

Journal of ANDROLOGICAL SCIENCES



Official Journal of
the Italian Society of Andrology



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FEMALE SEXUALITY
FEMALE TO MALE TRANSSEXUAL
PENILE REHABILITATION AFTER RADICAL
PROSTATECTOMY
CYCLING AND ERECTILE DYSFUNCTION

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Journal of ANDROLOGICAL SCIENCES

Official Journal of the Italian Society of Andrology

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A new format, a new challenge

V. Ficarra, A. Salonia¹

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¹ Department of Urology, University Vita-Salute "San Raffaele", Milan

It is a real pleasure for us to present the first issue of the *Journal of Andrological Sciences* (JAS), official Journal of the Società Italiana di Andrologia. The JAS follows the pathway tracked by his distinguished forefathers. The *Giornale Italiano di Andrologia* from 1994 to 2005, and the *Giornale Italiano di Medicina Sessuale e Riproduttiva* (GIMSeR) afterwards, have represented important instruments for the update of the Italian andrological community.

Born in 1994 from an idea and from the dynamic boost of Prof. Menchini Fabris, the Journal of the Italian Andrologists knew a first innovative moment in 2005, when our friends Edoardo Pescatori and Paolo Turchi became the Editors. Their great work presents us a Journal indexed by the Elsevier SCOPUS database, full of interesting cues on many of the subjects covered by the andrological discipline. The route of the GIMSeR has not been that easy. If we give a glance to the issues published in these last years, we appreciate the many important scientific contributions, particularly in the perspective of a Continuous Medical Education program, always taken in great consideration by the previous Editors¹. In fact, the GIMSeR has been the first scientific journal in the field of Sexual and Reproductive Medicine dedicated to the Continuous Medical Education. In order to keep in mind the articles of the last two years, and to make it easy to consult and quote them, we thought it useful to list them at the end of this first issue of the JAS. We do really know that it will be a hard task to carry on the path tracked by the previous Editors in Chief. Thank you.

Now We are the ones trying to run; certainly, together with many – we hope all – of the andrologists of the Società Italiana di Andrologia (SIA) who will help, criticize, and read us! The course we are sharing with the SIA Executive Committee has the ambition to cast the Journal in a more International setting, with a further indexing in other data bases, if possible also attributing an initial impact factor. These are very ambitious tasks, difficult to realize, we know it. As already told, these objectives are cannot prescind from the scientific contribution that, as we hope, You all will give to the pages of the JAS with your research in the andrological field. Our task will be to make the Journal as interesting as possible, granting the scientific rigour – already present in the previous contents – and implementing visibility and diffusion on a national and international scale.

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With the intent of reaching these objectives, and with the scientific curiosity that is our trademark, we thought to bring some changes.

A new name, as you read – Journal of Andrological Sciences, JAS in acronym. English the title, and English the official language of all the future contents.

The new name is an answer to the will of the SIA Executive Committee and of the SIA members to regain an “andrological” identity; *Andrological*, to be used as common denominator in the different fields of our beautiful discipline. At the same time, the Journal will continue to be conceived as an educational tool for all the professional figures operating in the different andrological sectors, such as Urologists, Endocrinologists, Sexologists, Gynecologists, and Biologists of the reproduction. Moreover, the name of the Journal loses the geographical connotation of an *Italian Journal*. According to the directives of the society Executive Committee, it is a further attempt to make the Journal more attracting, with a wider international vision.

The JAS will have a new graphic design, whose more important tract is the simplicity and the will to highlight the strong link between the Journal and the SIA. For this reason, we wanted that our “little man”, the “symbol” of the SIA, was the background of the cover page.

The Journal will also have a larger editorial board, in the perspective of better representing the several souls of the Society and of the Italian andrological scientific culture. Mainly, we thought to involve young experts in the field. We expect from them a concrete scientific contribution, in terms of both manuscript revision and submission of original articles and close examination of the most controversial andrological topics. In an initial phase, the Editorial Board will have an exclusively national connotation and it will represent the different geographical Italian areas; nevertheless, we have the strong desire of enriching it with the foreign experts that will have the interest in contributing to the growth of JAS.

As you can see in the pages of this issue, the JAS will publish editorials on highly topical issues, written upon invitation of the Editors in Chief; review articles,

original articles, case reports of peculiar interest and articles with an exclusively educational intent. Each issue will include a Case Study, and we hope it will stimulate the discussion through the Letters to the Editors. Finally, there will be the *SIA corner*, which will be the space where to report the results of the informational and educational campaigns that our Society will realize in the forthcoming years. In this issue, you will find a first article related to the important information campaign “Amare senza pensieri” (“Loving without thoughts”).

Finally, with the intent of further improving the quality and visibility of the JAS, we modified the rules for Authors, adapting them to those of the high impact international indexed journals. In this context, the peer-review process for the articles sent to the JAS will remain a rigorous process, just like in the past, but it is our intention to stimulate the exchange of ideas and opinions between Authors and Reviewers through the use of editorial comments and reply articles.

We love thinking that the Journal of Andrological Sciences will be a challenge; a challenge for the Editors in Chief, for the Editorial Board, but undoubtedly for and with the contribution of the whole Italian scientific andrological community. Among the numerous journals available, when you have to send your high-level contributions, think to Your JAS. The JAS is Our Journal! We will be glad to collect all the suggestions, ideas, and eventual proposals that everybody of You will give us to improve the quality of the Journal. We expect that the Letters to the Editors will become a useful means of discussion on the journal contents, but also an instrument in the hands of all Our readers to improve the allure and the interest of the journal.

A special thank goes to Prof. Menchini Fabris, who accepted to “christen” the first issue of the JAS with an article retracing the history of this Journal since 1994.

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Past, present and future of Andrology in Italy

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The term andrology was used for the first time in Italy in 1975, for the second edition of the “*Giornate endocrinologiche Pisane*” (Endocrinology Day in Pisa), to indicate disorders associated with infertility and male sexual impotence¹. In the same period, on a world-wide scale, a new medical figure was emerging, the andrologist, soon to be followed by the first societies of andrology².

After the founding of the *Società Italiana di Andrologia* (Italian Society of Andrology), the first School of Specialization in Andrology opened in Pisa in 1977 and over the next years corresponding structures followed in the cities of Turin and Aquila.

At the end of the seventies, the first important success arrived for Italian Andrology, upon initiative of the Pisan school – the introduction of andrological screening for young males presenting for their medical examination prior to beginning military service. As such, Italy was among the first countries in the world to carry out wide-scale checks on sexual health in the young population.

Andrologists found themselves facing several hurdles in those early years, prevalently associated with difficulties in challenging the integrity of the male genital apparatus, both from an aesthetical and functional point of view, as well as the erroneous interpretation of some sexual pathologies just emerging at that time. A typical example of this can be seen in the syndrome of Klinefelter, a disorder which was initially confounded with psychiatric illnesses, the result being that patients suffering from this were considered aggressive and socially dangerous, and were consequently treated as such.

In 1980 the first specialists in the subject completed their training in Pisa, among them a woman, Paola Loli.

Over the following years, andrology in Italy rose to the challenge of competing on a European and international level and it was precisely in this period that andrologists became more and more interested in the pathologies associated with penile aesthetics.

At the end of the nineteen-eighties, scientific research began to deal with the question of erectile dysfunction, even though only with empirical therapeutic trials and treatments that were not willingly accepted by patients.

In the meantime, the Society had grown and specialists in andrology had were by now over a hundred, who had cut out a niche for them-

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selves also in the network of information, thanks to which it became possible to speak of these pathologies without them being considered taboo.

The present state of andrology in my opinion began with the arrival of Sildenafil³, the commercial and media success of which was such to enable man to come out of the closet, as it permitted him not only to face such delicate issues that up to now had been strictly kept hidden, but even to joke about them⁴.

The pharmaceutical companies did not delay in reacting – in a short time, a further two molecules for the treatment of erectile dysfunction^{5 6} were brought out; at last, andrologists had found their own dimension, and this encouraged many clinicians to become interested in the subject, the more so as the demand for treatment of erectile dysfunction was vast and the cure was considered simple.

In actual fact, this was not quite the case, insomuch as the attention of andrologists was drawn also to secondary hypogonadism which however still required further study, as well as the necessity to overthrow another significant taboo represented by the reluctance to administer substitutive hormone therapies.

The nineties and the beginning of the twenty-first century represented a period of exponential growth in the field of penile surgery. In fact, while on the one hand demand for penile prostheses had diminished, thanks to the arrival of PDE-5 inhibitors, on the other, much more attention was being devoted to aesthetic aspects, determining an increase in new surgical techniques as requests for resolving aesthetic imperfections of the genitals became more numerous. Unfortunately in this period, the great enthusiasm for erectile dysfunction therapy and the success of the medically-assisted procreation techniques were largely responsible for shifting problems associated with male infertility out of the limelight, and neglecting the question of andrological prevention which between 2003-2004 suffered an abrupt setback as the obligatory medical visit for military service was abolished, thus taking us back thirty years or so.

In 2004, the direction of the “Italian Journal of Andrology” was entrusted to two young and competent andrologists (Paolo Turchi and Edoardo Pescatori)⁷ whose initiatives regarded among other things renewing the graphics of the journal as well as its name, “*Giornale Italiano di Medicina Sessuale e Riproduttiva*” (GIMSeR) or “Italian Journal of Sexual and Reproductive Medicine”. Thanks to Turchi and Pescatori’s work and commitment, an extremely important result was achieved with the indexation on Scopus, the largest abstract and citation database

of research literature and quality web sources. This acknowledgment constituted the first fundamental step towards indexation on Pubmed, together with the acquisition of an Impact Factor. During these years the Society developed new projects of communication directed towards the general public, such as the realization of a periodical dedicated to patients and agreements reached with newspapers in order to develop sectors specifically dedicated to andrology.

Currently the number of members has well exceeded a thousand while courses and master degrees in Andrology have multiplied all over Italy in the attempt to compensate for the closing down of the specialization school in 2007.

In the near future, andrology will be able to further carve out a niche for itself, as attested by the growing number of hospitals which are in the process of developing outpatients’ departments and operative units specifically dedicated to this clinical sector.

Also from a pharmacological point of view, interest in the field of andrology has markedly widened, particularly towards therapies such as those for premature ejaculation or those targeted at effecting a double-action, treating both erectile dysfunction and Lower Urinary Tract Symptoms simultaneously, not to mention the drugs which are designed to treat fertility disorders, especially in terms of motility of spermatozoa.

I am of the opinion that the primary goal our Society must aim to reach over the next few years regards the re-introduction of mass screening of youths, before other societies get there first, followed by the recognition of one or more schools of specialization at a national level, in order to guarantee a future for the teaching of andrology.

On the occasion of the meeting of the Andrology congress held last September, an important change was decided for the scientific journal of the Society: the direction was entrusted to two promising young andrologists, Vincenzo Ficarra and Andrea Salonia and the title was changed to “Journal of Andrological Sciences” with a view to stimulating greater competitiveness on an international level.

I personally would like to pass on my sincerest good wishes to the two new Directors and to all those who will have the responsibility and honour of collaborating with them in the future.

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Stilettoes, schizophrenia and sexuality

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Summary

Objective. In the collective imaginarium there is a close relationship between high heel shoes and sexuality but it is not clear whether or not this statement is based on scientific evidence or it comes from the common idea that all women that dress up can look sexy. Certainly in the collective imaginarium heeled footwear are not related to schizophrenia, although a medical hypothesis suggested this kind of relationship, alarming generation of women who usually wear heeled footwear, self-sentenced to complain of this severe mental disorder. On the other hand sexual functioning has received little attention as an important aspect of patient care for those suffering from schizophrenia. We tried to define possible relationships between stilettoes, schizophrenia and female sexuality.

Materials and methods. We performed a review of published in scientific journals and literature using as key words "sexuality", "schizophrenia", "footwear" and similar words. We widened our search using also articles not retrieved by our search, but quoted by retrieved papers.

Results. With a multiple keyword search we found only a letter concerning this intriguing issue. Only the already mentioned paper took into account a possible relationship between schizophrenia and heeled footwear. Several studies aimed at investigating female sexuality and sexual dysfunction in women with and without mental disorders such as schizophrenia. An increasing interest in female sexuality emerged and women are trying to recover their own sexual independence becoming from sexual subject to object, striving to conquer the equality in sex matter, respecting partners expectation as well.

Conclusions. Sexual wellbeing is one of the most complex parts of women life, being dynamic and multidimensional, and including biologic, psychological, socioeconomic, and spiritual components. In this holistic view, also little changes in initial parameters concerning apparently anatomically distant areas might lead to considerable and unexpected events, thus explaining possible relationship between foot, schizophrenia, and sexuality.

Keywords

Schizophrenia • Sexuality

"... all women that dress up can look sexy, so ladies do your thing please!" (SKG, Amsterdam, Netherlands)

"See how many heads turn when an average looking woman walks by a group of men when wearing flats. Try the same thing with a woman wearing 5-inch spikes ... Her self-esteem will surely increase with the added height" (Steve, Rossville, Georgia, USA)

"Hot women with fetching limbs in stiletto heels certainly enhance my sense of well-being" (Tony, Royal Oak, USA)

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All the above mentioned comments on Roger Dobson's article published in the Sunday Times (February 3, 2008) entitled "*Stiletto take women's sex life to higher level*", underline once again the strict relationship between high heel shoes and sexuality in the *collective imaginariu*m. Probably many women like heeled shoes because, although sometimes uncomfortable, try to appear more slender and taller, also gaining male approval. History taught us that male plaudit concerning female sexuality has been extremely important for the collective imaginariu

m, often without taking into account what really women asked and wanted. As a matter of fact, until the recent recognition of female sexual dysfunction (FSD) as a unique physiological and psychosocial complex, historical information and data for sexual-active women have taken the form of anecdotal evidence collected incidentally to research of male sexuality, extrapolated into a compendium of partner-related maladjustments¹. We have to wait until 1974 to have initial scientific constructs (such as social environment, personal knowledge, past experience, and current expectations all influencing satisfactory sexual functioning) able to validate female sexuality as an independent, as well as an interdependent, system^{1,2}. For the first time women were offered the hope that someone, somewhere, believed that equality in all matters finally included sex². As stressed by Bean in 2002¹, defining a role for the women in a sexual relationship is not difficult and can no longer be hidden by the guise of complexity: actually the difficulty was, and continues to be, in striving to characterize and classify the expressions of female sexuality. In 2008 all women, even separated by generation, education, and occupation, are clamouring at the same time for independence and knowledge and believe that the progression of women's sexuality from subject to object is at hand¹. Therefore, women have to take back all emblems labelled by the male collective imaginariu

m as "female sexual symbols", revising them according to their own sexual wellbeing. This aspect of female quality of life is strictly related to pelvic floor wellbeing. Pelvic floor is an anatomical structure, characterized by muscles, fasciae, and nerve fibres, whose role is fundamental in order to maintain a correct upright standing, avoiding a falling down of abdominal viscera. But it is also an opening for life (childbirth), death (urine and faeces expulsion; violence; sexual transmitted diseases; HIV), and pleasure (intercourse). Nevertheless, female sexuality and, on the other hand, any possible "*dissatisfaction with the female's self perception of sexuality*"¹ may not be confined to the genital area alone, but have to be inserted within an holistic view

of the feminine being, with its own manifold interrelations. This may explain why women's sexuality can be altered, temporarily or permanently, by acute or chronic illnesses. These latter often plays a much greater part in affecting women's sexuality. Women worry about the changes in their bodies, fulfilling their relationships, and meeting the needs of their partner and family, as well as about having to communicate about their sexual needs and desires in ways they did not have to previous to their illness³. Chronic health gynaecologic (endometriosis or premenstrual syndrome) and non gynaecologic (diabetes, hypertension, chronic obstructive pulmonary disease, arthritis, several forms of cancers) diseases may affect sexuality, as well as mental health problems. Acute mental distress related to loss, death, or other situations may cause a temporary alteration in women's sexual functioning. Women with developmental delays or mental retardation have sexual desires and are able to engage in sexual activities. Typically, it is their families or guardians who try to limit sexual expression in these women, believing that they will be abused, that they cannot participate fully so should not be sexual at all, or that they will become pregnant⁴. Serious and chronic mental health problems, such as depression, schizophrenia, and bipolar disease, may have persistent negative sexual consequences⁵, and, although therapies may cure the health problem, many treatments may also cause sexual problems, during the therapy or permanently. Actually, many medications and drugs [such as antipsychotics, antidepressants, and selective serotonin uptake inhibitors (SSRIs)] may alter sexuality in women, decreasing sexual desire, vaginal lubrication, and orgasm. Moreover, sexuality is an important life issue in people with severe mental disorders such as schizophrenia, but too little is still known about the natural history of sexual functioning in these people, mainly for two reasons: reluctance from psychiatric staff members to discuss sexual concerns with patients⁶⁻⁹; literature reports focusing on sexual functioning evaluated people only during treatment with conventional antipsychotics¹⁰. It is striking how little attention has been paid to the area of sexual functioning and schizophrenia. Patients with schizophrenia are open to discussing sexual issues, and more than 75% of those with severe mental illness believe that discussing sexual issues may actually be beneficial for their outcomes¹¹. Proper sexual education and counselling must be integrated into the treatment planning of patients with schizophrenia. Given the high rate of sexual dysfunction among patients with schizophrenia and its negative relationship to compliance, it is troubling that more

attention has not been paid to its assessment and much more attention to this topic is needed to improve treatment and outcomes for those who suffer from this devastating illness.

Moreover, concerning women sexuality, most studies on sexuality and schizophrenia addressed their attention only to male sexual dysfunction. Thus, the relationship between sexuality and schizophrenia is complex and although it is important to examine the relationship between medication and sexual disturbances in schizophrenia patients, it is also important to take into account patients' gender and all their possible underlying neuro-endocrine disturbances that pre-exist or contribute to sexual disturbances that occur¹². Concerning these last remarks, few years ago a medical hypothesis on the relationship between heeled footwear and schizophrenia was published, alarming generation of women who usually wear high heel shoes, self-sentenced to complain of schizophrenia¹³. It is a historical research across the centuries in support of the very close association between the use of heeled footwear and schizophrenia. This statement might be questioned in many instances but it very hard to confute this hypothesis because all findings reported would seem to support that in all facts without contradiction. We do not have the skills to refute or confirm this hypothesis, but let's see the advanced pathophysiological mechanisms underlying this medical hypothesis. During walking synchronised stimuli from mechanoreceptors in the lower extremities increase activity in cerebellothalamo-cortico-cerebellar loops through their action on NMDA-receptors. Using heeled shoes leads to weaker stimulation of the loops. Reduced cortical activity changes dopaminergic function which involves the basal gangliathalamo-cortical-nigro-basal ganglia loops, predisposing to schizophrenia development. But this is a deductive hypothesis based on the literature suggestion that electrode stimulation of the anterior parts of the cerebellum could improve functioning in schizophrenia¹⁴, and being these parts normally stimulated by impulses from stretch receptors in the lower extremities, bicycling would reduce depression in schizophrenia, probably due to the improved lengthening contractions of the triceps surae¹³. An extremely interesting point is that, according to this pathophysiological hypothesis, shoes look quite flat but providing with insoles that are somewhat thicker in the heel part, would function as heeled shoes as well: thus we all must always walk barefoot in order to avoid schizophrenia! Joking apart, currently there are neither cross-sectional prevalence studies as-

sessing the association between the use of heeled footwear and schizophrenia in immigrants from regions with a warmer climate or in groups of people who began to wear shoes at different ages, nor studies evaluating the effects of the use of heeled and flat shoes during shorter or longer periods of time on cortical excitability, and on connectivity in cerebellar and basal ganglia loops in patients with schizophrenia. It is important to stress that, if any thickness in the heel part might be involved in the development of schizophrenia, another interesting research area could be the study of the so called "plantar fat pad" in people with schizophrenia and other mental disorders¹⁵. Thus, foot, sexuality and mental disorders seem to be tightly linked, although these areas of interest look so distant each other.

