into six sub-scale scores, including sexual desire (two questions), arousal (four questions), vaginal lubrication (four questions), orgasm (three questions), satisfaction (three questions), and pain (three questions). All sub-scores range from 0 to 5 and their values provided the total score for FSFI. An overall score of 26.55 or lower has been identified as the cut-off value for FSD [15]. As no validated cut-off points for the lubrication domain exist, a score less than 3.6 on the FSFI lubrication sub-scale was used to identify women with impaired vaginal lubrication, as previously proposed by Jiann et al. in the general population [16].

Metabolic syndrome and laboratory measures

As the most commonly used definitions for MetS by World Health Organization (WHO) [17], third adult treatment panel of the National Cholesterol Education Project (ATP III) [18] and International Diabetes Federation (IDF) [19] may be inappropriate in persons with SCI, MetS was diagnosed according to the SCI-appropriate modified IDF criteria proposed by Gater and colleagues in a series of 473 veterans with SCI [20]: BMI $\geq$ 22 kg/m^2 and two or more of the following: triglycerides $\geq$ 150 mg/dL (or actual treatment), HDL < 50 mg/dL, hypertension (or actual treatment), fasting glucose $\geq$ 100 mg/dL or diabetes mellitus type 2.

A fasting morning venous blood sample was obtained from each subject between 8:00 a.m. and 9:00 a.m. Standard methods and commercial kits (Instrumentation Laboratory Company; Lexington, MA, USA) were used for all biochemical and hematologic measurements.

Statistical analysis

Statistical analysis was performed using the R statistical software (version 3.5.0, the R Foundation for Statistical Computing; Vienna, Austria). After assessing that data were non-normally distributed by the Shapiro–Wilk test, the Wilcoxon rank-sum test was used to compare continuous variables between participants dichotomized according to the presence (FSFI lubrication sub-score < 3.6) or absence (FSFI lubrication sub-score $\geq$ 3.6) of impaired vaginal lubrication. Proportional differences were assessed using the Fisher's exact test. A multiple logistic regression analysis, including significant predictors identified by univariate regressions, was performed to assess independent associations with impaired vaginal lubrication.

Results

A value < 3.6 in the domain of FSFI lubrication, suggestive of impaired vaginal lubrication [16], was reported by 53.7% (15/28) of the study population. Table 1 shows the characteristics of the series categorized by the vaginal lubrication state. When compared to women with normal lubrication, a significantly higher proportion of women with impaired lubrication exhibited a SCI level below T6 and met the SCI-appropriate criteria for MetS. No other differences were observed between the two groups.

As shown in Table 2, women with impaired vaginal lubrication reported significantly lower total scores at the FSFI as compared to women with normal lubrication. Significant differences were also found in the desire ($p = 0.03$), arousal ($p = 0.02$), and orgasm ($p = 0.01$) domains.

At the univariate logistic regression analyses, the impaired vaginal lubrication was positively predicted by the presence of MetS (OR = 3.5, 95% CI 1.8, 5.9, $p = 0.003$), as well as by a lesion level below T6 (OR = 3.1, 95% CI 1.4, 5.5, $p = 0.008$). When these two variables selected in the univariate analyses were included in a multiple logistic regression model (Fig. 1), only the presence of MetS exhibited a significant independent association with the vaginal impaired lubrication (OR = 3.1, 95% CI 1.2, 5.8, $p = 0.01$).

Discussion

A spinal cord injury is a traumatic event that could impair different aspects of a patient's life, resulting in a multitude of clinical–psychological issues that could be directly or indirectly linked to neurologic damage and may result in a global disability. Among these, sexual function is regarded as one of the most common impaired and underestimated dimensions. Actually, the literature on FSD owing to SCI is scarce, especially in comparison to several studies that have investigated sexual health in men with SCI. This could be attributed to the fact that following injury women did not lose menses and fertility as compared to men, who suffered from erectile dysfunction, ejaculatory dysfunction, and poor quality of semen, resulting in infertility [21]. Over the

Table 1 Characteristics of the study population categorized by the FSFI lubrication sub-score, as "normal" (score ≥ 3.6) and "impaired" (score < 3.6)