In the 1960's the meteorologist and mathematician Edward Lorenz was attempting to simulate the behaviour of the atmosphere on a computer. At that time it was assumed that all that was needed to provide the perfect weather report was the right model and big enough computing grunt ... What Lorenz had shown was that the future state of the system was very sensitive to the initial conditions used for the calculation and hence even a deterministic system could be inherently unpredictable in the long-term. With reference to Lorenz's strange attractor the famous statement on chaos says that "*the flapping of a butterfly's wings in Tokyo can cause a tornado in Texas*". Applying Lorenz's idea to the human body and following the hypothesis that in a complex system (such the human body is) little changes in initial parameters might lead to considerable and unexpected events, also in apparently anatomically distant areas, the relationship between foot, schizophrenia, sexuality and (don't forget!) pelvic floor wellbeing may be easily explained.

Thus, heeled shoes may be linked to sexuality and pelvic floor wellbeing not only by the collective imaginariuim but also by real physiological pathways that have to be still well analysed.

Three years ago the hypothesis that in an upright position different ankle inclinations might effectively facilitate pelvic floor muscles activity through enhanced pelvic tilt was published in the literature¹⁶. Few years later we started an interdisciplinary collaboration in order to corroborate the hypothesis that variations ankles inclination might affect pelvic floor muscles performance. Our preliminary study results (still in fieri!) would seem to corroborate the initial hypothesis¹⁷. We realized that our experimental model using a basculant platform reproduced what worldwide happens when a women rests upon the

heel of the shoes. This intuition lead us to turn, using a suitable formula, the different platform inclination degrees into heel height. The following steps will be the assessment of heel influence on pelvic floor muscles using a model of female daily activities in order to suggest applicable and pleasant tools aiming at reducing daily pelvic floor impairment discomfort. When we talk about stilettos we must take into account not only the heel height but also its width. The width of the heel may affect ankles stability, thus resulting in further pelvic floor muscles adjustments. This is a further effect we want to investigate in the next future. Changing ankles inclinations (thus wearing heel shoes) might represent a valid adjunctive option in order to teach and learn pelvic floor muscles training exercises in women during their daily life.

Concerning possible implication on female sexuality, there is an emerging opinion in the current literature stating that in women with genital problems such as chronic pelvic pain (an highly spread and debilitating condition affecting both males and females) a hypertonus of the pelvic floor muscles is able to produce and maintain pain poorly localized to the perirectal and perigenital areas¹⁸. A relaxation of this muscles group induced by heels, might have beneficial effects reducing the burden of this distressing condition. But, as Karl Popper teaches, this is a further hypothesis that we are trying to refute.

Moreover, when wearing heeled shoes, the pelvis tilts posteriorly, the promontory moves superiorly and posteriorly, and the tip of the coccyx moves anteriorly^{16,19}. This position would seem to be similar to that assumed during intercourse in missionary position²⁰.

Conclusion

In this era of women's emancipation, the interest in female sexuality is increasing. Women are trying to recover their own sexual independence becoming from sexual subject to object, striving to conquer the equality in sex matter, respecting partners expectation as well. Therefore, women have to take back all emblems labelled by the male collective imaginari-um as "female sexual symbols", revising them according to their own sexual wellbeing. This aspect is one of the most complex parts of women life, being dynamic and multidimensional, and including biologic, psychological, socioeconomic, and spiritual components. In this holistic view, also little changes in initial parameters concerning apparently anatomically distant areas might lead to considerable and

unexpected events, thus explaining possible relationship between foot, schizophrenia, and sexuality. Therefore when we think of women sexuality we cannot forget Lorenz butterfly!!

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Editorial comment

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Women loving stiletto heels you can go on walking quietly on stilts!!!

This is the result from a study of Maria Angela Cerruto from the Urologic Clinic of University of Verona; stiletto suits to women a wonderful gait, but also the possibility to increase the male erotic fancy and probably increases sexual pleasures stimulating those pelvis muscles that are involved with the orgasm ¹!

Whereas on the one end we should be glad for strengthening our sex appeal and improving our performances on the aspect of the sexual quality of life, on the other hand some researchers showed a direct connection between stilettos and mental illness.

Jarl Flensmark of the Malmo University in Sweden states that can demonstrate that the first cases of schizophrenia appeared with the invention of the high-heeled dizzy shoes one thousand years ago; he maintains that the first boots with heel appeared in the Mesopotamian area, in which where observed the first schizophrenic patients.

In North American natives, that use flat shoes, they don't ob-

serve so much mental illness ². Their scientific explanation is based upon the hypothesis that when we walk "sole on ground" the movements of the foot stimulates the receptors of our limbs and increase the activity of brain cells; walking with the heel lifted causes a lower stimulation of the inner production of dopamine, that is known for being an important factor in the genesis of schizophrenia.

Is difficult to refute those observations because all the result seem to be in agreement with this theory! Sexuality, mental illness and foot health seems then to be correlated despite the distance among all those several areas of interest!!! Should we walk barefooted to avoid psychiatric pathologies?

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Female to male transsexual: definition, diagnosis and surgical aspects

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Summary

Objectives. There are still controversies regarding the ideal medical and surgical management of female to male transsexualism. The aim of this review manuscript is to give a definition of the condition and to describe the process of sex reassignment from diagnosis to surgery.

Material and methods. A non structured Medline-based search for full length reports in English has been carried out. The keywords "transsexualism", "gender identity disorders", "gender reassignment surgery", "penile reconstruction", "phalloplasty" and "metoidioplasty" were used in the search.

Results. The management of this condition requires the strict collaboration of a multidisciplinary team that involves psychiatrists, endocrinologists, urologists, gynaecologists and plastic surgeons. With regards to phallic construction, although many of the techniques may achieve closely the goals of a neopenis with normal urination, none of them is perfect and therefore none has achieved universal acceptance.

Conclusions. The surgical management of female to male transsexuals remains a challenging procedure for the surgeon. However, phallic construction techniques now allow patients to void in a standing position and to engage in penetrative sexual intercourse, thus guaranteeing a significant improvement in the quality of life.

Keywords

Transsexualism • Gender identity disorders • Gender reassignment surgery • Penile reconstruction • Phalloplasty and metoidioplasty

Definition

Transsexualism (TS) and Gender Identity Disorder (GID) are both terms used in scientific literature to represent a condition of strong and persistent cross gender identification that stems from a persistent patient's discomfort with his/her sex and a sense of inappropriateness in the gender role of that sex. This disturbance is not associated with any physical condition (eg. intersex), chromosome abnormality or any mental disorder, such as schizophrenia, and results in an impairment in social interaction and occupational activities^{1,2}.

Transsexuals desire to live permanently in the social role of the opposite gender and are keen to undergo sex reassignment surgery (SRS)³. The term "transsexualism", initially used by Hirschfeld in 1923⁴, appeared for the first time in the psychiatric classification

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system DSM III in 1980⁵, and was subsequently replaced by GID in the most recent version of the system¹.

Epidemiology

The prevalence of GID among the general population and the ratio between male to female and female to male TS varies according to different Authors. This may reflect either social or cultural factors, the availability of centres dedicated to gender reassignment surgery or the presence of more accurate and comprehensive registers of the population. Among the countries considered in the survey, Singapore has the highest incidence of GID. All countries with the exclusion of Serbia present a higher prevalence of male to female TS when compared to the female to male counterpart (Table I).

Diagnostic aspects

The diagnosis of GID is determined by mental health professionals, who firstly have to exclude any underlying medical condition such as schizophrenia, imbecility, severe personality disorder, egodystonic homosexual orientation, transvestism and feticism. A thorough medical examination is also mandatory to rule out a disorder of somatosexual development, such as an intersex condition⁹.

In the literature there is no general consensus regarding the time spent living as a female to male TS (FTM TS) before undertaking gender reassignment surgery. However current common practice suggests a period of one year as being adequate with at least 6 months of hormonal treatment^{17 18}.

Hormonal treatment

Hormonal therapy is mandatory before surgery for a period of at least 6 months¹⁷ supervised by a physician or an endocrinologist with regular assessments of liver and renal function, blood clotting, lipid profile, hormonal (estrogen, testosterone) and pituitary function (LH, FSH and prolactin).

In FTM TS androgens play a key role, since their administration is necessary to confer masculine features and the typical change in the pitch of the voice. Other hormones such as progestins are required to suppress the menstrual bleeding. Some Authors consider that hormonal treatment should be administered in two phases; the first phase is reversible and involves the administration of progestins whilst the second involves the introduction of androgens and is associated with irreversible changes in the patient¹⁸.

Surgical treatment

Gender reassignment surgery for the female to male transsexual involves breast surgery, hysterectomy, salpingo oophorectomy, vaginectomy, metoidioplasty or phalloplasty and placement of testicular prostheses. For its specific purpose this review paper will concentrate only on the phallic construction and metaidioplasty.

According to Gilbert¹⁹, phallic construction should ideally address the following requirements:

- 1) it should involve a limited number of surgical stages that can be predictably reproduced;
- 2) it should allow the creation of a competent neourethra to allow micturition in standing position;
- 3) it should create a phallus that has both tactile and erogenous sensibility;

Table I. Prevalence of GID and sex ratio.

AUTHOR	YEAR	COUNTRY	MTF PER 100,000	FTM PER 100,000	RATIO (MTF:FTM)
Pauly ¹⁰	1968	USA	1.00	0.25	4:1
Walinder ¹¹	1968	Sweden	2.70	1.00	3:1
Hoeing and Kenna ¹²	1974	Great Britain	3.00	0.93	3:1
Ross ¹³	1981	Australia	4.20	0.67	9:1
Tsoi ⁶	1988	Singapore	35.20	12.00	3:1
Eklund ¹⁴	1988	The Netherlands	18.00	54.00	3:1
Van Kesteren ¹⁵	1996	The Netherlands	8.80	3.20	3:1
Gomez Gil ¹⁶	2006	Catalonia/Spain	4.70	2.10	2.6:1
De Cuyper ⁸	2007	Belgium	7.70	3.00	2.4:1
Vujovic ⁷	2008	Serbia	0.88	0.95	1:1

Key: GID = Gender Identity Disorder; male to female transsexualism (MTF TS); female to male transsexualism (FTM TS)

- 4) it should allow for enough bulk to tolerate the insertion of a prosthetic stiffener, for successful sexual penetration;
- 5) it should produce a result that is aesthetically acceptable to the patient;
- 6) it should be linked to minimal scarring and disfigurement and no functional loss in the donor area.

The complex anatomy and physiology of the penis and the fact that there is no good substitute for the unique erectile tissue of the corpora renders reconstruction prohibitive for the surgeon. The concept is highlighted by the fact that, despite a variety of surgical techniques that have been described, none fulfils all the criteria and is currently accepted as best method²⁰. Among all phallic reconstruction techniques, metoidioplasty deserves separate discussion. This procedure should be only offered to patients in whom the androgen treatment has stimulated the growth of the clitoris to the point where the organ can serve as a penis. Metoidioplasty, first described back in 1973, involves one or two stages and consists in the release of the ventral clitoral chordee and ligaments with consequent straightening and lengthening of the clitoris and an urethroplasty to the tip of the clitoris with the use of vaginal and labial flaps. The labia majora are also reconstructed and configured as a scrotum^{21 22} (Figs. 1 and 2a-c).

Figure 1. Metoidioplasty technique.

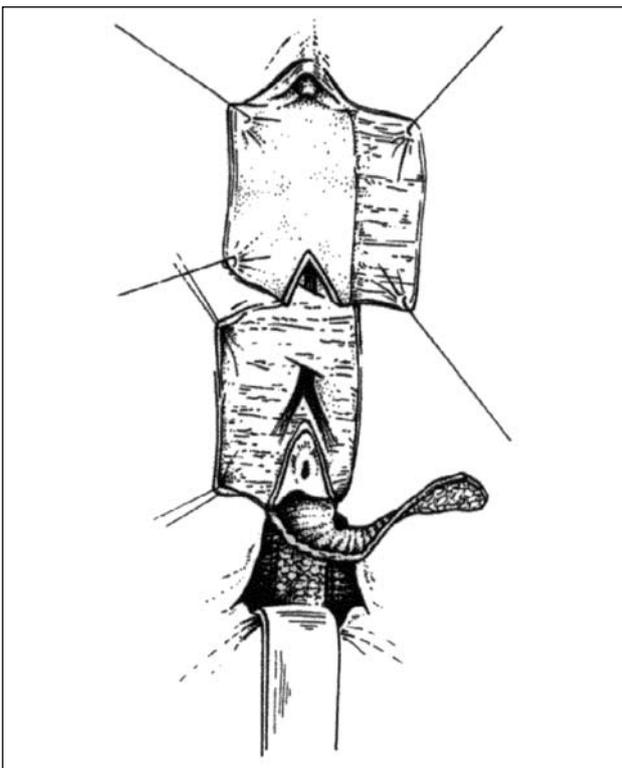
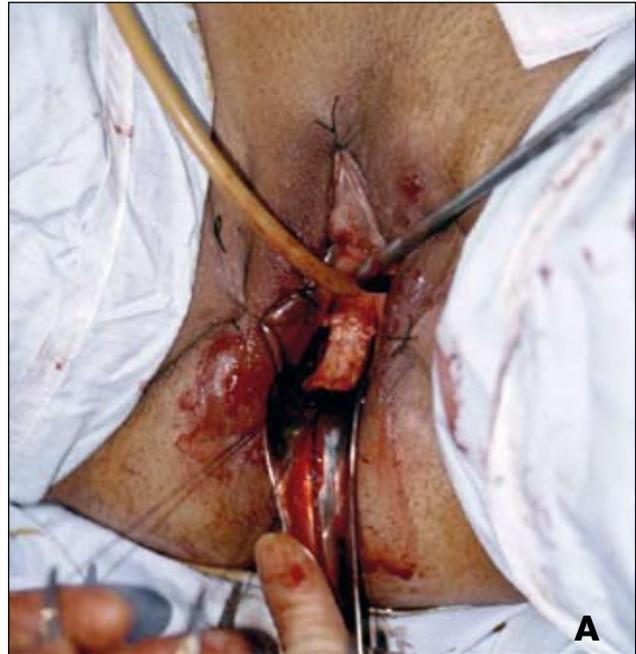


Figure 2. a) Intraoperative view. b) The labia mayora are used to fashion a pseudoscrotum. c) Post operative result.



Metoidioplasty, despite a high rate of complications such as fistulas and strictures, with up to 88% of patients requiring revision surgery, is still considered by some Authors the method of choice in patients who are still in doubt about their need for phalloplasty^{9 23}.

The development of total phallic construction techniques has paralleled the evolution of flap development in plastic surgery. At the moment more than 20 different types of flaps are available for phallic construction.

The first total phallic reconstruction was attempted in 1936 by Bogoras who used a random pedicled oblique abdominal singular tubularized flap with no incorporated neourethra. Phallic rigidity was obtained by the insertion of a rib cartilage inside the flap²⁴.

Bogoras' technique was then improved by Matz and Gillies who fashioned a phallus which incorporated a neo-urethra using the "tube within a tube" concept. These procedures involved a multi staged tissue transfer resulting in extensive scarring and disfigurement of the donor area. Since these techniques did not involve nervous coaptation, the phallus produced was without any tactile or erogenous sensation^{25 26} (Figs. 3 and 4).

Figure 3. Description of Gillies phalloplasty.

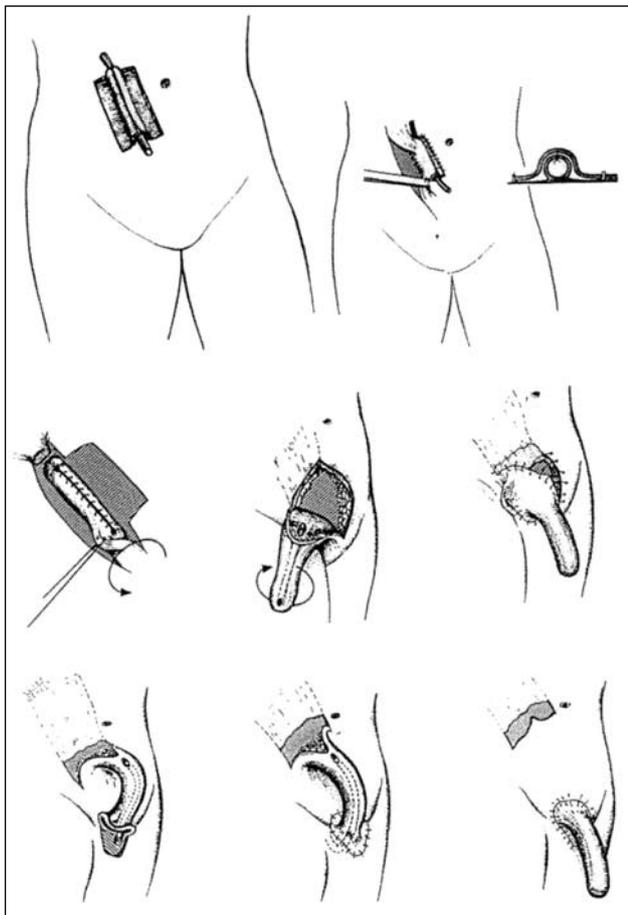


Figure 4. The phallus is joined to the recipient site and is ready to be detached from the abdominal wall.



The search for flaps more suited to phallic construction, then lead to the use of infraumbilical skin and groin flaps²⁷⁻³². Despite initially poor results, due to the formation of a non-sensate and wedge shaped phallus, the infraumbilical flap technique has been progressively improved and a neourethra made from a pedicled tube of labial skin has been incorporated in a one or two stage procedure to allow patients to void in standing position (Figs. 5a-e and 6a-b). In particular, in a series of 85 female to male patients, the Ralph's group reported 68% of the patients fully satisfied with the results of surgery; 16 patients were also able to have penetrative sexual intercourse without the insertion of penile prosthesis³³.

Musculo-cutaneous thigh flaps based on the gracilis muscle were used in the selected group of patients in which abdominal flaps couldn't be harvested due to extensive abdominal scarring from previous surgery or radiotherapy. However the cosmetic and functional results were poor due to muscular contracture and therefore this type of flap has been abandoned³⁴⁻³⁹.

With the advent of microsurgical techniques, a new era has started for total phallic reconstruction.

Originally described by Song in 1982, the use of the radial artery free flap phalloplasty (RAFF) was first published in 1984 by Chang that used this technique successfully for total penile reconstruction in 7 patients that had previously experienced a penile amputation^{40 41}. The reconstructive procedure involved the creation of "a tube within a tube" using forearm skin with the urethra fashioned from the non hair bearing area and the whole flap base on the radial artery. This technique allowed the creation of a cosmetically acceptable phallus; sensation was also maintained due to the coaptation of the antebrachial nerves to the dorsal nerve of the clitoris or to the iliohypogastric and ilioinguinal nerves (Figs. 7a-e, 8a-d, 9a-c).

Following the success of this series many teams have adopted this technique and applied some modifications in flap design in order to improve the cosmesis of the neophallus and to minimize the overall complication rate that may occur in up to 45% of cases. In particular the shape of the forearm flap has been modified in order to improve the blood supply to the flap and to reduce the risk of meatal stenosis. Ulnar artery based flaps have also been used to reduce the amount of hair bearing skin incorporated⁴²⁻⁴⁷. In a further attempt to minimize donor site morbidity, free osteocutaneous fibular flaps and upper arm flaps have been introduced; however due to the nature of the flap, the neourethra cannot be fashioned according to the “tube within a tube” technique and is instead prelaminated by tunneling a skin graft or bladder mucosa graft^{48 49}. Another problem that reconstructive surgeons have to face in phallic construction is the necessity to

confer rigidity to the phallus adequate for penetration. Since only in a limited group of patients fibrosis, oedema and congestion induce rigidity adequate for intercourse, the majority of patients will require a stiffener. Stiffeners can be classified as transplants, implants and external devices. Transplants consist of autologous bone or cartilage. As they are autologous, they confer the advantage of being rarely extruded. However, resorbtion, curving and fractures

Figure 5. a) The 12 by 12 cm flap is drawn on the infraumbelical area. b) The flap is raised. c) The flap is tubularized to fashion a phallus. d) The donor site is closed with rotation flaps. e) Post operative result.

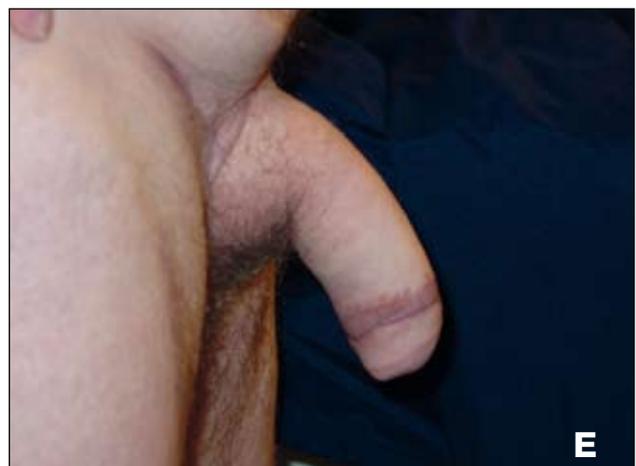
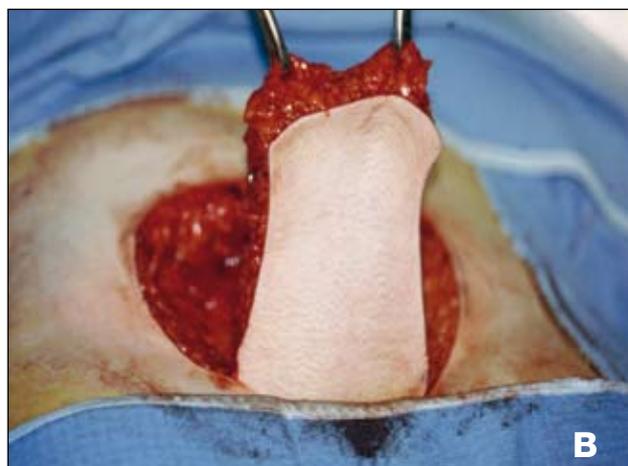
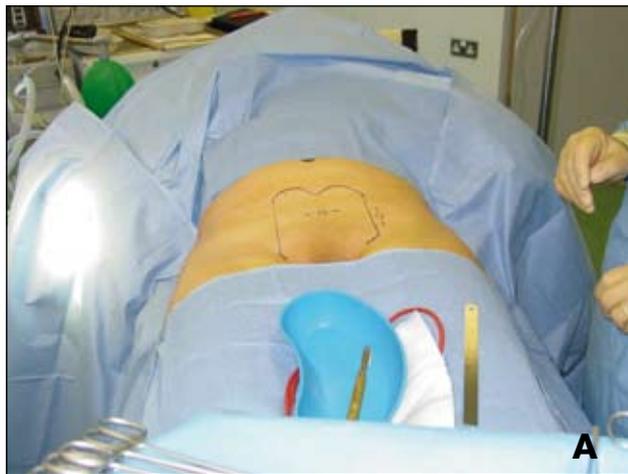


Figure 6. a) A neourethra is fashioned with labial flaps. b) Post operative result.



Figure 7. a) The radial artery based forearm free flap. b) the flap is raised. c) The phallus is fashioned with a "tube within a tube" principle around a 16 Ch catheter. d) Grafts to cover the forearm. e) Followup of the forearm.

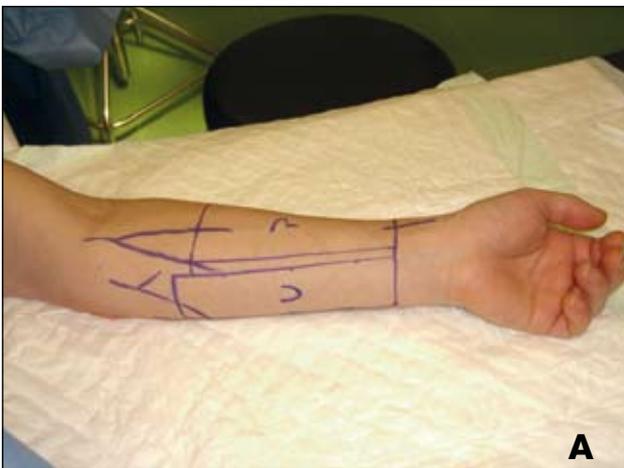
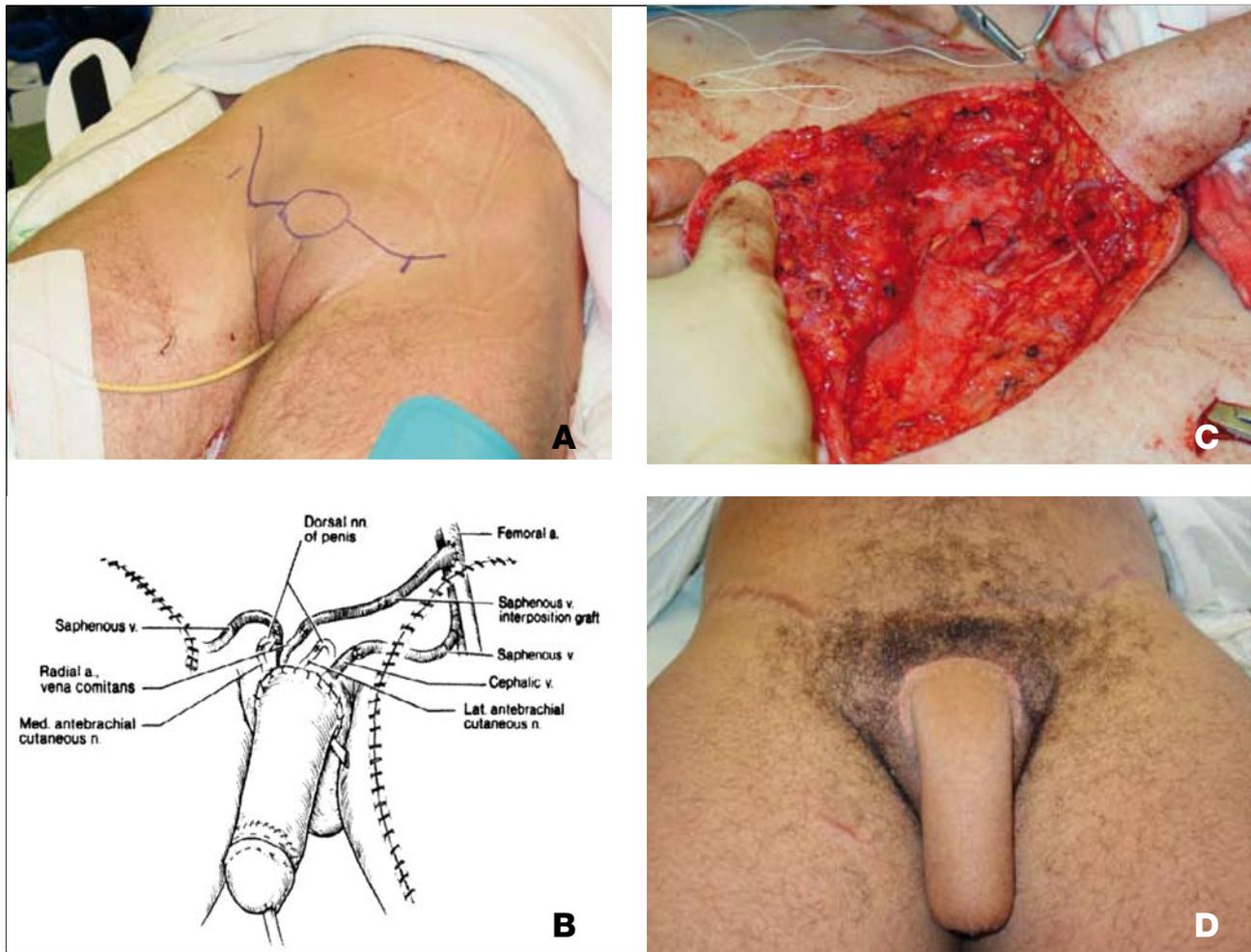


Figure 8. a) The recipient site. b, c) The radial artery is anastomosed to the inferior epigastric artery, the flap veins are anastomosed to the long saphenous veins, the dorsal nerve of the clitoris and iliohypogastric and ilioinguinal nerves are coapted to the antebrachial nerves. d) Follow-up result.



are common and are the most frequent cause of failure. Moreover, transplants produce a constantly rigid difficult to conceal and may constitute a source of embarrassment to the patient.

Penile implants can also be used to confer rigidity in the phallus. Dacron socks and tips are used to anchor the prosthesis to the pubic bone with non absorbable sutures and also to reduce the risk of distal erosion. Inflatable penile prosthesis proved to be superior to the malleable counterparts. This is because the constant rigidity conferred by a malleable implant can serve as a source of embarrassment and may induce distal erosion. However, unlike non hydraulic implants, inflatable devices frequently show mechanical failure. Moreover, infections of the device are 10 to 20 times more frequent compared with penile prosthesis implanted in biologically male patients due to the presence of Dacron⁹. The insertion of a penile prosthesis is usually carried out in two

sessions; in the first one, a testicular prosthesis is inserted in the neoscrotum and an inflated reservoir is positioned in the Retzius space. The second stage is usually performed 3-6 months later to allow the formation of a mature capsule around the reservoir and testicular prosthesis and involves the insertion of one or two cylinders of an inflatable penile implant. The testicular prosthesis is then moved into the contra lateral neoscrotal pouch and the pump of the device is inserted in the cavity that was initially used to house the testicular implant (Figs. 10 and 11a-e, 12a-b).

Due to the high rate of complications linked to prosthetic surgery, such as infection, extrusion and mechanical failure, some Authors suggest the use of externally applied rigidity devices like transurethral stiffeners or external baculums. Condoms and the vacuum constriction device may also improve the rigidity of the phallus due to an increase in venous congestion.

Figure 9. a, b, c) The glans is sculptured according to the Norfolk technique.



Conclusions

The process of gender reassignment is complex and requires the cooperation of a multidisciplinary team formed by mental health professionals, endocrinologists, gynecologists, plastic surgeons and urologists.

Figure 10. Insertion of reservoir and of one testicular prosthesis.

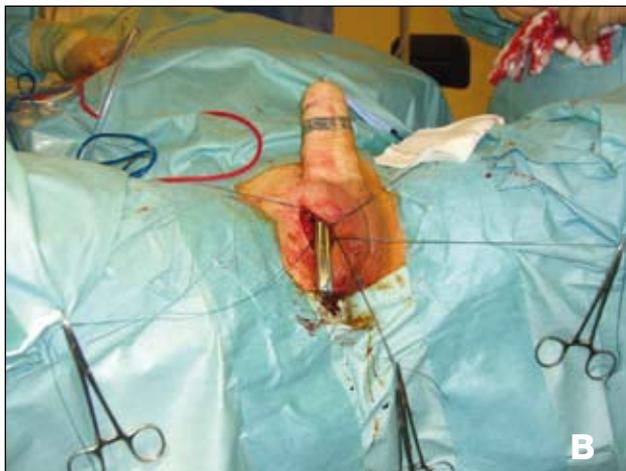
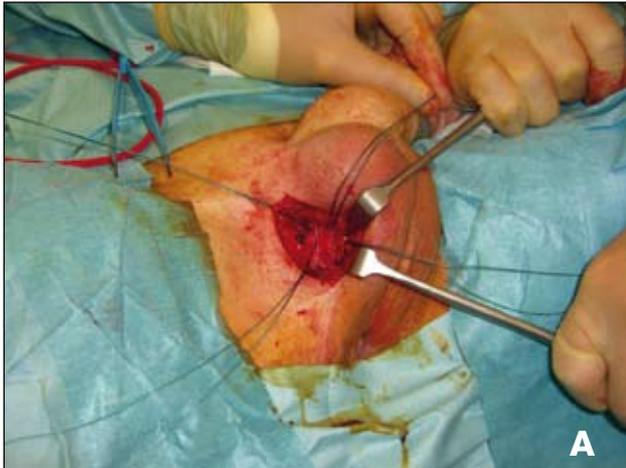


Although many of the phalloplasty techniques may achieve closely the goals of a neopenis with normal urination, none of them are perfect and therefore none has achieved universal acceptance. Therefore the various techniques should be discussed preoperatively with the patient highlighting the pros and cons of each procedure. The final decision should be taken considering patients body habitus, concomitant diseases, surgeons experience and the patients desire to void in the standing position and to have penetrative sexual intercourse.

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Figure 11. a) Dacron tip and sock. b, c, d) The sock is anchored to the pubic bone with ethibond sutures. e) The pump is inserted in the space that used to house the testicular prosthesis.



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Figure 12. a, b) Inflation and deflation of the cylinders.



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Penile rehabilitation after nerve-sparing radical prostatectomy. A critical review of the literature

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Summary

Objective. To describe the pathophysiology of nerve injury and to evaluate critically the clinical evidence supporting the use of penile rehabilitation following nerve-sparing radical prostatectomy (RP).

Material and methods. A non-systematic literature search of MEDLINE was done. A "free text" search through the fields "Title and abstract" of the records was done, using the following key words: "penile rehabilitation" and "radical prostatectomy". The search was limited to the papers published in English language after 1997.

Results. The cavernous nerve neuropraxia can prevent erections during the initial 12-18 months after RP, initiating a cascade of events which can lead to fibrotic remodelling of corpora cavernosa. The aim of penile rehabilitation is to prevent this cavernous tissue damage by providing an adequate oxygenation to the corpora cavernosa.

The advantages of penile injection were first shown in a small randomized controlled trial (RCT) evaluating the use of intracavernous injection of alprostadil. The study's results, however, have never been reproduced. More recently, another RCT suggested sildenafil (50 mg or 100 mg at bedtime) increased the recovery of spontaneous erections, compared to placebo. However, the study suffers of several methodological drawbacks. A recently published double-blind, multicentre RCT enrolling 628 men showed that nightly dosing of vardenafil did not allow significantly higher potency rates after nerve-sparing RP, compared to the on-demand dosing.

Conclusions. The exact etiology of the fibrotic changes in the corpora cavernosa following nerve-sparing RP remains unknown. No high level evidence support any program of penile rehabilitation following nerve-sparing RP, while recent data showed that on-demand dosing was effective in improving both erectile function and sexual intercourse completion rates after RP.

Keywords

Penile rehabilitation • Radical prostatectomy • Sildenafil • Vardenafil • Tadalafil • Alprostadil • Erectile dysfunction

Introduction

Radical Prostatectomy (RP) is a common treatment for patients with clinically localized prostate cancer and a life expectancy longer than 10 years¹. Erectile dysfunction is one of the most important complication after RP. The improvements in the knowledge of the anatomy

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of periprostatic fascias and cavernous nerves led to significant updates of the nerve-sparing technique improving significantly the potency recovery rates following RP. Even after a meticulous dissection to preserve both neurovascular bundles, however, erectile function may take up to 12-18 months to return, as consequence of post-operative neuropraxia.

Data coming from referral centres showed 12 or 18 months potency rates ranging from 60 to 80% after nerve-sparing retropubic RP²⁻³; from 45 to 76% after pure laparoscopic RP⁴⁻⁵ and from 70 to 80% after robot-assisted laparoscopic RP⁶⁻⁸. Significant poorer results were reported in community hospitals with lower operative volume, regardless of the surgical approach⁹.

High survival rates in young and sexually active men undergoing RP mean that many patients lives for a long period of time with erectile dysfunction with a significant negative impact on quality of life, self-esteem, and self-image. These findings contributed to the development of an increasing interest in the pathophysiology of post-operative erectile dysfunction as well as in its potential prophylaxis and treatment¹⁰.

Historically, after nerve sparing RP patients have been encouraged during the neuropraxia period to continue waiting for the return of erectile function without any active intervention. With the aim of speed up the recovery of spontaneous erections after RP, since 1997 some Authors proposed the use of specific protocols of penile rehabilitation to prevent the cavernous tissue damage that occurs during the period of neural recovery, providing adequate oxygenation to the cavernous tissues.

Although a lot of experimental and clinical studies supported the use of penile rehabilitation after bilateral or unilateral nerve-sparing RP, the rationale and mechanism for their use in penile rehabilitation programs have not been fully elucidated¹¹. Moreover, a recent randomised, double-blind, double-dummy, multicentre, parallel group study conducted at 87 centres across Europe, Canada, South Africa, and the United States showed that in men with ED following bilateral NSRP, vardenafil was efficacious when used on demand, supporting a paradigm shift towards on demand dosing with phosphodiesterase 5 inhibitors (PDE5-I) in this patient group¹².

The aim of this non systematic review of the Literature is to describe the pathophysiology of nerve injury and to evaluate critically the clinical evidence supporting the use of penile rehabilitation following nerve-sparing RP.

Material and methods

The literature search was performed using MEDLINE, including only "free text" protocol and using the following terms "penile rehabilitation" AND "radical prostatectomy" across the fields "title and abstract" of the records. We selected only papers published in English after 1997, the year of the publication of the first randomized comparative study concerning penile rehabilitation¹³. The information obtained from the retrieved papers were inserted in the following sections of the article: pathophysiology of cavernous nerve injury; clinical evidence for early use of intracavernosal penile injections; clinical evidence for early use of oral therapy with 5-phosphodiesterase inhibitors; clinical evidence for on demand therapy after nerve-sparing RP.

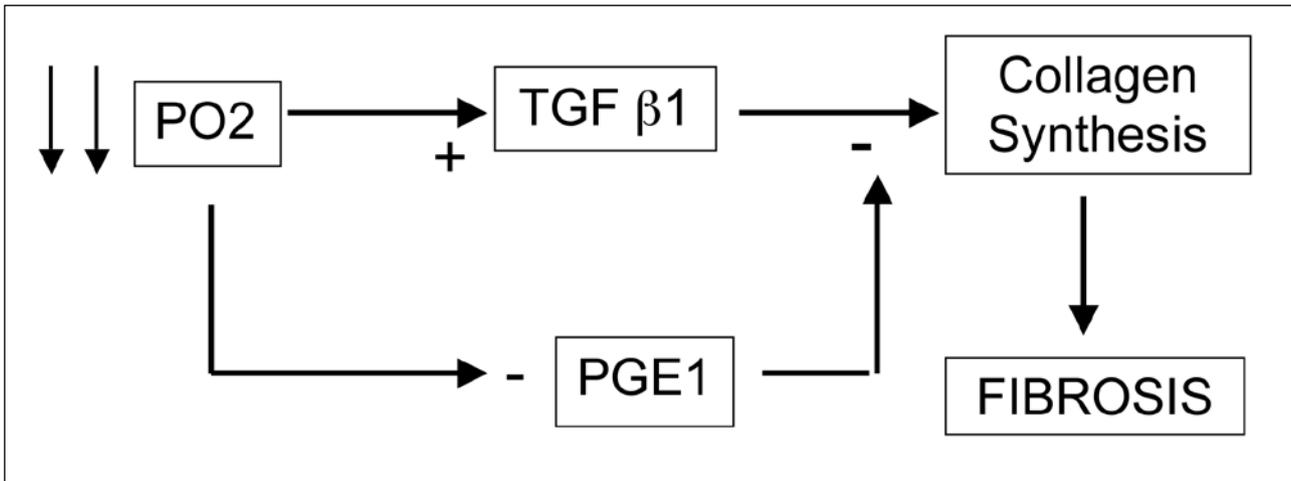
Pathophysiology of cavernous nerve injury

Several investigators demonstrated that normal smooth muscle content and function were essential in initiation and maintenance of erections. The integrity and function of any smooth muscle cell was usually related to the tissue oxygenation and fibrosis has been suggested to be the most probable cause of erectile dysfunction in patients with arterial insufficiency. However, the exact mechanism of collagen accumulation in patients who have penile hypoxia has not been established¹⁴.

In vitro studies showed that penile hypoxia induced transforming growth factor-beta1 (TGF- β 1), which is implicated in the collagen deposition. At the same time, prostaglandin E1 (PGE1) is able to suppress the TGF- β 1-induced collagen synthesis¹⁵. However, the production of PGE1 in strips of rabbit cavernosum tissue was also oxygen dependent¹⁶. These studies suggest that the collagen content in the corpus cavernosum was regulated by oxygen tension through the increased or decreased expression of TGF- β 1 and PGE1 (Fig. 1). Although elegant in the design, however, the "in vitro" studies of hypoxic environments should be correlated to the situation of a flaccid penis with caution. In fact, to date, no studies have proven any "in vivo" derangement of endothelial or smooth muscle cell metabolism secondary to a prolonged flaccid state. Therefore, the role of hypoxia in penile fibrosis after nerve-sparing RP remains a controversial issue.