Characteristics	Vaginal lubrication		*p* value
	Normal ($n = 13$)	Impaired ($n = 15$)	
Demographic and lifestyle variables			
Age (years)	42.0 (32.0–46.0)	48.0 (36.0–53.0)	0.09
Marital status, *n* (%)			
Occasional partner	4 (30.7%)	4 (26.7%)	0.3
Stable partners	9 (69.3%)	11 (73.3%)	
Current smokers, *n* (%)	6 (46.1%)	7 (46.7%)	0.9
Blood biometric measures			
Glycaemia (mg/dL)	83.5 (73.5–91.5)	84.0 (81.0–96.0)	0.5
Triglycerides (mg/dL)	97.0 (62.3–120.5)	116.0 (99.0–158.0)	0.1
HDL (mg/dL)	40.0 (39.0–70.0)	49.0 (44.0–58.0)	0.9
Clinical variables			
BMI (kg/m^2)	24.7 (20.1–28.9)	25.9 (23.4–27.8)	0.8
BMI ≥ 25 kg/m^2, *n* (%)	8 (61.5%)	6 (40%)	0.9
BMI ≥ 30 kg/m^2, *n* (%)	2 (15.4%)	0 (0%)	0.2
Metabolic syndrome, *n* (%)[a]	1 (7.6%)	11 (73.4%)	0.0006
Hypertension, *n* (%)	2 (15.4%)	5 (46.7%)	0.1
Diabetes mellitus type 2, *n* (%)	0 (0%)	1(6.6%)	1
Dyslipidemia, *n* (%)	0 (0%)	1 (6.6%)	1
Antihypertensive drugs, *n* (%)	2 (15.4%)	5 (33.3%)	0.1
Antidepressant drugs, *n* (%)	2 (15.4%)	7 (46.7%)	0.1
SCI-related variables			
Level of lesion, *n* (%)			
At or above T6	8 (61.5%)	1 (6.6%)	0.003
Below T6	5 (38.5%)	14 (93.3%)	
Cause of the lesion, *n* (%)			
Degenerative	7 (53.8%)	6 (40%)	0.7
Traumatic	4 (30.6%)	7 (46.7%)	
Vascular	2 (15.4%)	2 (13.3%)	
Lesion completeness, *n* (%)			
Complete motor lesion (AIS A–B)	7 (53.9%)	5 (33.4%)	0.7
Incomplete motor lesion (AIS C–D)	6 46.1%)	10 (66.6%)	
Able to walk, *n* (%)	2 (15.4%)	3 (20%)	1
SCIM score			
Functional independence SCIM	59.0 (49.0–71.0)	65.0 (29.0–67.5)	0.9
Bowel-bladder SCIM sub-score[b]	17.5 (8.0–25.0)	15.0 (8.0–17.5)	0.6
Duration of injury (months)	54.0 (22.0–198.0)	30.0 (20.0–120.0)	0.6
Pain intensity (NRS score), *n* (%)	4 (4–5)	5 (2.5–6)	0.7
Ashworth Scale score at lower extremities	1.3 (0.8–2.5)	1 (0–3)	0.7

Data were expressed as median (25–75th percentile) for continuous parameters and as percentage when categorical

According to Jiann et al. [16]

AIS ASIA (American Spinal Injury Association) Impairment Scale, *BMI* body mass index, *FSFI* female sexual function index, *HDL* high density lipoproteins, *IDF* International Diabetes Federation, *NRS* numeric rate score, *SCI* spinal cord injury, *SCIM* Spinal Cord Independence Measure, *T6* thoracic spine 6th

[a]Metabolic syndrome was defined according to SCI-appropriate modified IDF criteria proposed by Gater et al. [20]: BMI ≥ 22 kg/m^2 and two or more of the following: triglycerides ≥ 150 mg/dL (or actual treatment), HDL < 50 mg/dL, hypertension (or actual treatment), fasting glucose ≥ 100 mg/dL or diabetes mellitus type 2

[b]Bowel-bladder function SCIM sub-score = items 6 and 7 of the SCIM

Table 2 Female Sexual Function Index (FSFI) score and sub-scores in spinal cord-injured women with and without impaired vaginal lubrication

	FSFI lubrication sub-score[a]		*p* value
	Normal (≥ 3.6) *N* = 13	Impaired (< 3.6) *N* = 15	
Desire score	3.1 (1.8–3.6)	1.8 (1.2–2.1)	0.03
Arousal score	3.3 (1.7–4.2)	0.8 (0.3–1.9)	0.02
Orgasm score	4.0 (4.0–5.8)	1.5 (0.0–3.4)	0.01
Satisfaction score	4.8 (4.0–6.0)	3.2 (2.1–4.9)	0.2
Pain score	4.8 (3.8–5.8)	4.8 (2.8–6.0)	0.8
Total score	25.7 (19.6–27.6)	11.4 (8.7–15.1)	0.01

Data were expressed as median (25–75th percentile). *FSFI* female sexual function index

[a]According to Jiann et al. [16]

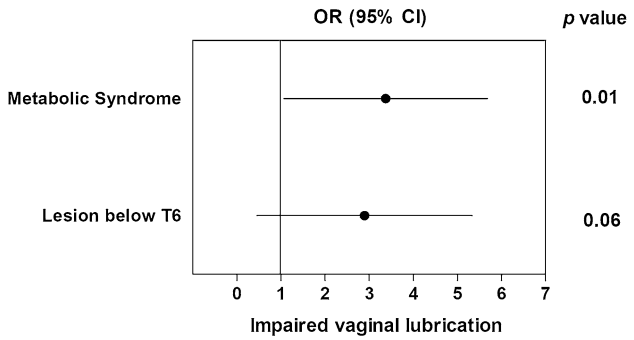

Fig. 1 Multiple logistic regression analysis of the relationship of impaired vaginal lubrication with metabolic syndrome and level of the lesion in spinal cord-injured women. According to Jiann et al. [16], a FSFI lubrication sub-score < 3.6 identified women with impaired vaginal lubrication. Metabolic syndrome was defined according to SCI-appropriate modified IDF criteria proposed by Gater et al. [20]: BMI ≥ 22 kg/m^2 and two or more of the following: triglycerides ≥ 150 mg/dL (or actual treatment), HDL < 50 mg/dL, hypertension (or actual treatment), fasting glucose ≥ 100 mg/dL or diabetes mellitus type 2. *CI* confidence interval, *FSFI* female sexual function index, *IDF* International Diabetes Federation, *OR* odds ratio, *T6* thoracic spine 6th

different domains of the female sexual function, we investigated the vaginal lubrication that was impaired in a large percentage of women: in our series, a FSFI lubrication sub-score < 3.6, which showed the highest accuracy in discriminating patients with vaginal hypolubrication in the general population [16], was exhibited by 53.5% of women.

Vaginal lubrication significantly increases during the excitatory phase of the female sexual response. It represents a neurovascular event, similar to the erection in males, which shares neurophysiologic control mechanisms as well as risk factors for dysfunction. The nervous control of the genital excitatory response, widely known and well-characterized for erectile response in men, involves a double regulation pathway by the spinal cord. The "reflex pathway" involves the sacral parasympathetic center that is triggered by peripheral sensory stimuli, thereby inducing intense genital excitatory responses. On the contrary, the "psychogenic pathway," controlled by the thoracolumbar sympathetic centers, which are modulated by supra-axial erotic impulses, induce less intense and functional genital excitatory responses. Therefore, the genital response to sexual arousal after SCI will depend on the level of injury. In distal lesions resulting in a paraplegic state, the impairment of sacral parasympathetic centers eliminates the reflex pathway, although a psychogenic (poor functional) genital response could be obtained by the intervention of sympathetic thoracolumbar centers. On the contrary, a proximal lesion level, leading to a tetraplegic state, is associated with the integrity of the sacral center and, therefore, with effective reflex genital responses. These neurophysiologic aspects could explain why men with paraplegia, with a lower degree of disability, have a higher prevalence of erectile dysfunction than those with tetraplegia [22]. The relationship between SCI and vaginal lubrication dysfunction has received less attention in the literature. It is well known that erection and lubrication have the same mechanisms and pathways of nerve control [23]. In line with this assumption, in our study, 93.3% of women with vaginal hypolubrication exhibited a distal level of lesion (below T6), potentially compromising the integrity of the parasympathetic reflex center.

In the present study, when compared to women with normal lubrication, those with hypolubrication did not show poorer sub-scores in the pain domain or in the satisfaction domain of the FSFI. Although this finding warrants further investigation, it could be speculated that, unlike erectile dysfunction in males, impaired vaginal lubrication might not be perceived as a relevant sexual disorder by women with SCI, owing to sub-lesional hypo/anesthesia and consequently reduced/abolished subjective perception of vaginal dryness. Moreover, the negative consequences on the penetration and therefore on the partner erectile function could be easily counteracted by the use of lubricating gels, which, however, was not assessed in our series.