Regardless of the previous critical issues, in patients who underwent a nerve-sparing RP a key role in the cause of erectile dysfunction is represented by initial neuropraxia. The etiology of cavernous nerve neuropraxia include mechanical stretch injury during retraction, ischemia from accessory vessel disruption

Figure 1. Penile hypoxia induces transforming growth factor-beta1 which is implicated in the collagen synthesis and decreases the production of PGE1 that is able to suppress the TGFβ1-induced collagen synthesis.



during the dissection, thermal injury from electrocautery use, and inflammation from surgical trauma. Neuropraxia can prevent erections during the initial 12 to 18-month period after nerve-sparing RP, initiating a cascade of deleterious events characterized by the reduction of blood flow to corporeal bodies, ischemic and hypoxic injuries, fibrotic remodelling, and apoptosis^{17,18}. Using penile biopsy in human models before, 2 and 12 months after RP, Iacono et al. showed a significant postoperative decrease in the elastic fibers and smooth muscle content, compared to the preoperative biopsy¹⁹. Cavernosal apoptosis and collagen deposition can lead to veno-occlusive disease. Specifically, the incidence of venous leak increases with the post-operative time interval. Mulhall et al. reported that the incidence of veno-occlusive dysfunction was 14% 4 months after nerve-sparing RP and raised to 35% at 9 to 12-month follow-up evaluations²⁰ (Fig. 2). Therefore, in any patient undergoing RP, the insult can be primarily neurogenic (neuropraxia), vasculogenic (veno-occlusive mechanism) or mixed and it should be considered a dynamic process from surgery to recovery.

Penile Rehabilitation following nerve-sparing radical prostatectomy

The goal of penile rehabilitation is to prevent the cavernous tissue damage that occurs during the period of neural recovery providing an adequate oxygenation to the corpora cavernosa. Moreover, restoring nocturnal erections must be considered an alternative way to increase oxygenation of the cavernosal bodies using oral PDE5-I.

The potential options for early treatment of erectile dysfunction following nerve-sparing radical prosta-

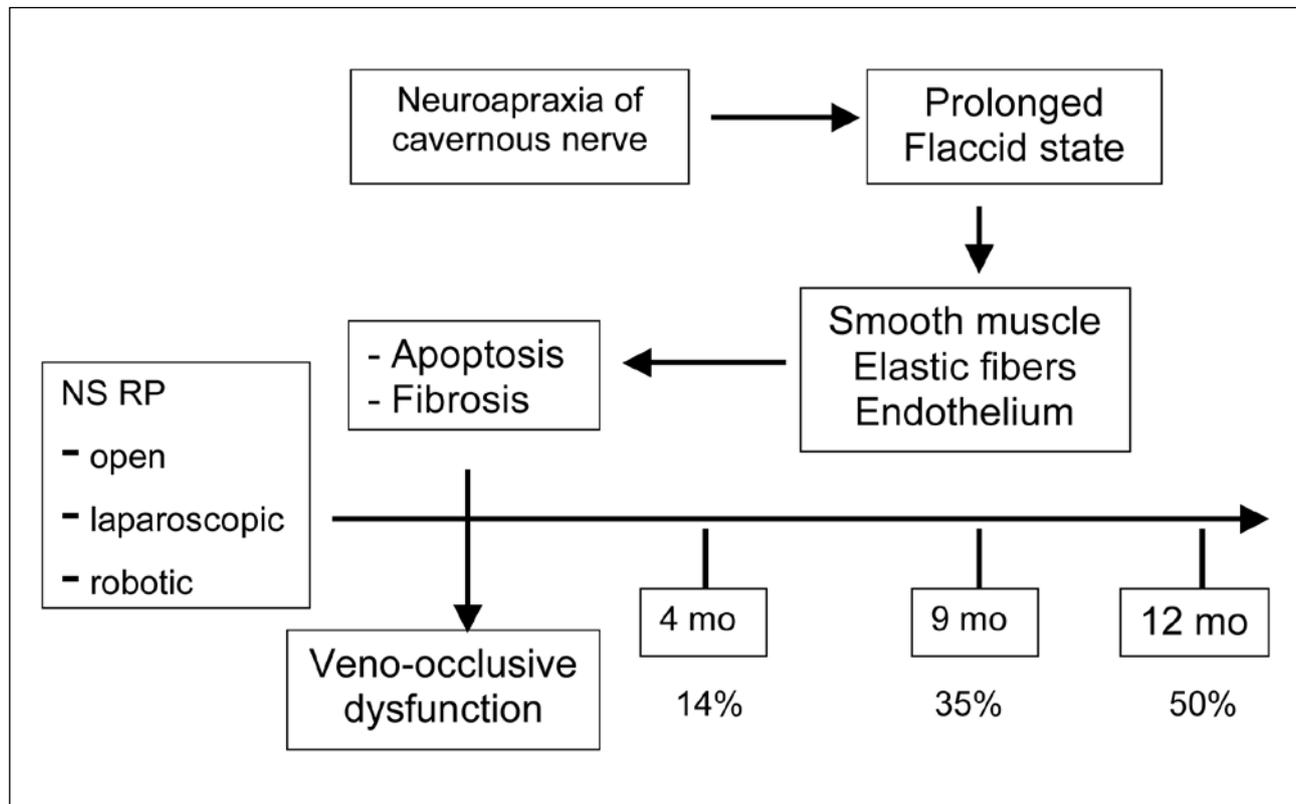
tectomy encompass pharmacologic and non-pharmacologic agents. The first group includes the oral PDE5-I (sildenafil, vardenafil and tadalafil), intracavernous agents (alprostadil, papaverine and phentolamine) and intraurethral agents (alprostadil). The main non-pharmacologic tools used for early penile rehabilitation are vacuum constriction devices (VCDs).

Clinical evidence for early use of intracavernosal penile injections

Intracavernosal injection of Alprostadil allows the activation of an alternative pathway to induce the relaxation of smooth muscle fibres in the cavernous tissue. Specifically, PGE1 activates the adenylate cyclase transforming ATP in AMPc, which, similar to GMPc, reduces cytoplasmic concentration of Ca⁺⁺ allowing relaxation of the smooth muscle fibres and, consequently, erections.

Montorsi et al. first demonstrated the advantages of penile injection of Alprostadil as an early intervention strategy in a randomized, controlled study, including 30 patients undergoing bilateral nerve-sparing RP¹³. One month after surgery, 15 patients were randomized to intracavernous alprostadil 2-3 times/week for 12 weeks, while 15 received no treatment. After a minimum follow-up of 6-month, 8 of 12 patients (67%) had spontaneous erections sufficient for intercourse, compared to 3 of 15 (20%) of those who were not injected. Moreover, penile Doppler ultrasonography revealed veno-occlusive dysfunction in only 2 of 12 patients (17%) included in the treatment group, compared to 8 of 15 (53%) in the control group. This study must be considered as one of the most original and impor-

Figure 2. Pathophysiology of cavernous nerve injury following nerve-sparing radical prostatectomy.



tant contribution in the urologic and andrological literature. However, it suffers of some important limitations. Firstly, the study was neither blinded nor placebo controlled. Secondly, the number of patients enrolled in the trial was limited. Thirdly, only 12 of the 15 patients randomized to treatment were evaluated at the 24-week follow-up. The analysis “per protocol” limited to those 12 patients showed a statistically significant advantage in favour of the treatment group but the “intention-to-treat analysis” failed to show any statistically significant difference (chi-square 3.589 – $p = 0.06$). However, in our opinion, the most important issue is that the data of this study were never confirmed. In the everyday clinical life, however, the use of PGE1 for penile rehabilitation following nerve-sparing RP did not become a mainstream option due to the limited patient compliance. Penile pain due to intracavernous injection and the throbbing penile discomfort secondary to long-lasting prostaglandin effects are two important limitations in the routine acceptance of this early treatment. Moreover, the logistic administration of an early injection program in most of the normal office practice is sometimes prohibitive because multiple visits are required to find the correct dose and to make sure that injec-

tions are done properly. However, in our opinion, the most relevant limitation to the diffusion of intracavernous therapy was the advent of PDE5-I.

Clinical evidence for early use of oral therapy with 5-phosphodiesterase inhibitors

These drugs act within the smooth muscle cell by inhibiting the enzyme PDE5 which naturally degrades cGMP, which acts as the second messenger in the process of smooth muscle cell relaxation. Increased levels of cGMP lead to the activation of cGMP-specific protein kinases that activate further intracellular events, finally leading to reduction of intracellular calcium and relaxation of the smooth muscle cells. It had long been believed that PDE5-I needed an intact neural pathway to be effective, which is a doubtful issue during the neuropraxia period after nerve-sparing RP. Some proponents for the use of this class of agents in penile rehabilitation protocols, however, argue that this drugs might act through a separate, neural-independent mechanism, affecting the endothelium cell function. Several studies in the last few years showed an overall improvement in endothelium cell function after use of PDE5-I. However, these studies were performed in diabetic patients²¹ or in patients with vascular (arteriogenic)

erectile dysfunction^{22 23}. In our opinion, this global improvement in endothelial cell function might suggest a possible role for PDE5-I during the period of neuropraxia after nerve-sparing RP.

Another basic concept related to the mechanism of action of PDE5-I in the patients who underwent RP is the bedtime administration, in order to facilitate the occurrence of nocturnal erections, which are believed to have a natural protective role on the baseline function of the corpora cavernosa. Bannowsky et al. using the NPT recorded a residual erectile function the first night after catheter removal in 25 of the 27 patients (93%) who underwent nerve-sparing RP. Conversely, in a small control group of 4 patients treated with non nerve-sparing technique, no nocturnal erections were reported early after catheter removal²⁴. According to the Authors, patients with residual nocturnal erections should be enrolled in a penile rehabilitation program with PDE5-I, while, on the contrary, patients without residual erections should be treated early with alprostadil intracavernous injection. The absence of the randomization and the limited number of patients evaluated in the study are relevant limitations, while the number of patients with residual erectile seems really high. In our opinion, further studies are needed to confirm the rationale of this approach.

The most relevant clinical evidence in favour of the nightly use of PDE5-I in a rehabilitation protocol is represented by the randomized controlled trial published by Padma-Nathan et al. For many years we had only the possibility to evaluate the data of this randomized, double-blind, placebo-controlled, trial in the abstract format²⁵. Recently, the Authors published also the final version of the study on a peer-review journal²⁶. In this study, 4 weeks after nerve-sparing RP, patients entered a 36-week double-blind, treatment during with sildenafil 50mg or 100 mg (once daily at night time), or placebo. After the end of the double-blind treatment and a 8-week wash-out period, erectile function, nocturnal penile tumescence and, in a subgroup, rigidity were assessed. Although the authors randomized 125 patients in the three arms, only 82 men completed the 36-week double-blind treatment and only 76 patients the subsequent 8-week drug-free period. Specifically, 23 patients in the sildenafil 50 mg group, 28 in the sildenafil 100 mg group and 25 in the placebo arm. Limiting the analysis to these 76 cases, the study showed a statistically significant advantage in those patients receiving sildenafil in terms of spontaneous erections sufficient for intercourse, compared to those taking placebo.

Specifically, 27% of the patients in treatment arm reported erections sufficient for intercourse, compared to 4% in the placebo group ($p = 0.02$)²⁶. The trial, however, presents many important drawbacks. Firstly, it is not possible to know the real allocation of the 125 randomized patients in the three arms of the study, which make impossible any intention-to-treat analysis. Secondly, the conclusions of the study were limited only to 76 of the 125 randomized patients. Finally, the 48-week potency rate detected in the placebo arm of the study (4%) seems to be unusually low following nerve-sparing RP. Therefore, in our opinion, the results of this study cannot be extrapolated to the general population of nerve-sparing patients.

Clinical evidence for on demand therapy after nerve-sparing RP

The most critical issue to accept the opportunity to prescribe in our patients a penile rehabilitation protocol after nerve-sparing radical prostatectomy is represented by the positive results observed with “on demand” PDE5-I administration schedule.

In 2006, Montorsi et al. reported a prospective non-randomized study evaluating the potency recovery following bilateral nerve-sparing RP. Specifically, those patients were subdivided in four different groups: 1) those receiving no erectile therapy; 2) those having intracavernosal injection of PGE1 on demand; 3) those taking PDE5-I on demand; 4) those having a rehabilitative PDE5-I therapy. After 12-month follow-up, the authors showed no significant difference in the mean International Index Erectile Function scores between patients who received “on demand” or those treated with a “rehabilitative” protocol²⁷. Obviously, the main limit of this study is the lack of randomization.

The efficacy of “on demand” therapy in this particular and difficult setting of patients has been recently confirmed by a randomised, double-blind, double-dummy, multicentre, parallel group study which enrolled a total of 628 men aged to 18-64 years. The study design consisted of a 9-month double-blind treatment period, a 2-month single-blind washout period, and an optional 2-month open-label period. The results showed that nightly dosing with vardenafil did not have any effect beyond that of on-demand use. Moreover, the data of this study indicated that the use of on-demand vardenafil is of greater benefit than nightly treatment in patients following nerve-sparing RP, and support the on-demand use of PDE5-I following nerve-sparing surgery over a daily dosing regimen¹².

Conclusions

In our opinion, the critical issue in preservation of erectile function in patient who underwent RP is the quality of nerve-sparing procedure. A better technique is fundamental to reduce the period of neuropraxia and enhance the probability to reach spontaneous erections. The exact etiology of the fibrotic changes in the corpora cavernosa following nerve-sparing RP remains unknown.

This critical analysis of the literature highlighted that no high level evidence support any program of penile rehabilitation following nerve-sparing RP. However, the use of drugs during the early post-operative period reduces the time of potency recovery and improves the long-term results in terms of spontaneous or PDE5-I assisted erections. Recent data showed that on-demand dosing is more effective in improving both erectile function and sexual intercourse completion rates after RP. These data prompt reconsideration of the current practice of prescribing PDE5-I rehabilitation protocol. At the same time, the prescription of a rehabilitative protocol or an early "on demand" therapy following nerve-sparing RP can be considered an excellent strategy to give our patients the feeling that we are doing something to improve their probability to recover erectile function. In our opinion, however, patients should be aware that the exact benefit of rehabilitative protocols will remain highly controversial until better data become available.

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Mondor's penile disease: personal experience

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Summary

Objective. Mondor's disease of the penis is an uncommon genital condition usually characterized by a painless and tender cord-like lesion involving the distal part of the penile shaft and/or the coronal sulcus in a circumferential manner or, more rarely, the prepuce. Although this disorder is almost always self limited, it may be associated with considerable psychological stress and sexual disharmony. This clinical picture is related to a superficial dorsal penile vein thrombosis or thrombophlebitis. The goal of this paper is to summarize our experience on such a disease and to focus on the treatment of the 5 cases we observed.

Material and methods. During the last 3 years, we had the chance to examine and treat 5 patients, with an average age of 40.4 years, affected by a thrombophlebitis interesting the superficial vein of the penis.

Results. The primary therapy of Mondor's disease was essentially conservative: non-steroidal antiinflammatory agents were used for the symptomatic relief. Resolution, following spontaneous venous recanalization, occurred in all cases in a period of time ranging between 8 and 12 weeks (mean time 9.4 weeks).

Conclusions. Mondor's disease of the penis is a quite rare and relatively benign condition. The attending physician should be aware of this self-resolving condition even to avoid erroneous differential diagnosis and possible wrong and over-aggressive treatments. In such a way, useless physical and emotional traumas can be avoided.

Keywords

Mondor's disease • Dorsal penile vein • Venous thrombosis

Introduction

Mondor's disease of the penis, or otherwise known as superficial dorsal penile vein thrombosis or thrombophlebitis, is an uncommon genital condition usually presenting as a painless and tender cord-like lesion which involves the coronal sulcus in a circumferential manner or, more rarely, the prepuce and the distal part of the penile shaft^{1,2}. Historically, superficial vein thrombosis of the thoraco-epigastric veins and/or their confluent vessels was initially described by Mondor³ in 1939. In 1955, Braun-Falco⁴ described the penile involvement as a superficial phlebitis of the dorsal vein of the penis. An isolated superficial penile thrombosis was first reported by Helm and Hodge⁵ in 1958. According to Kluten⁶, a similar clinical picture may involve also the extremities.

Regarding Mondor's disease, our experience is based on 5 cases who were examined and treated in the last three years at our service.

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Materials and methods

Five male patients complaining for a prominent enlargement of the penile dorsal vein, came to our observation: their age ranged between 34 and 46 years, with a mean age of 40.4 years. An associated mild discomfort or pain was reported in 3 of them. Three out of these 5 men were married. Previous medical history was silent in 4 cases; in one, the patient had undergone a previous left varicocelelectomy in his adolescence. All denied any family or personal history of deep venous thrombo-embolism, coagulation disorders, recent periods of immobilization or any kind of recent surgery. Patients were in a good physical condition; they were not overweight nor usual smokers. Prior to medical evaluation, 3 patients reported recent prolonged and vigorous sexual intercourse; one masturbation. The last one denied recent penile erections of any sort: in such a case, it is allowable to think of the so called idiopathic Mondor's disease. On the physical examination, in the 4 cases there was a variably long (ranging from 2 to 4 cm), indurated, cord-like lesion, palpable within the superficial dorsal vein of the penis. These findings extended to the base of the penile shaft (Fig. 1). The dorsal vein was poorly compressible, minimally tender with no evidence of edema nor cellulitis. In the remaining case the thrombotic picture occurred in the sulcus coronarius.

Results

A penile discomfort and/or pain was reported in 3 out of the 5 cases; the others were completely painless. In all patients the doppler-ultrasound examination of the penis showed the peculiar sign of a thrombus: a non-compressible distended vein with an echodence structure in the adjoining blood vessel segments (Fig. 2).

In every case, the primary therapy was conservative: the 2 patients, presenting no pain, were treated only with local application of some nonsteroidal anti-inflammatory ointment. The 3 others were prescribed with some oral nonsteroidal anti-inflammatory drugs. All presented a progressive regression of the clinical picture and of the painful symptoms, when present, in the following few weeks.

No patients underwent any additional manoeuvre. A complete resolution of the disease was obtained in a variable period of time ranging from 8 to 12 weeks.

Discussion

Penile Mondor's disease is a benign condition affecting the superficial dorsal vein of the penis, interesting sexually active men. The pathogenesis

of the disease is unknown and still controversial as, on the histopathologic exam, lymphatic channels as well as non-lymphatic vessels have been equally involved, in some way.

A lot of predisposing factors can lead to the development of Mondor's penile disease. All these factors relate to Virchow's triad of vessel wall damage, stasis and some hypercoagulable state (intimal vessel damage, secondary to trauma, inflammation and infection; venous stasis; change in blood constituents such as coagulation abnormalities)⁷.

A traumatic origin was likewise considered; as well as some locally confined toxic processes.

Figure 1. Dorsal vein thrombosis of the penis.



Figure 2. Internal echogenicity in penile superficial dorsal vein.



Sexual activities, specifically of traumatic, vigorous, prolonged or excessive characteristics, may play a consistent predisposing factor. These are usually reported to have occurred 24-48 hours prior to the development of the clinical signs⁸⁻¹¹: these activities may induce stretching or torsion of the vein, causing endothelial lesions and subsequent thrombus formation¹². Other possible precipitant events include traumas to the genitals such as penile strangulation, venous occlusion due to the presence of a pelvic tumor or distended bladder, enteroviral infections or sepsis, circumferential scarring from previous circumcision, past inguinal hernia repair, contact with menstrual blood, possibly acting as an irritant agent, prolonged sexual abstinence^{8 9 13} and intravenous drug abuse.

Furthermore, migratory phlebitis associated with cancer is seldom reported¹⁴.

Kumar et al. examined 1296 patients attending the sexually transmitted diseases (STD) clinic during the period of time 1991-2003. Eighteen of these patients were found to have a Mondor's disease of the penis (with an incidence of 1.39%). Although one fourth of the 105 previously reported cases have demonstrated a close temporal relation to STDs, it was difficult to determine whether these patients had a greater incidence of STDs than an otherwise analogous at-risk population group or whether frequent sexual activities exposed them to both the acquisition of a STD and the development of Mondor's phlebitis². Day et al. reported the first case of superficial dorsal penile vein thrombosis in relation to a recent long-haul flight. The aetiology of the superficial thrombophlebitis has been associated with one or more components of the Virchow's triad¹⁵. Evans et al. did not identify any coagulation abnormalities during the extensive work-up of the cases they had examined presenting a superficial dorsal penile vein thrombosis. In the absence of any trauma, inflammation and sepsis, or with no clear predisposing factors for the development of Mondor's disease, and in view of the previous history of varicose vein superficial thrombophlebitis, venous stasis due to prolonged immobility and dehydration as a result of the long-haul travel may be the precipitating event in the development of Mondor's disease¹⁶.

In any cases, the thrombosis of the penis may occur without a clear aetiological factor. For the idiopathic penile thrombosis, protein S deficiency was considered to be a risk factor. Protein S is an anti-thrombus plasma protein acting as a co-factor for another plasma protein (activated protein C).

Deficiency of antithrombin III, protein C, and protein

Figure 3. A non-compressible distended vein for the presence of thrombosis.



S represent important genetic factors for venous thrombosis process. These defects were discovered in 15% to 20% of all families with thrombophilia¹.

Histopathological examination of the resected specimen coming from patients with Mondor's disease, showed a variable wall thickness of the examined veins (2.1 to 3.2 mm). Thrombotic material, consisting of red blood cells, platelets and fibrin, was found to obstruct most of the vessel lumen for 5 mm.

Usually, under the clinical point of view, patients notice a sudden, cord- or string-like induration of the superficial dorsal vein of the penis, measuring up to 5 cm in length, and refer a mild discomfort or pain, often associated with a localized inflammation of the tissues around the dorsal vein.

Thrombosis may occur close to the sulcus coronarius in the proximity of the penis root and along the entire penile shaft. Sometimes a true acute thrombophlebitis may be present, and in this case, pain and fever are often associated with a significant inflammation of the penis⁹.

The diagnosis of superficial penile vein thrombosis is commonly based on clinical findings (history and physical examination). Ultrasound and doppler-ultrasound examinations can be useful in case of diagnostic uncertainty, as they may reveal a non-compressible distended vein^{8 15}. Ultrasound examination

is used only to clarify the extent of the thrombosis and, mainly, to follow-up these patients. According to our experience and to the results of the published series, additional invasive diagnostic procedures don't seem to provide further or clearer information on the extension of the thrombosis and they are not considered as necessary. Imaging techniques may find some indications in case of a deeper investigation or in case of recurrence or in order to exclude the presence of any pelvic tumor⁹.

Even if this disease has been infrequently investigated, the diagnosis often results quite easy and invasive techniques, such as the penile biopsy, are not recommended. In any case, for the evaluation of the pathogenesis of the penile thrombosis, determination of protein S, free protein S, antithrombin III, and protein C levels may be helpful¹.

Differential diagnosis of penile swelling and painful deformity should include the rupture of the corpora cavernosa, Peyronie's disease, lymphoedema and sclerosing lymphangitis. Sclerosing lymphangitis is characterized by the presence of thickened, dilated lymphatic serpiginous vessels.

Peyronie's disease results from a thickening of the tunica albuginea and presents a well defined fibrotic plaque on the penis. If any doubt persists, even after taking the history and performing the physical examination, ultrasonography may be considered. If the vein appears non-compressible, this is consistent with the diagnosis of venous thrombosis⁷.

Spontaneous resolution following venous recanalization occurs within a mean time of 3 weeks, but it can take more time lasting till to eight weeks. A rigid subcutaneous induration may remain even for 1 year. Non-steroidal anti-inflammatory agents may be used for symptomatic relief of the pain, although they don't affect the resolution rate. On the contrary, there is no evidence on the efficacy of eventual anticoagulant agents, even if the use of a local dressing with heparin ointment, in all cases, proved to have some therapeutic efficacy. For refractory cases, venous resection can be effective with the aim of reducing pain, resolving induration and improving cosmesis^{8,9}. Certainly, the temporary abstention from any sexual intercourse till the thrombosis has completely disappeared, represents the most effective measure.

Despite thrombophlebitis of the superficial penile vein is a benign condition, some complications may occur: phimosis has been reported, even if rarely secondary to oedema¹⁷; erectile difficulties don't result although Mondor's disease can mimic Peyro-

nie's disease¹⁵. Recurrence may occur in relation to predisposing sexual activity⁸.

Conclusion

Mondor's disease of the penis is a rare benign, self resolving condition, therefore it's mandatory in the management of this disease to prevent misdiagnosis and overtreatment.

In our opinion, a proper explanation, strong reassurances and temporary sexual abstinence should remain the mainstay of the treatment, unless the disease is very symptomatic or the lesions last for a longer than the average healing time: in these cases non-steroidal anti-inflammatory agents can be used to improve the patient's discomfort.

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Editorial comment

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In this issue of JAS, Gigli et al. report a very interesting article concerning five cases of penile Mondor's disease¹.

Penile Mondor's disease is a rare benign condition and many predisposing factors can lead to the development of the disease. As reported in the previous article, penile Mondor's disease has been associated with prolonged sexual activity, trauma, injection of illegal substances into the dorsal vein, venous compression due to a tumor or distended bladder².

The Authors describe well the pathogenesis of the disease and pointed out that also idiopathic penile vein thrombosis can occur. It should be emphasized that in all cases a precise and careful medical history should always be taken to determine the underlying factors. In fact the diagnosis is almost based on the information obtained during history and physical examination. Only few data are available in literature on Mondor's disease but probably the number of cases reported is underneath real ones. Also in our experience we did not consider early this diagnosis in a recent case.

A 53-year-old male presented with a high flow priapism. Two weeks before, due to elevated levels of prostate specific antigen, the patient was referred to another hospital and an ultrasound-guided transrectal biopsy of the prostate was performed. The histologic examination was negative. Physical examination of the patient revealed a cord-like induration on the dorsal surface of the penis which could be followed superiorly under the pubic symphysis (Fig. 1). The patient reported pain when the cord was palpated. Full blood count, platelet count and partial thromboplastin time were within normal ranges. Penile Doppler ultrasonography detect a high flow priapism and did not detect flow signals in the superficial vein which was thrombosed.

Magnetic resonance angiography (MRA) demonstrated the absence of a clinically significant causative vascular lesion of high-flow arterial priapism and clearly identified the subcutaneous dorsal vein thrombosis (Fig. 2).

Primary therapy for high flow priapism was conservative with daily cold packs as described by Ficarra et al.³. After 3 days we observed a spontaneous resolution of the priapism. We treated with oral nonsteroidal anti-inflammatory drugs the penile Mondor's disease for 10 days and the patient was seen after 1 and 3 months and reported a progressive decrease of the thrombosed vein and the resolution of pain.

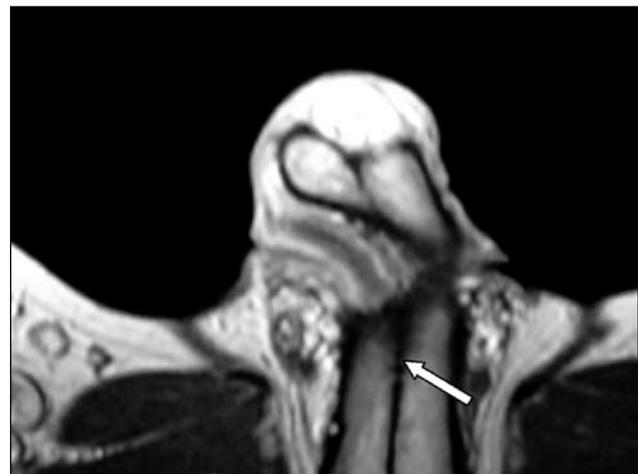
Figure 1. Physical examination: rope like cord on the dorsum of the penis.



Therefore, we agree with Gigli et al. who pointed out in this article that the primary therapy should be conservative in all cases till a spontaneous complete resolution of the disease is obtained.

Some Authors suggest the application of local heparin creams but still there is no evidence on the efficacy of these drugs⁴.

Figure 2. In the transverse plane, MRI angiography clearly demonstrates the absence of signal in the dorsal vein (white arrow).



In conclusion, this paper provides interesting information because it deals with a rare disease that has been poorly explored so far. Urologists might be expected to be more aware and diagnose and treat better cases of penile Mondor's disease after reading this article.

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Do lunar phases influence semen parameters?

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Summary

Objective. The aim of this retrospective study was to analyze semen parameters of a large group of individuals during a lunar cycle.

Material and methods. We analyzed the semen parameters of a continuous series of 386 male patients by optical microscope according to WHO guidelines. Data were grouped according to the four primary phases of the moon: the new moon (nm), the first quarter (fq), the full moon (fm) and the last quarter (lq) and the values were statistically compared.

Results. This study failed to show any statistically significant difference in semen parameters during the four lunar phases. Nevertheless, the median value of semen volume during the full moon phase showed a trend towards lower values (3.3 ± 1.57) compared to the median values observed during the other phases of the moon (nm, 3.67 ± 1.66 ; fq, 3.52 ± 1.8 ; lq, 3.45 ± 1.86) as well as the frequency of increased viscosity was very reduced during the new moon phase (15.53) compared to the other phases (fq, 26.25; fm, 26.47; lq, 22.77).

Conclusions. Lunar cycle seems do not affect semen parameters. A large study considering semen samples from the same patient for each lunar phase should be set up in order to better clarify whether lunar rhythm could influence male fertility.

Keywords

Sperm motility • Sperm morphology • Sperm concentration • Lunar phases

Financial support

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Introduction

The lunar cycle is believed to influence human and animal activities, physiological processes and behavior, but these effects have not been explored extensively. Zimecki¹ reviewed available data regarding effects of the lunar cycle in humans on fertility, menstruation and births, hospital admissions and in animals. Many fertility studies of women, in particular the possibility of a lunar effect on the menstrual cycle, have been postulated^{2,3}. Folkloric beliefs in the moon's influence on birth have not yet been fully demonstrated. Some research has shown no relationship between lunar cycles and the birthrate⁴⁻⁷, whereas Criss and Marcum⁸, Guillon et al.⁹ and Ghiandoni et al.¹⁰ have claimed a relationship.

It has been reported in the literature that in some animals, such as fish, physiology is influenced by lunar periodicity. In particular, a correlation between hormonal changes in the testis and the lunar cycle was found in the forktail rabbitfish which spawns synchronously around the last quarter moon¹¹ and weekly changes in sperm motility peaked

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around the last quarter moon. The pH and osmolarity in seminal fluid increased and decreased around the same lunar phases, respectively¹¹.

No studies, however, have yet been available analyzing semen parameters during a lunar cycle.

For this reason a large scale study was set up at the Interdepartmental Centre for Research and Therapy of Male Infertility to explore whether lunar periodicity could in some way influence seminal characteristics.

Material and methods

We retrospectively assessed the sperm samples of all patients that came to the Interdepartmental Centre for Research and Therapy of Male Infertility between January 2005 and December 2006. In this non randomized study, all data regarding semen parameters were grouped according to the four primary phases of the moon and the data were statistically compared.

Light microscopy

Semen samples were collected by masturbation in the laboratory of the Centre after 4 days of sexual abstinence and examined after liquefaction for 30 min at 37 °C. First, we evaluated volume and pH; sperm concentration and motility percentages were quantified according to WHO guidelines¹². Modified Papanicolaou staining was used in sperm smeared on glass slides in order to assess morphology according to the protocol reported in WHO guidelines¹². Two hundreds sperms were evaluated from each sample.

Statistical Analysis

Statistical analysis was performed by StatgraphicsPlus (version 5.0). All p values of less than 0.05 were considered to be statistically significant. Results for the seminal parameters were expressed as mean \pm SD, median, and interquartile ranges.

Standardized skewness and kurtosis evaluated normal distribution of the data and Levene's test was used to check the homogeneity of variances.

The Anova F test was used to compare the differences of the examined variables and the Kruskal-Wallis test was performed when some significant non normality in the data was indicated.

The chi square test was carried out to evaluate the relationship between viscosity and the phases of the moon. A chi square test with the Yates' correction was performed to compare the number of patients in the different lunar phases divided considering the reasons why they performed semen analysis. All p values < 0.05 were considered statistically significant.

Results

The mean age of the 386 consecutive patients that came to the Interdepartmental Centre for Research and Therapy of Male Infertility for semen analysis was 33 ± 12 . One hundred and three patients performed the semen analysis in the new moon phase, 80 in the first quarter, 102 in the full moon phase, and 101 in the last quarter.

The primary reason to seek counselling in our Centre was infertility problems, however we also analysed semen samples from men who wanted to check their fertility status. The presence of andrological diseases such as varicocele, genitourinary infections, as well as the infertility without other explanation, were homogeneously distributed in the analysed groups (Table I) as demonstrated by the analysis with chi square test.

The means and standard deviations (SD), medians and interquartile ranges of values of pH, semen volume, sperm concentration, rapid (a) and slow (b) progressive motility and morphology and the frequency of elevated viscosity are reported in Table II.

No statistical significance was detected comparing values related to different semen parameters during the four lunar phases. However, we noted that the median value of semen volume during the full moon phase tended to be lower compared to the median values observed during the other phases (Table II, Fig. 1), even though the differences were not statistically significant.

Moreover, the frequency of altered viscosity tended to be reduced during the new moon phase compared to the other phases (Table II, Fig. 2), even though the values did not reach statistically significant differences.

Figure 1. Median volumes of the semen samples analyzed during the four lunar phases.

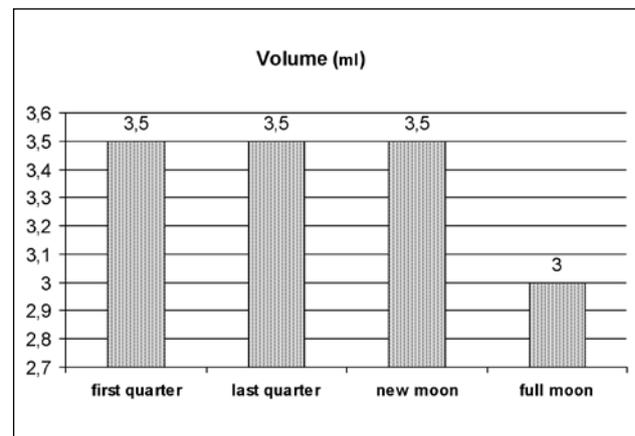


Table I. Number of patients in the different lunar phases, grouped according to the reasons why they performed semen analysis (χ^2 p value not significant).

PATIENTS # IN LUNAR PHASES	REASONS WHY THEY PERFORMED SEMEN ANALYSIS					
	VARICOCELE	INFECTIONS	VARICOCELE + INFECTIONS	INFERTILITY WITHOUT EXPLANATION	CRYPT-TORCHIDISM	FERTILITY STATUS CHECK
New moon #103	10 (9.7%)	11 (10.7%)	9 (8.7%)	51 (49.5%)	4 (3.9%)	15 (14.6%)
Full moon #102	9 (8.8%)	13 (12.7%)	9 (8.8%)	48 (47.1%)	5 (4.9%)	16 (15.6%)
First quarter #80	7 (8.75%)	10 (8%)	7 (8.75%)	43 (53.75%)	3 (3.75%)	10 (8%)
Last quarter #101	9 (8.9%)	11 (10.9%)	10 (9.9%)	51 (50.5%)	4 (3.9%)	15 (14.9%)

Table II. Mean \pm standard deviation, medians and interquartile ranges of semen parameters of 386 patients divided according to lunar phases.

LUNAR PHASES		VARIABLES					
		VOL (ML) P = 0.5033 (K)	PH P = 0.5764 (K)	CONCENTRATION SPERM/ML P = 0.4615 (K)	MOTILITY (A + B) % P = 0.6710 (F)	MORPHOLOGY P = 0.25 (F)	HIGH VISCOSITY % P = 0.2129 (χ^2)
New moon #103	Mean \pm SD	3.67 \pm 1.66	7.60 \pm 0.20	70 \pm 55	38 \pm 13.6	31.1 \pm 9.58	Rel. frequency %
	Median	3.5	7.6	56	40	32	15.53
	Interq Ranges	2.4-4.5	7.4-7.8	30-104	31-46	24-36	
Full moon #102	Mean \pm SD	3.3 \pm 1.57	7.62 \pm 0.24	78 \pm 61	36 \pm 15	32.5 \pm 9.27	Rel. frequency %
	Median	3	7.6	70	38	34	26.47
	Interq Ranges	2-4.2	7.4-7.8	24.5-112.5	23.5-49.5	25.5-38	
First quarter #80	Mean \pm SD	3.52 \pm 1.8	7.63 \pm 0.22	66 \pm 59.81	38 \pm 14	32 \pm 11.8	Rel. frequency %
	Median	3.5	7.6	47	39	34	26.25
	Interq Ranges	2-4.5	7.4-7.8	20.4-103	28.5-49	26-40	
Last quarter #101	Mean \pm SD	3.45 \pm 1.86	7.63 \pm 0.24	71.88 \pm 53	37 \pm 14	30 \pm 10	Rel. frequency %
	Median	3.5	7.6	58	36	30	22.77
	Interq Ranges	2-4.5	7.4-7.8	23.5-11.25	29-48	24-36	

F: ANOVA F- Test; K: Kruskal-Wallis Test; χ^2 : chi-square

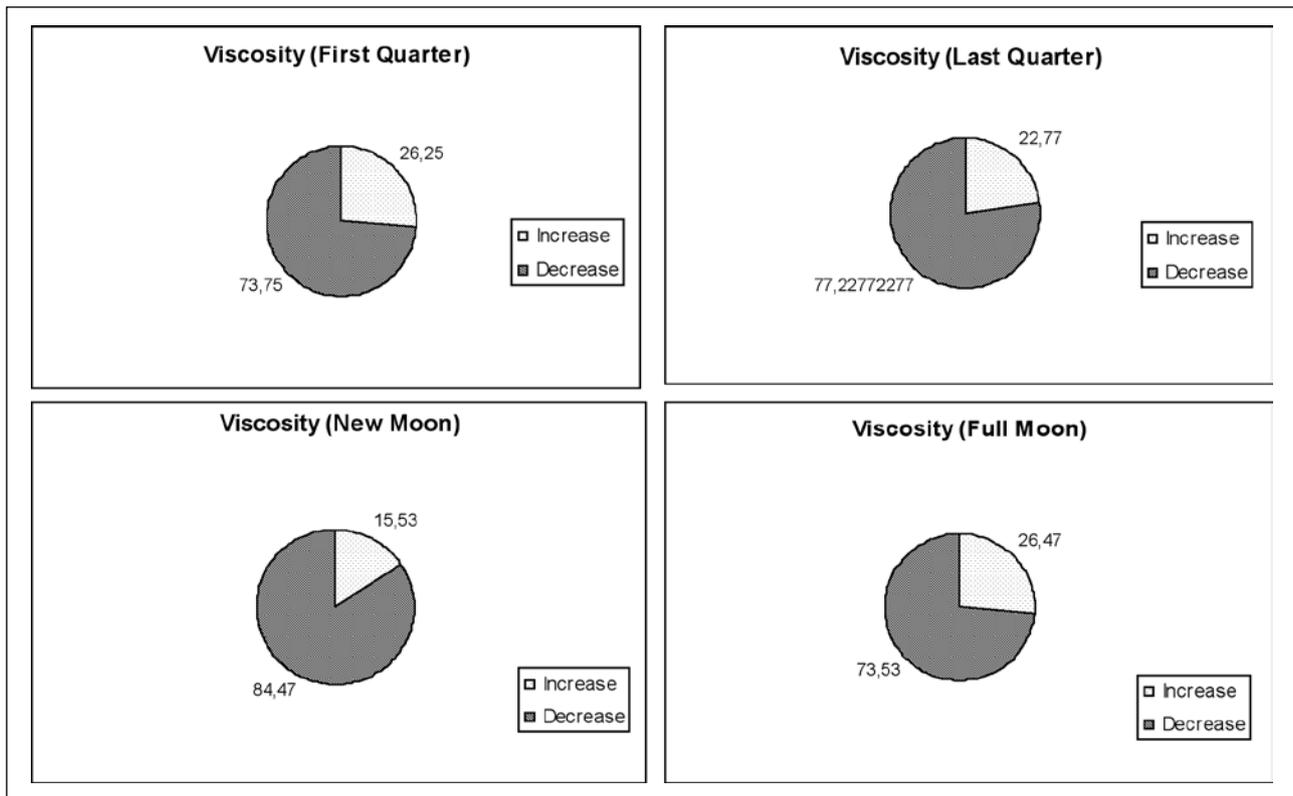
Discussion

The historical records of Claudius Ptolemy, in the 2nd Century AD, advised farmers to “direct the copulation of their flocks and herds ...” during the full moon phase for a profitable outcome. Human and animal physiology are subjected to seasonal, lunar and circadian rhythms. Little is known

about the effects of the lunar cycle on the behavior and physiology of humans and animals.