Vaginal lubrication is not only a neurogenic process but also involves relevant vascular mechanisms. Therefore, lubrication dysfunctions could represent a potential marker of systemic vascular disease [3, 4]. Similar to males, vascular disorders associated with systemic conditions can predict defective genital excitation in women as well [3, 4]. The first experimental data on the role of vascular factors in inhibiting genital excitation in female animals date back to 1998 [24], when diabetes mellitus, a recognized cardiovascular risk condition owing to its microangiopathic and neuropathic complications, has been demonstrated to be a key determinant of deficient genital sexual arousal in women

[25]. Therefore, even in women, cardiovascular risk factors may be associated with impaired genital excitatory response (i.e., vaginal lubrication) on a vascular basis [26]. This could explain the association between vaginal hypolubrication and MetS arising from the present study.

MetS represents a clinical condition in which several related factors contribute to increasing the risk of developing cardiovascular diseases owing to several metabolic anomalies, such as central obesity, dyslipidemia, insulin resistance, hypertension and, more generally, endothelial dysfunction. In patients with chronic SCI, the definition of MetS and its clinical implications are strongly conditioned by the lack of validated diagnostic criteria. In particular, the diagnosis of obesity poses specific challenges in this population: on the one hand, waist circumference tends to overestimate visceral fat mass, due to abdominal muscle paralysis; on the other hand, BMI tends to underestimate overall body fat mass (see introduction). In the present study, using the revised IDF definition proposed for people with SCI by Gater and colleagues [20], the diagnostic criteria for MetS were met by 73.4% of women with impaired vaginal lubrication and only by 7.6% of those with normal vaginal lubrication ($p = 0.0006$). Noteworthy, at the multiple logistic regression model, the presence of MetS, but not a lesion level below T6, exhibited a significant independent association with impaired vaginal lubrication (Fig. 1). Interestingly, when the groups with and without vaginal hypolubrication were compared, no significant differences were found in the proportion of women exhibiting the single components of MetS. This result, which seems to be at the variance with findings from the general population [27–29], confirms the unsuitability of customary metabolic risk factors, when taken individually, in predicting vascular-related disorders in people with SCI.

The present study suffers from some limitations. Firstly, the study comprised a very small sample size, which, however, was enough to demonstrate significant and independent associations, likely due to the high prevalence of the disorders under investigation in women with chronic SCI. Secondly, a representativeness bias could result from the relatively advanced age of the study population, albeit counterbalanced by the exclusion of menopausal women. It should be recalled that, under an epidemiological point of view, the older age of women compared to men with SCI would reflect gender differences in the prevalent etiologies: traumatic causes being more common in young males and the degenerative/vascular ones, peculiar to senescence, in females. Accordingly, in our series, a degenerative/vascular SCI was overall exhibited by 60.7% of women. As another major flaw, although the use of antidepressant drugs was recorded, no specific psychometric tools were used to assess psychological and sexual-related distress, which could play a pivotal role in promoting and worsening FSD. Finally, specific limitations are inherent in the FSFI, although it represents the customary tool for assessing FSD and it has already been used also in people with SCI [30, 31]. In particular, no shared cut-off points for the lubrication domain exist, and a score less than 3.6 on the FSFI lubrication subscale, here used to identify women with impaired vaginal lubrication, has been proposed but not validated by Jiann et al. only in the general population [16]. The assessment of vascular bed by objective methods, such as vaginal plethysmograph or clitorideal color-Doppler ultrasound, would have enabled us to prove the impairment of genital excitement, thus corroborating the FSFI results. Interestingly, it has been previously reported that clitoral vascular resistance is positively associated with MetS, decreased sexual arousal, body image concerns, and increased somatized anxiety symptoms in able-bodied women [29]. Unfortunately, such an approach is not available at our center.

In conclusion, the results of the present study show that in women with chronic SCI, the presence of MetS was associated with a 3.1-fold increased odd of having vaginal hypolubrication irrespective of the level of the lesion. In this scenario, FSD could require a multidisciplinary approach to identify and manage underlying modifiable cardiovascular risk factors. Indeed, further prospective studies are warranted to clarify the cause-effect relationships and to explore whether an intervention on the metabolic profile in this population could result in an improved vaginal lubrication and overall sexual function.

Author contributions Conceptualization: AB, SD'A; methodology: AB, SD'A; formal analysis and investigation: AB, SD'A, CC, GF; writing-original draft preparation: SD'A, EM, VP, MT; supervision: AB, SF, GF, FF.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards**.** The local ethics committee approved the study protocol.

Informed consent Informed consent was obtained from all individuals included in the study.

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