It is still being debated whether lunar phases could affect fertility and births, however they seem to play a role in hormonal changes in early phylogenesis (insects). In fish, the lunar clock influences reproduction and involves hypothalamus-pituitary-gonadal axis¹.

Figure 2. Frequency of viscosity in the samples analyzed during the four lunar phases.



Our research was aimed at highlighting whether the lunar phases could affect semen parameters in some way. For this reason, we divided our large group of patients according to the lunar phases, and spermogram data were compared by statistical analysis. Human spermatogenetic cycle takes 70-75 days to be completed, about two and half lunar phases and the idea could be of an influence of lunar rhythms on testicular development; in lower organisms it is well known the influences of lunar periodicity on reproductive processes, for example the synchronous increase in testicular activity supports the hypothesis that lunar periodicity is a major factor for testicular development of *Siganus guttatus*¹¹.

This study failed to show any statistically significant difference in semen parameters during the four lunar phases. However, the values of semen volume showed a trend to be lower in the full moon phase, but they did not reach statistical significance. It is believed that the effect of lunar tidal pull can influence the cyclical changes of water constituting the 80% of human body¹³. Moreover, the frequency of increased viscosity of seminal fluid was reduced in the samples obtained during the new moon phase, however also this data was not statistically different from that carried out from other moon phases. A possible explana-

tion of this phenomenon could be the contemporaneous presence during the new moon of a higher semen volume vs. other moon phases.

The aim of this research was to investigate the possible existence of a changing trend in semen parameters during the lunar clock. It should be pointed out that this retrospective study shows some limit concerning mainly the presence of andrological diseases, that are however homogeneously distributed in all examined groups, and the fact that infertile and fertile patients were considered for the analysis.

In any case, a large further study considering semen samples from the same patient for each lunar phase should be set up in order to better clarify whether lunar rhythm could influence male fertility.

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Editorial comment

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Lunar phases are the result of our observation of the appearance of the illuminated portion of the Moon as seen from the Earth. The lunar phases vary cyclically as the Moon orbits the Earth, following to the changing geometry of the Earth, Moon, and Sun. The portion of the illuminated lunar hemisphere that is visible to an observer from the Earth can vary from 100% (full moon, when the Sun and Moon are on opposite sides of the Earth) to 0% (new moon, also named dark Moon-not visible at night-when the Sun and Moon are on the same side). As the amount of illuminated lunar surface as seen from Earth increases, the lunar phases progress from new moon, crescent moon, first-quarter moon, gibbous moon and full moon phases, before returning through the gibbous moon, third-quarter moon, crescent moon and new moon phases. The time between two full moons (or between successive occurrences of the same phase) is about one month (29 days, 12 hours, 44 minutes) on average ¹.

The cyclic variations of lunar phases are used facetiously as a random parameter which something is said to depend on. Sometimes implies unreliability of whatever is dependent, or that reliability seems to be dependent on conditions nobody has been able to determine. A few years ago, engineers of CERN (European Center for Nuclear Research) were baffled by some misleading experiments involving the particle accelerator. As the whole amount of data generated by such device is heavily processed by computers before being evaluated by humans, many people suggested the software was somehow sensitive to the phase of the moon. A few engineers discovered the truth, i.e. the error turned out to be the result of a tiny change in the geometry of the 27 km circumference ring, really caused by the physical deformation of the Earth by the passage of the Moon! This story has entered physics folklore as a Newtonian vengeance on particle physics and as an example of the relevance of the simplest and oldest physical laws to the most

modern science.

The idea that the Moon exerts a determinable influence on living organisms on the Earth is as old as man. The idea is found embedded in the folklore of many ancient societies, ranging from the Celts in early Britain to the Maoris in New Zealand ². As far as recorded comments on the subject are concerned, Pliny the Elder (AD 23-79), the Roman historian, in his *Natural History* gives many instructions on how to regulate agricultural activities according to the cycles of the Moon. Furthermore the ancient Roman (of Hellenistic ethnicity) mathematician, geographer and astronomer Claudius Ptolemeus, known in English as Ptolemy (AD 83-168) reported that the farmers of the Roman Empire “*notice the aspects of the Moon, when at full, in order to direct the copulation of their herds and flocks, and the setting of plants or sowing of seeds, and there is not an individual who considers these general precautions as impossible or unprofitable*” ³.

The light of the sun, moon, planets and stars reaches the earth in regular rhythms and regulates important functions as well as reproductive hormone secretion that is known to have a photoperiodism in humans and other primates involving both neurologic (the retinohypothalamic tract and suprachiasmatic nucleus) and endocrine (the pineal and melatonin) pathways ⁴. The lunar effects on human reproduction have been claimed by several studies showing more births occurring in particular lunar phases with significant seasonal variations in the pregnancy rates also in the case on in vitro fertilization ⁵⁻⁸.

While the effects of lunar phases on female reproductive activity and fertility rates have been investigated, the possible effects of lunar phases in reproductive function in the male have not been elucidated yet in mammals and in particular in man. In the present issue of *The Journal of Andrological Sciences* a study from the University of Siena (Italy) by Moretti et al. ⁹ report the results of a retrospective study evaluating the seminal

standard parameters in a group of young subjects referring to the infertility center for semen analysis from January 2005 to December 2006. In this study the Authors correlated patients' sperm parameters with the different lunar phases the moon was at the time of semen examination. The Authors did not find any difference between sperm parameters of semen samples examined during the different lunar phases. Only mean semen volume of the samples analyzed during the full moon phase was found to be lower to that found during the other lunar phases although with no statistical significance⁹.

From the data of this study it seems that the cyclic lunar phases do not exert any influence on seminal parameters in humans. The observation of a lower semen volume during the full moon phases might easily and humorously recall the well known effect of lunar phases on ocean water obviously due to the gravitational effect that the moon has on earth oceans. But at yet it is known that physiologically semen volume is under the hormonal control of male accessory glands without any known gravitational regulation which influence, if any, could be studied in the astronauts residing for many months in the absence of gravity within the orbiting international space station.

As sentenced by Patrik Holden, director of the Soil Association, when discussing on the beneficial effects of the moon phases on seeds growth: "I accept the lack of scientific evidence to support this approach. But this reflects the inadequacy of current tools to measure its success, rather than the system itself",

there is much job to do on this specific topic but that the moon has some still unknown role in human male fertility seems to be confirmed by some anatomical "humorous" features relating the moon phases to human sperm as depicted in the figure (Figs, 1, 2).

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Figure 1. Lunar phases 1834.

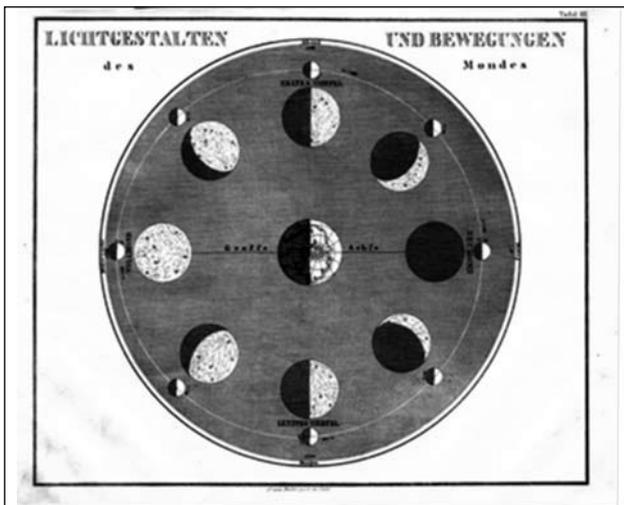
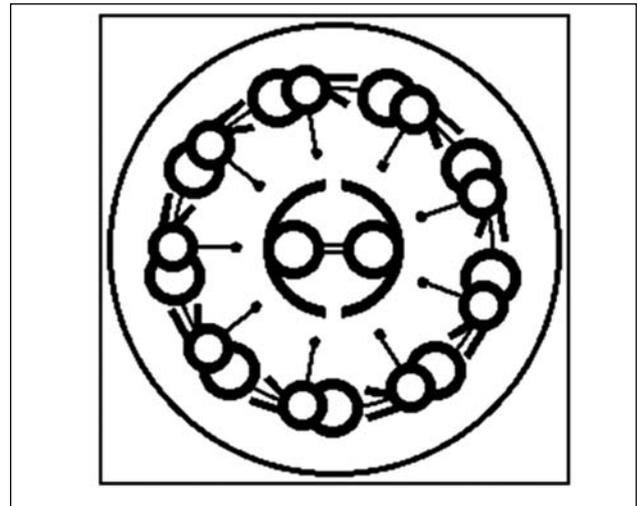


Figure 2. Schematic electron micrograph of a cross section of human sperm tail with outer microtubule doublets and central microtubules.



Recovery of erectile function after bilateral nerve-sparing retropubic radical prostatectomy: an Italian multicenter study

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Summary

Objective. To assess erectile function in patients subjected to bilateral nerve-sparing retropubic radical prostatectomy (NSRRP).

Materials and methods. We assessed 620 patients subjected to bilateral nerve-sparing retropubic radical prostatectomy in six participating centres from 2003 to 2008. The average period of follow-up was twelve months (range 6-18). Erectile function was assessed by means of the IIEF (International Index Erectile Function) before and subsequently 3, 6, 12 and 18 months after the radical prostatectomy. All patients were prescribed Tadalafil at a dose of 20 mg every 3 days for six months at a distance of one month from the operation. In the event of no erectile response, administration of PGE1 at least once a week was advised. Patients were defined potent if the post-operative IIEF was > 17 and if they were capable of achieving penetration during intercourse with their partner.

Results. In the follow-up phase 238 patients out of 620 (38.3%) recuperated their erectile function. 81 out of 238 (34%) presented spontaneous erections; 112 out of 238 (47%) presented drug-assisted (Tadalafil) erections; 45 (18.9%) used intracavernous PGE1s. Erectile function recovery was observed in 73 out of the 238 (30.6%) three months after the operation, in 121 (50.8%) after six months and in 215 (90.3%) after one year. 382 subjects out of the total 620 complained of erectile dysfunction. 273 out of 382 (71.4%) were over 65 years old and 175 out of 382 (45.8%) presented an important comorbidity. 73.5% of the patients took Tadalafil at doses of 20 mg twice/week, 25.1% once/week and 1.6% three times/week. 20% of subjects dropped out within three months after the operation, and 40% within six months. Costs and inefficacy of the rehabilitation protocol were the main causes for drop-out from the study.

Conclusions. Bilateral nerve-sparing retropubic radical prostatectomy has had in all a success rate of 38% of the cases. Age younger than 60 years and absence of comorbidity constitute the main predictive factors of erectile recovery. Only 30% of potent patients do not require drug assistance after the nerve-sparing radical prostatectomy. More than 40% of patients drop out of the rehabilitation regime due to elevated costs and inefficacy of the therapy.

Keywords

Nerve sparing • Retropubic radical prostatectomy • Erectile function • Rehabilitative protocols • Tadalafil • Dropout

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Introduction

The carcinoma of the prostate gland is the most frequent neoplasia and the second cause of death in the male sex. Over the last years, more and more frequent recourse to timely screening programmes has led in general to a progressive increase in the prevalence of this pathology and in particular of the localized stage. This in turn has led indirectly to a parallel increase in the number of cases subjected to radical surgical treatment. The young age of the patients awaiting curative treatment has attracted the attention of urologists, not only for the oncological aspects but also for the functional ones. Urinary incontinence and erectile dysfunction constitute the main long-term complications related to radical prostatectomies, regardless of whether the surgical techniques adopted for access are traditional, laparoscopic or robot-assisted¹. Despite evermore frequent use of the nerve-sparing techniques specifically targeted at preserving the cavernous nerves responsible for the erectile mechanism, data in literature underline how the percentage of patients with erectile dysfunction varies in 20-70% of cases¹. These results may be partially explained by the difficulty in carrying out an appropriate nerve-sparing technique in all cases, considering the anatomical variations of the cavernous nerves and the various penile rehabilitation protocols employed in the post-operational period. In fact, recuperation of the erectile capacity may be reached following an extremely long period of up to 24 months after the surgical operation, during which time the phenomenon of fibrosis may be observed of the *corpora cavernosa* that are responsible for the onset of veno-occlusive erectile dysfunction and which could jeopardize the possible successful outcome of the nerve-sparing surgery². Over the last few years, there has been a tendency in the scientific environment to prescribe a rehabilitative protocol of the *corpora cavernosa* to all patients undergoing nerve-sparing radical prostatectomy³. Moreover, universally accepted criteria regarding drugs, dosages, models and length of rehabilitative protocols are currently still lacking⁴. One last aspect that continues to receive scarce attention in literature concerns the cost of these rehabilitation protocols and the percentage of patients adhering to the prescribed protocol. Bearing these considerations in mind, we decided to carry out this study with a view to clarifying the following issues: assessment of recuperation of erectile function in patients undergoing nerve-sparing radical prostatectomy; identification of predictive factors of a positive response and verification of actual compliance of

patients with the above-mentioned rehabilitation protocols.

Materials and methods

Data relating to all patients undergoing NSSRP were collected prospectively in six centres participating in the study (Negrar/Verona; Merano; Bolzano; Vicenza; Udine) in the period from January 2003 to February 2008. Selection criteria for the nerve-sparing surgery varied from centre to centre. However, all patients were potent before the operation and strongly motivated to undergo surgery. Patients were subjected to a retropubic anatomical radical prostatectomy in line with the Walsh technique. All patients were assessed pre-operation with regard to presence of cardiovascular disease, diabetes mellitus, endocrine pathologies and any other possible causes capable of predicting a possible future failure to recuperate erectile potency. Erectile function before surgery was determined through use of the International Index Erectile Function (IIEF-5). This questionnaire was also used to measure erectile function in the course of the follow-up period at three, six, twelve and eighteen months after surgery. The current assessment was carried out on an average follow-up of 12 months (range 6-18). Rehabilitation of the *corpora cavernosa* was started one month after the radical prostatectomy and included administration of Tadalafil 20 mg every three days for six months. Patients who did not respond to treatment with Tadalafil 20mg were prescribed Alprostadil on-demand at the minimum effective dose (range 5-20 mcg). After surgery, patients were defined potent with IIEF values > 17 and ability to regularly achieve penetration during intercourse with their partner.

Results

In the period of assessment 620 bilateral nerve-sparing retropubic radical prostatectomies were performed. Patients presented ages varying from 46-74 years. In the follow-up phase of twelve months, 238 out of 620 patients (38.3%) were potent and capable of achieving penetration duration intercourse (Fig. 1). In this subgroup of patients, 81 out of 238 (34%) presented spontaneous erectile activity without any therapeutic assistance. This subpopulation consisted of patients aged between 46 and 60 years without any significant comorbidity. 112 patients presented a satisfying recovery of erectile potency only after administration of PDE5 inhibitors (Tadalafil 20 mg). Lastly, 45 patients (18.9%) resorted to in-

Figure 1. Erectile function recovery 12-month after bilateral nerve-sparing retropubic radical prostatectomy (N = 620).

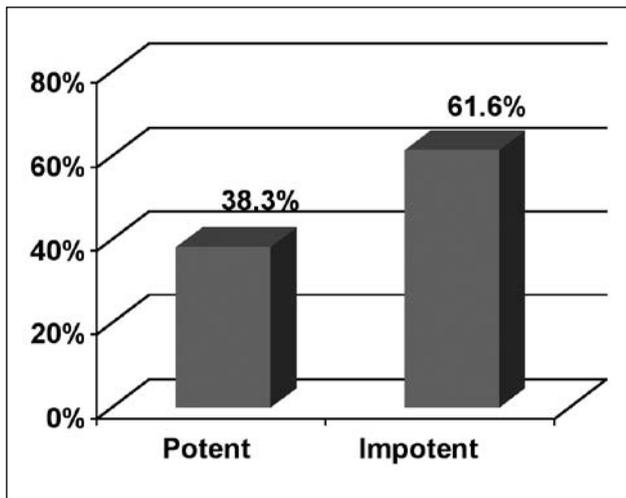
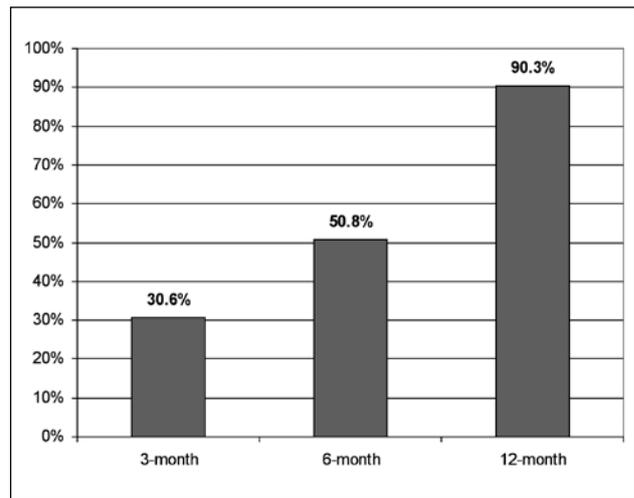


Figure 2. Potency recovery rates 3, 6 and 12 months following radical retropubic prostatectomy (N = 238).



tracavernous therapy with PGE1 at dosages varying between 5 and 20 mcg (Table I).

With regard to the post-operation period, 73 patients (30.6%) presented recovery of erectile activity within the third month after surgery, 121 (50.8%) within six months and 215 (90.3%) within 12 months (Fig. 2). Analyzing the 382 patients (61.6%) who at a year after surgery did not present any signs of recovery of erectile function, we observed that 109 out of 382 (28.6%) were aged < 65 years while 273 (64.2%) were over 65 years of age. Moreover, 175 (45.8%) presented significant cardiovascular comorbidity before surgery. In 51 patients (13.3%), assessment of the erectile function was not reliable due to the necessity to administer hormonal therapy after surgery. As for compliance of the patients with the advised rehabilitation protocol, only 73.5% adhered to the recommendations furnished at the moment of discharge from hospital. 25.1% reported weekly assumption of Tadalafil, while in contrast 1.6% took the drug three times a week (Fig. 3). The percentage of patients who dropped out of the proposed rehabilitation programme was 20% after one month of treatment and 40% within six months. Reasons for drop-out were correlated to the presentation of

side effects in about 10% of cases. In the remaining 90% of cases drop-out was attributed to costs of the therapy and dissatisfaction on behalf of the patients with the results obtained.

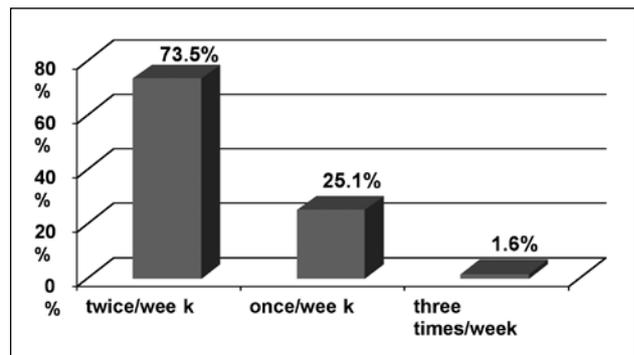
Discussion

The results of this study underline how in a subpopulation of patients subjected to bilateral nerve-sparing retropubic radical prostatectomy, in six urology centres in northeast Italy, the percentage of success at twelve months stands at about 35% of cases. The best results were registered in patients aged < 60 years with no significant comorbidity. Furthermore, only 34% of the potent patients do not have to resort to pharmacological support therapies. In particular, 47% of potent patients utilize PDE5 inhibitors and 19% use prostaglandins. These results are less favourable than those reported in literature in the context of the series of references, which may be

Table I. Percentage of spontaneous or drug-assisted erection after nerve-sparing bilateral radical retropubic prostatectomy.

	PATIENTS (N = 238)	PERCENTAGE (%)
Spontaneous	81	34.0
PDE5 (Tadalafil 20 mg)	112	47.1
PGE1 (Alprostadil 5-20 mcg)	45	18.9

Figure 3. Compliance of patients studied in advised programme of rehabilitation.



partially explained in consideration of the different volume of operations performed¹. Moreover, the data of this study underline how much success in the field of nerve-sparing surgery depends on an attentive selection of the patients to be operated⁵. This last aspect could represent a potential bias for our study, in view of its multicentricity and the non-restrictive enrolment techniques adopted by some of the centres which participated.

Another issue emerging from this study regards patients' poor compliance with the rehabilitative protocols for the *corpora cavernosa*. 25% of our patients did not adhere to the indications furnished at the time of discharge from hospital and a good 60% interrupted the rehabilitation from between the third and sixth months onwards due to elevated costs and reduced efficacy. In our opinion these data offer interesting points of discussion on aspects which are still to date very controversial in this field. It is likely that the length of our rehabilitation protocol was excessive; a programme no longer than four months long, more in line with the data in literature, brought the drop-out rate down to 20-30%⁶.

We consider that these data take on particular significance in the light of the recent work published by Montorsi et al. on the use of Vardenafil on demand in this category of patients. The randomised, multicentric study which compares a population of patients treated with Vardenafil bedtime to those treated with Vardenafil on demand or placebo has evidenced how rehabilitative therapy does not produce better results in comparison with drugs taken on demand⁷. This work may therefore constitute a starting-point for undertaking a new, more economical method of treating patients after NSSRP.

Another factor to examine which may help improve therapies in future years may be correlated to the less traumatic effect induced on the cavernous nerves during nerve-sparing surgery through use of robot-assisted laparoscopic surgery.

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Editorial comment

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Radical prostatectomy (RP) is the most widely performed procedure for patients with clinically localized prostate cancer (PCa) and a life expectancy of at least 10 years¹. However, this procedure may be associated with treatment-specific sequelae affecting health-related quality of life. Since the diagnosis of PCa is becoming ever more frequent in younger patients, erectile function impairment certainly represents the most significant disorder negatively impacting the overall sexual health in patients who underwent RP. Research in post-RP recovery indicates that approximately 25-75% of men experience postoperative erectile dysfunction (ED)². This broad range of postoperative erectile function impairment can be attributed to

several study design factors, including differences in baseline tumor and sexual health sample characteristics, surgical technique, surgeons' surgical volumes, length of follow-up from surgery, and the quality of study methodologies in assessing both prevalence and severity of male ED³.

Vecchio et al. reported the results of a multicentric study assessing the rate of erectile function (EF) recovery after bilateral nerve-sparing RP (BNSRP)⁴. The authors reported a rate of erectile function recovery (defined as a post op IIEF-EF > 17) of 38% at 1 year after surgery. As recognized by the Authors, this rate is slightly lower than the results from major academic centers, with higher volume. However, the follow-up is still too

short (mean follow-up 12 months) in order to definitively assess the rate of EF recovery. Moreover, the study included patients treated with either tadalafil every 3 days or intracavernous injections with alprostadil, if not responding to oral compound. It may be hypothesized that other treatment strategies, with different oral compounds and/or different schemes of assumption, may provide different results. The results reported by Vecchio et al. are encouraging and the Authors should increase their follow-up and vary their therapeutic strategy in order to individualize the optimal treatment for each patients. These corrections may further improve the rate of potency recovery after surgery.

However, which are the predictive factors for EF recovery after BNSRP? Pre-operative potency represents a major key factor associated with erectile function recovery after surgery and candidates for BNSRP should indeed be ideally potent prior to the procedure⁵. This is of major importance as patients who report some degree of ED prior to the procedure are more likely to develop severe ED postoperatively, regardless the surgical technique used. Similarly, co-morbid conditions seem also to negatively affect the recovery of spontaneous erections postoperatively, as they may impact on baseline penile hemodynamics⁵.

In order to preserve erectile function a rigorous NS technique is mandatory⁶. The cavernous nerves course adjacent to small vessels forming the so called neurovascular bundle (NVB) along the postero-lateral margin of the prostate, bilaterally, and are located between the visceral layer of the endopelvic fascia and the prostatic fascia. However, recent studies have demonstrated that the course of NVB is more complex than what historically thought, with a wide distribution of the nerve fibers belonging to the NVBs which are spread all around the prostatic capsule⁷. Based on the latter findings, some Authors advocate a modification of the standard nerve sparing approach, suggesting an intrafascial RP, aimed at maximizing the nerve fibres preservation^{6,8}.

The advent of phosphodiesterase type 5 inhibitor (PDE5-I) in the treatment of ED has deeply modified the management of post-prostatectomy ED. Several Authors investigated various strategies aimed at identifying a potential prophylaxis and/or treatment for patients affected with erectile dysfunction after RP. A key post-RP factor associated with erectile function improvement is represented by administration of pro-erectile drugs. Historically, patients complaining of postoperative ED had several therapeutic options that may increase the likelihood of obtaining valid erections for satisfactory sexual intercourse, including intracavernous injections, urethral microsuppository, vacuum device therapy, and penile implants³. At present, PDE5-I represent the first-line oral pharmacotherapy for the treatment of post-RP ED in patients who underwent either a unilateral nerve-sparing (UNS) or BNS surgical approach. Since its introduction in 1998, several studies have shown that PDE5-I are significantly efficacious in ED patients after BNSRP and several success predictors have been clearly outlined^{5,6}.

Sildenafil is the drug which has been studied most extensively in this patient subgroup since its introduction in 1998. In general terms, sildenafil has been acknowledged to obtain the best results in young patients (< 60 years old age) in patients treated with a bilateral NS procedure and in patients who show some degree of spontaneous post-operative erectile function. Typically the response to sildenafil has been shown to improve as time passes by after the procedure: best results are seen from 12 to 24 months post-operatively. In different trials, the response rate to sildenafil treatment for ED after RP ranged from 35 to 75% among those who underwent NS surgery and from 0 to 15% among those who underwent non-NS surgery⁹.

Tadalafil was also evaluated in a large multicenter trial conducted in Europe and in USA involving patients with ED following a bilateral NS procedure. Seventy-one percent of patients treated with tadalafil 20 mg on-demand reported an improvement of their erectile function as compared to 24% of those treated with placebo ($p < 0.001$). Tadalafil 20 mg allowed to achieve a 52% rate of successful intercourse attempts which was significantly higher than the 26% obtained with a placebo ($p < 0.001$)¹⁰.

Similarly, vardenafil has been tested in patients treated with ED following a uni- or bilateral NS prostatectomy in a multicenter, prospective, placebo-controlled, randomized study from USA and Canada. Seventy-one percent and 60% of patients treated with a bilateral NS procedure reported an improvement of erectile function following the administration of vardenafil 20 and 10 mg, respectively. A positive answer to sexual encounter profile (SEP) 2 question was seen in 47 and 48% of patients using vardenafil 10 and 20 mg, respectively. A positive answer to the more challenging SEP 3 question was seen in 37 and 34% of patients using vardenafil 10 and 20 mg, respectively¹¹.

Despite a great interest, only few clinical trials assessed the role of chronic (namely, continuous/prophylactic) PDE5-I in men treated with RP. The basic concept would be to administer a PDE5-I at bedtime in order to facilitate the occurrence of nocturnal erections which are believed to have a natural protective role on the baseline function of the corpora cavernosa. Montorsi et al. showed that when sildenafil 100 mg is administered at bedtime in patients with ED of various etiologies, the overall quality of nocturnal erections as recorded with the RigiScan device is significantly improved than those obtained after the administration of placebo¹². Bannowsky et al. evaluate the effect of low-dose sildenafil for rehabilitating erectile function after NSRP. Forty-three sexually active patients were randomized to receive either placebo or sildenafil 25 mg/day at night. In the group taking sildenafil, 47% achieved and maintained a penile erection sufficient for vaginal intercourse at 1 year after NSRP, compared with 28% in the control group with no low-dose sildenafil¹³. Padma-Nathan et al.¹⁴ investigated the prospective administration of sildenafil 50 and 100 mg vs. placebo, daily and at bedtime, in patients undergoing bilateral NSRP who were potent pre-operatively. Interestingly, 27% of the patients receiving sildenafil were responders, i.e., demonstrated return

of spontaneous normal erectile function compared to 4% in the placebo group ($p = 0.0156$).

Surprisingly, the potential benefit induced by a continuous PDE5-I has rarely been compared to an on demand PDE5-I administration schedule in methodologically rigorous studies. As reported by Vecchio and colleagues, the only study investigating the role of on-demand vs. daily administration of PDE5-I after BNSRP has been recently published¹⁵. In this randomised, double-blind, double-dummy, multicentre, parallel group study, 628 men were randomized to receive vardenafil nightly, vardenafil on-demand or placebo for 9 months. Surprisingly, in contrast to the prophylactic use of PDE5 inhibitors for penile rehabilitation and treatment of ED in men following NSRP surgery, this study suggest a paradigm shift towards on-demand dosing with PDE5 inhibitors for the treatment of ED in patient treated with BNSRP.

In conclusion, radical prostatectomy is an increasingly performed procedure in patients with prostate cancer. As the mean age of this patient subgroup is progressively declining due to the advent of prostate-specific antigen testing and prostate cancer screening programs, the demand for optimal post-operative quality of life is becoming more important. Use of on-demand oral treatments in patients subjected to RP has been shown to be effective and safe, with better results seen in select young patients treated with a bilateral NS approach. Pharmacological prophylaxis, either with oral or intracavernosal drugs, may potentially have a significantly expanding role in the future strategies aimed at preserving post-operative erectile function. Large, multicentric, placebo-controlled trials are needed in order to identify the best regimen able to provide the best strategy for the recovery of erectile function after radical prostatectomy.

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Prevalence of erectile dysfunction and lower urinary tract symptoms in cyclists

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Summary

Objective. To verify the presence of erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) in a population of cyclists. We also assessed the possible presence of prospective factors predictive of impairment in sexual and urinary functioning in cyclists.

Materials and methods. The data collected in a study population consisting of 404 cyclists were compared with those of a control population of 408 men. All the subjects enrolled in the study were invited to fill in a specific questionnaire designed for the purpose of collecting information on their general characteristics. For assessment of the LUTS the IPSS (International Prostate Symptom Score) was used, while sexual functioning was assessed by means of the IIEF (International Index Erectile Function). The characteristics of all the recruited subjects were correlated with the IPSS and IIEF scores. Subsequently the characteristics and results recorded for the cyclist population were compared with those of the control group. Multiple logistic regression was used for the multivariate analysis of the data. In the group of cyclists, the same analysis was used to see whether, and to what extent, the severity of each symptom reported by the athletes examined could be attributed to the characteristics of the subjects enrolled.

Results. Of the whole sample of 812 subjects studied, the IPSS, QL AND IIEF-5 showed to be significantly correlated ($p < 0.001$). The IPSS, QL, and IIEF-5 revealed significantly worse scores in the population of cyclists ($p < 0.001$). Moreover, in the multivariate analysis, age and amount of cycling practised showed to be the most predictive risk factors of a worsening of the urinary and erectile functioning. Considering solely the group of cyclists, the symptoms of compression of the perineal cavernous spaces when seated on the bicycle saddle showed to be significantly correlated with age and level of intensity of cycling.

Conclusions. The population of cyclists presents a higher prevalence of ED and/or LUTS compared to that found in the control group of non-cyclists. The most important predictive factors capable of interacting with sexual and urinary functioning were age and cycling, as well as the intensity of cycling within the cyclist group.

Introduction

The presence and intensity of the lower urinary tract symptoms (LUTS) secondary to cervico-urethral obstruction is significantly correlated

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to an increase of the prevalence of sexual dysfunctions¹, including erectile dysfunction (ED), ejaculatory dysfunctions (Dej) and loss of libido. There are multiple physiopathological hypotheses at the basis of this correlation (Table I), suggesting a cause-effect relation that to date has still not been exhaustively explained. Clearly the relation between LUTS and sexual dysfunctions may have a significant impact on the quality of life of those affected.

An increase in incidence of the sexual dysfunctions has been observed above all in cyclists who cover large distances^{11 12} in particular erectile dysfunction, that may be attributed to compression of the neurovascular structures of the genito-perineal region¹³. For this reason technological research in recent years has focused on realizing a model of saddle that is capable of preventing excessive compression in the perineal region^{14 15} while at the same time limiting possible repercussions regarding the sexual functions and also reducing the incidence of LUTS. In particular, Leibovitch et al. underlined the fact that the lower urinary tract symptoms seem to present more frequently in the cyclist population in comparison with the control group¹⁶.

The aim of this study is to carry out a large-scale epidemiological investigation in order to examine the actual incidence of ED/LUTS in a population of cyclists and in a comparative group of non-cyclists, considering also the possibility of determining factors capable of predicting worsening of sexual and urinary functioning.

Materials and methods

We enrolled 404 amateur cyclists who covered average to long distances on their bicycles. Recruitment was carried out through distribution of invitations in cycling-gear shops or sport/recreational clubs. The control group for comparison consisted of 408 volunteers from various work environments who

participated spontaneously in the project. Some of these subjects reported practising sports other than cycling at an amateur level, while others referred no physical activity at all. All participants in the study filled in a specific questionnaire prepared by the authors for the purpose of collecting general information (Table II). Also the IPSS (International Prostate Symptom Score) and the IIEF-5 (Index Erectile Function) were completed for assessment of the presence of LUTS and of sexual functioning. Subjects were classified according to age (≤ 39 years; 40-49 years; ≥ 50 years) and severity of symptoms: mild-moderate LUTS (IPSS ≤ 19) or severe (IPSS ≥ 20); QoL (normal = 0-3; pathological = 4-6); moderate erectile dysfunction (IIEF ≥ 11) or severe (IIEF ≤ 10). The results obtained in the population of cyclists were then compared to those of the control group. A sample of about 400 subjects per group, in the case of prevalences around 50% (worst case), permits us to identify differences of 10% between cyclists and non-cyclists as being 95% significant (evaluation obtained with the Fleiss method)¹⁷.

For the statistical analysis we studied the bivariate relations between the characteristics of the subjects being examined and the IPSS, QoL and IIEF-5 scores. In particular, the parametrical or non-parametrical correlations, and any dependencies, between general characteristics and results of the questionnaires were assessed by means of the chi-

Table I. Physiopathological hypotheses LUTS/sexual dysfunctions.

Theory of autonomous hyperactivity ²⁻³
Theory of endothelial dysfunction ⁴⁻⁵
Theory of activation of the Rho kinase system ⁶
Theory of the metabolic syndrome ⁷
Theory of atherosclerosis and of associated chronic ischemia ⁸
Theory of anatomical factors for volumetric increase of the prostate and of the detrusor urinae muscle ⁹
Hormone theory ¹⁰

Table II. Questionnaire for data-collection filled in by participants.

Age (< 39; 40-49; > 50)
Weight
Smoking
Sports practised
Concomitant illnesses
Previous surgical operations
Drugs taken
Cyclist
Cyclist for 10 years
Hours on bike/week (< 3; 3-6; > 6)
Urinary infections
Tingling sensation in perineal region
Perineal pain
Perineal nodules
Haematuria
IPSS-QL
IIEF-5

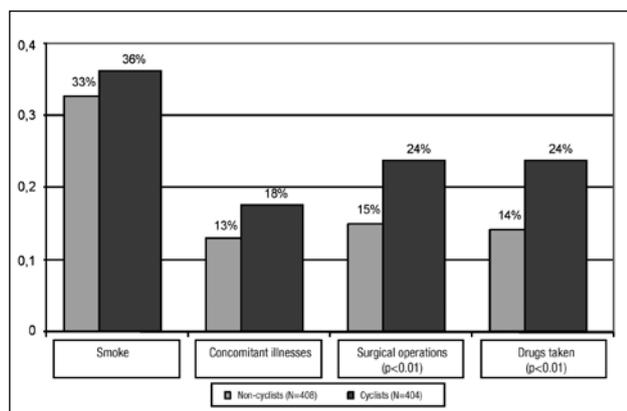
squared test. Differences between the two groups in terms of IPSS, QoL and IIEF-5 were analysed using Student's t-test. The multivariate analysis was performed through application of multiple logistic regression. Solely in the group of cyclists, the multivariate analysis was carried out to see whether and to what extent the presence and severity of each symptom (urinary infections, tingling sensation in the perineal area, perineal pain, perineal nodules, haematuria) could depend on the characteristics of the subjects recruited. The results of the logistic regression were expressed as odds ratio (OR) and confidence intervals (CI) at 95%. The statistical significance was considered for two-tailed values of $p < 0.05$. Statistical analysis of the data was performed with SPSS 12.0.21 for Windows, SPSS INC., Chicago, Illinois.

Results

The descriptive characteristics of the sample are shown in Table III. The average age of the 812 subjects was 46.4 years (± 11.5 SD) (standard deviation) and the average weight was 74.8 kg ± 6.9 . There were some smokers among the subjects in the sample (non-cyclists 32.7%, cyclists 36.1%); others were affected by concomitant pathologies (non-cyclists 13%, cyclists 17.6%), or had already undergone abdomen-pelvic surgery (non-cyclists 15%, cyclists 23.8%).

Figure 1 shows the distribution of the main characteristics of the cyclists and non-cyclists, highlighting that the percentages of surgical operations undergone and drugs taken were significantly different in the two groups ($p < 0.01$). The cyclists and the control group had an average age of 47.8 and 45 years respectively; statistical analysis also considered the subjects of each single group classified in three age-groups as follows: ≤ 39 years; 40-49 years; ≥ 50 years.

Figure 1. Characteristics of the population studied.



The median scores on the IPSS (non-cyclists: $5.6 \pm 5,1$; cyclists: $13.9 \pm 7,3$), on the IIEF-5 (non-cyclists: $22.4 \pm 2,6$; cyclists: $18.5 \pm 3,7$) and on the QoL (non-cyclists: $1.2 \pm 0,9$; cyclists: $3.0 \pm 1,3$) were signifi-

Table III. Descriptive characteristics of the sample.

	TOTAL	NON-CYCLISTS	CYCLISTS
<i>No. of patients</i>	812	408	404
<i>Average age</i>	46,4	45,0	47,8
\pm SD	11,5	12,1	10,6
-39	27%	33%	22%
40-49	26%	26%	25%
50+	47%	42%	52%
<i>Average weight</i>	74,8	75,2	74,4
\pm SD	6,9	7,1	6,7
<i>Smoking</i>	279	133	146
%	34,4%	32,7%	36,1%
<i>Sport</i>	549	154	404
%	67,6%	37,7%	100%
<i>Concomitant illnesses</i>	124	53	71
%	15,3%	13,0%	17,6%
<i>Surgical operations</i>	157	61	96
%	19,3%	15,0%	23,8%
<i>Drugs taken</i>	154	58	96
%	19,0%	14,2%	23,8%
<i>IPSS</i>	9,7	5,6	13,9
\pm SD	7,5	5,1	7,3
<i>IIEF-5</i>	20,5	22,4	18,5
\pm SD	3,8	2,6	3,7
<i>QL</i>	2,1	1,2	3,0
\pm SD	1,4	0,9	1,3
<i>Cyclist for</i>			
-10 years			128
%			31,7%
+10 years			276
%			68,3%
<i>Hours on bike</i>			
-3 hours/wk			48
%			11,9%
3-6 hours/wk			241
%			59,7%
+6 hours/wk			115
%			28,5%

cantly different between the two groups ($p < 0.001$). Graphs 2-4 show the distribution of the subjective evaluations of state of health (IPSS, QL, IIEF-5) in the two groups in question and in relation to the three age-groups considered.

In the total sample of subjects recruited, the IPSS, QoL and IIEF-5 showed to be significantly correlated ($p < 0.001$) with regard to almost all of the characteristics of the participants: age, concomitant illnesses, surgical operations, drugs administered, sport practised in general, cycling ($p < 0.001$).

Table IV illustrates how much the characteristics of the subjects initially assessed significantly influence the scores of the IPSS and QoL. With regard to the IIEF-5, the test is mainly non-significant or not applicable due to the low number of severe cases recorded, all of whom were cyclists (Tab IV). In the multivariate analysis, age and cycling emerged as the most significant risk factors for worsening of erectile and urinary functioning. The probability that cyclists have high scores on the IPSS was ten times greater (Confidence Interval at 95%: 5.3-20.7) compared to the non-cyclists. QoL is correlated to urinary symptoms and the probability of scoring between 4-6 is almost 27 times greater for cyclists (CI 12.8-56.7). The probability of having moderate or severe scores on the IIEF-5 is 15 times greater for cyclists (CI 7.8-30.1). As for age, subjects in the age-groups of 40-49 years and over 50 years present a probability of having severe scores on the IPSS respectively more than 20 times (CI 2.9-164.3) and more than 30 times (CI 4.3-235.6) greater when compared to subjects younger than 40 years.

When analyzing solely the group of cyclists, the presence of urinary infections, tingling sensation in the perineal area, perineal pain and haematuria emerged as being statistically correlated to severity of LUTS and to the presence of erectile dysfunction

(Tab. VI). The multivariate analysis illustrates how the urinary infections, tingling sensation and perineal pain depend significantly on age and on intensity of cycling (intended as number of hours per week), while only occasionally on smoking (urinary infections) or number of years spent cycling (perineal pain). The probability that cyclists over 40 years old present urinary infections or perineal nodules is respectively 2.4 (CI 1.4-4.2) and 2.9 (CI 1.6-5.1) times greater than those younger than 40 years old. For the same symptoms the probability is more than 4 times greater for those who do more than 6 hours of cycling a week (more than 3 hours for the urinary infections), compared to those who do less than 3 hours/week. The presence of haematuria does not appear to significantly depend on any of the predictors considered.

Discussion

Our epidemiological study, carried out on a vast sample of subjects, has revealed a greater incidence of erectile dysfunction and LUTS in the population of cyclists compared to the control group of subjects not practising this sport. Moreover, the results obtained in our study demonstrate that when considering solely the group of cyclists, age and intensity of cycling (hours/week) are the two factors that prevalently influence urinary and erectile function in a negative sense. These data, which refer to an Italian population, are in line with what has already emerged in international literature. In cyclists, prevalently in those who cover long distances^{11,12}, an increase has been observed in the incidence of pathologies that may be attributed to direct compression of the structures of the genito-perineal region. This compression is responsible for the manifesting of various clinical

Table IV. Impact of the principal characteristics of the population studied on IPSS, IEF-5 and QoL (chi-squared).

	IPSS	IIEF-5	QoL
Age	< 0,001	NA	< 0,001
Weight	= 0,019	NA	= 0,047
Smoking	< 0,001	NS	< 0,001
Sports practised	< 0,001	= 0,036	< 0,001
Concomitant illnesses	< 0,001	NS	< 0,001
Surgical operations	< 0,001	NS	< 0,001
Drugs taken	< 0,001	NS	< 0,001
Cyclist	< 0,001	= 0,002*	< 0,001

* Fisher's exact test.

Figure 2. IPSS: comparison between cyclists and non-cyclists.

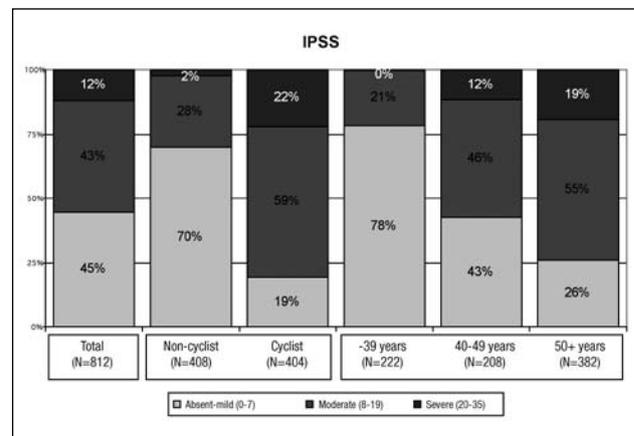


Table V. Multivariate analysis on whole population studied. Multiple logistic regression.

PREDICTORS	IPSS MILD-MODERATE (697) VS. SEVERE (87)		IIEF-5 ABSENT-MILD (684) VS. MODERATE-SEVERE (126)		QOL 0-3 (631) VS. 4-6 (103)	
	Severe/total (%)	OR (CI at 95%)	Moderate-severe/total (%)	OR (CI at 95%)	[0-3]/total (%)	OR (CI at 95%)
<i>Age</i>						
-39	1/222 (0)	Reference	8/222 (4)	Reference	2/222 (1)	Reference
40-49	24/208 (12)	21,7 (2,9-164,3)**	42/208 (20)	5,8 (2,5-13,1)**	38/208 (18)	21,57 (5-93,0)**
50+	74/382 (19)	31,8 (4,3-235,6)**	77/382 (20)	4,2 (1,87-9,3)**	107/382 (28)	29,7 (7,0-125,4)**
<i>Weight</i>						
-69	8/142 (6)	Reference	18/142 (13)	Reference	16/142 (11)	Reference
70-79	74/519 (14)	2,5 (1,1-5,6)*	81/519 (16)	1,3 (0,7-2,4)	98/519 (19)	1,7 (0,9-3,3)
80+	17/151 (11)	1,7 (0,7-4,3)	28/151 (19)	1,7 (0,8-3,5)	33/151 (22)	2,1 (1,0-4,6)
<i>Smoking</i>						
No	49/532 (9)	Reference	76/532 (14)	Reference	76/532 (14)	Reference
Yes	50/279 (18)	1,5 (0,9-2,4)	51/279 (18)	1,0 (0,6-1,6)	71/279 (25)	1,6 (1,0-2,6)*
<i>Cyclist</i>						
No	10/408 (2)	Reference	10/408 (2)	Reference	8/408 (2)	Reference
Yes	89/404 (22)	10,4 (5,3-20,7)**	117/404 (29)	15,4 (7,8-30,1)**	139/404 (34)	26,9 (12,8-56,7)**
<i>Concomitant illnesses</i>						
No	65/688 (9)	Reference	96/688 (14)	Reference	104/688 (15)	Reference
Yes	34/124 (27)	1,8 (0,9-3,5)	31/124 (25)	1,0 (0,5-1,9)	43/124 (35)	1,5 (0,8-2,9)
<i>Surgical operations</i>						
No	60/655 (9)	Reference	83/655 (13)	Reference	92/655 (14)	Reference
Yes	39/157 (25)	1,2 (0,7-2,2)	44/157 (28)	1,6 (0,9-2,7)	55/157 (35)	1,5 (0,8-2,5)
<i>Drugs taken</i>						
No	59/658 (9)	Reference	84/658 (13)	Reference	94/658 (14)	Reference
Yes	40/154 (26)	1,1 (0,6-2,2)	43/154 (28)	1,4 (0,7-2,6)	53/154 (34)	1,0 (0,5-1,8)

** p ≤ 0.001; * p ≤ 0.05.

symptoms such as tingling sensation in the perineal area, sexual dysfunctions, erectile deficit, prostatitis, LUTS, priapism, haematuria, perineal nodular lesions, infertility etc., all of which may exert a negative influence on the sexual and urinary functions of the cyclist.

It is commonly known that cycling has become increasingly popular in recent years, which has led to the development of new technical potential and

sporting gear. The data of our study support the need for progress in this field to advance in the realization of specific models of bicycle saddles that are designed to prevent excessive compression of the perineal region^{14,15}. With this sort of technological progress, the possible repercussions on sexual functioning due to compression of the neuro-vascular structures may be limited, thus permitting also a reduction of the incidence of lower urinary tract symptoms which seem to be more frequently found in the cycling population compared to those who do not practise this sport¹⁶.

Research has thus moved in the direction of realizing bicycle saddles that are capable of avoiding excessive perineal compression. An important contribution has been that of identifying a product which limited the compression of the neuro-vascular structures while at the same time presenting a conformation compatible with the exigencies of cyclists.

The SMP¹⁵ saddle seems to have many of the tar-

Table VI. Impact of the principal symptoms registered in the population of cyclists on IPSS, IIEF and QoL.

	IPSS	IIEF-5	QOL
Urinary infections	< 0,001	NS	< 0,001
Tingling in perineal area	< 0,001	< 0,05	<0,001
Perineal pain	< 0,001	< 0,005	< 0,001
Perineal nodules	< 0,1	< 0,005	NS
Ematuria	< 0,01	< 0,05	< 0,005

Figure 3. QoL: comparison between cyclists and non-cyclists.

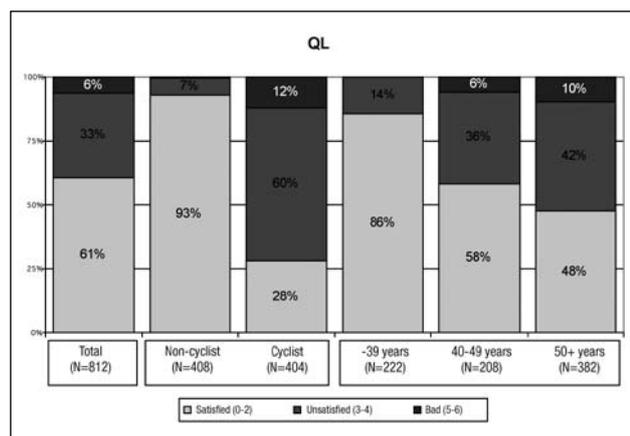
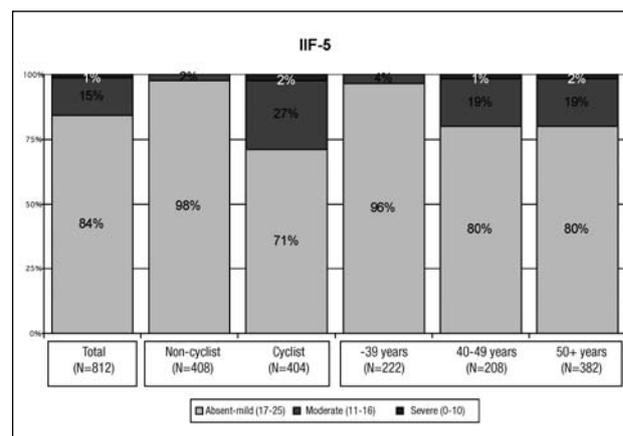


Figure 4. IIEF-5: comparison between cyclists and non-cyclists. SMP saddle



geted requisites, presenting a sitting position that is uniformly distributed over the gluteal muscles, the ischial tuberosity and the ischium while leaving the perineal region clear. Moreover, the inclined 'beak' of the saddle leaves the external genitalia completely free of compression. These advantages have been acquired in consideration of the dimensions preferred by cyclists. In fact, this model presents a posterior width of 140 mm and an anterior width of 45 mm where the structure has an inclination of

60°. The central width is 75 mm, while the geometry of the saddle conforms to the musculature of the thighs, the specific purpose being to avoid rubbing or friction of the gracilis and adductor muscles which can subsequently provoke irritation in the lower limbs during the action of pedalling. In actual fact, it is typical of professional cyclists to pedal with knees turned in towards the frame of the bike in order to increase strength and output.

In line with what has been widely reported in many

Table VII. Multivariate analysis in the cyclist population. Multiple logistic regression: cyclist population.

PREDICTORS	OR (CI AT 95%)				
	URINARY INFECTIONS	TINGLING SENSATION IN PERINEAL AREA	PERINEAL PAIN	PERINEAL NODULES	HAEMATURIA
<i>Age</i>					
-39	Reference	Reference	Reference	Reference	Reference
+40	2,4 (1,4-4,2)**	2,9 (1,6-5,1)**	1,8 (1,1-3,0)*	1,2 (0,5-2,5)	1,8 (0,6-5,5)
<i>Weight</i>					
-74	Reference	Reference	Reference	Reference	Reference
+75	1,1 (0,7-1,7)	1,7 (1,0-3,0)*	1,2 (0,7-1,9)	0,9 (0,5-1,6)	0,9 (0,4-1,9)
<i>Smoking</i>					
No	Reference	Reference	Reference	Reference	Reference
Si	1,6 (1,0-2,5)*	1,2 (0,7-2,1)	1,3 (0,8-2,2)	2,5 (1,4-4,6)*	1,8 (0,8-3,9)
<i>Cyclist for</i>					
-10 years	Reference	Reference	Reference	Reference	Reference
+10 years	0,8 (0,5-1,2)	1,5 (0,9-2,6)	2 (1,2-3,3)*	1 (0,5-2,1)	2,2 (0,8-6,3)
<i>Hours on bike</i>					
-3 hours/wk	Reference	Reference	Reference	Reference	Reference
3-6 hours/wk	4,1 (1,8-9,5)**	1,5 (0,7-2,9)	2,8 (1,4-5,4)*	1,6 (0,5-4,8)	0,8 (0,2-3,0)
+6 hours/wk	4,5 (1,8-11,3)**	4,8 (1,9-12,2)**	2,6 (1,2-5,7)*	1,8 (0,5-6,0)	1 (0,2-4,2)

* p ≤ 0,05; ** p ≤ 0,001.

other studies, also our contribution has highlighted the prevalence of ED and LUTS in the cyclist population compared to a control group; as such, our findings confirm that cyclists undoubtedly represent a category which deserves monitoring with greater attention for its higher incidence of urological and andrological pathologies.

Conclusions

The data obtained from our epidemiological study have evidenced how cyclists present a very significant incidence of ED and LUTS in comparison with a non-cyclist population. The most important predictive factors that are capable of interacting with sexual and urinary functioning are age and cycling. Within the cyclist group, intensity of cycling (in terms of hours/week) seems to be the most important element for determining a worsening of erectile and urinary functions. The onset of symptoms such as tingling sensation and perineal pain, together with urinary infections in the cyclist population depends significantly on the age of the subject and on the intensity with which he practises cycling.

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Doctor, I have a problem: “I have a terrible headache”. Case report of a locally advanced squamous cell carcinoma of the penis

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Summary

Penile carcinoma is an uncommon malignant disease, with low incidence and prevalence in developed countries. Patient presentation with a locally advanced disease is particularly uncommon. We aim to present an unusual case of penile cancer due to both the exceptionally locally advanced disease and uncommon presentation variety. A 75 year old homeless man was brought to our attention following observation of a necrotic mass at the pubic with deep central ulceration and a total absence of genitals. The pathological evaluation showed a squamous cell carcinoma of the penis. Bone scintigraphy showed metastasis in several bone districts without any lymph node metastases found at total body CT-scan. The patient died 45 days after hospitalization. The case was explained and a revision of the literature in order to discuss the uncommon clinical presentation and natural history was, then, performed.

Keywords

Squamous cell carcinoma • Penile cancer • Prognosis • Outcome

Introduction

Penile cancer is uncommon in most Western countries, affecting about 1/100,000 men and accounting for less than 0.5% of all neoplasm in men in the United States (US) and Europe ^{1,2}. Moreover, in 2007, according to the American Cancer Society, 1,280 cases were diagnosed, with about 290 deaths ³. Nevertheless, it is common in developing countries, such as India and a number of countries in Africa and South America, especially where circumcision is not performed routinely and genital hygiene is poor ¹. Patients are in the age range of 15 to 90 years, with a mean of approximately 60 years ¹. Several risk factors have been described for penile cancer, such as lack of circumcision, poor hygiene, phimosis, smoking, viruses and the presence of underlying lichen sclerosus ⁴. Therefore, penile cancer is extremely unusual in individuals who were circumcised in infancy ⁵. Although the data indicate that circumcision at birth provides excellent protection, it appears that equally low incidence rates can be achieved in uncircumcised males who practice

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good hygiene. It is the cause of a lower incidence of penile cancer in Europe and US. Moreover, a viral etiology has also been suggested for penile cancer. It has recently been demonstrated that sexually transmitted Human Papilloma Virus (HPV) infection is the major risk factor, with phimosis, for penile cancer⁶. Nucleic acid analysis by in-situ hybridization for HPV 16 or 18 has demonstrated this virus in both primary and metastatic penile cancer⁷. Moreover, HPV 11 and 30 have also been associated with this neoplasm⁷. In addition, the fact that several studies found altered expression or function of p53 and/or p21, should be considered indirect evidence of the role of HPV in penile cancer pathogenesis⁸. Symptoms are related to a growing mass on the distal penis, occasionally with ulceration or bleeding or discharge. Even if these features are early symptoms, patients contact physicians many months after⁹. Penile pain, difficulty in voiding and lymphadenopathy are other presenting symptoms⁹. The tumor features are usually either papillary or ulcerative in gross appearance¹⁰. Most arise in the glans or the prepuce, and rarely involve the penile shaft and urethral meatus⁴. Squamous cell carcinoma accounts for 95% of all cases, 48% of which affect the glans, with sarcoma accounting for most of the remaining 4-5%. Invasive tumors initially occur on the glans in 48% of cases, followed by the prepuce (25%), glans and prepuce (9%), coronal sulcus (6%) and shaft (2%). It subsequently invades local structures, the corpora cavernosa and the urethra, and metastasizes to the inguinal lymph nodes¹¹. Due to the lack of large randomized trials and the rarity of the disease, the management of penile cancer is up to the present debatable¹². However, it is universally accepted that all patients need multidisciplinary management in cancer centers¹³. Adequate surgical excision of penile cancer provides effective local control and remains the cornerstone of treatment of primary carcinoma of the penis in the US¹⁴. However, in patients with clinically impalpable lymph nodes and a high-risk primary lesion, prophylactic lymphadenectomy aims to prevent the development of regional and distant metastases¹³. Thus, better management of lymph nodes is essential for improving survival even when conservative therapy is used to treat the primary¹⁴. However, surgery of the penis means partial or total amputation with subsequent functional and psychosexual morbidity, which is obviously difficult for the patients to accept¹⁵. Nevertheless, appropriate surgery in the majority of cases reduces subsequent long-term problems in sexual function, cosmesis, psychology, and survival¹⁶. The aim of the present case report is to present an unusual case of penile

cancer due to both the exceptionally locally advanced disease and the uncommon presentation variety.

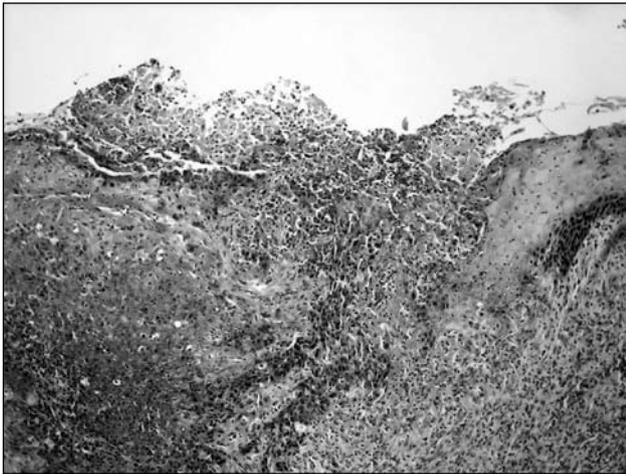
Case report

A 75 year old homeless man was admitted to the Emergency Department of our hospital for a head trauma, due to an accidental fall. He came to our attention, following the observation a necrotic mass at the pubic with deep central ulceration and a total absence of genitals (Fig. 1), reporting a total absence of pain. The patient underwent standard blood examinations, that revealed only a general inflammatory status (WBC 13,600, VES 45, PCR 4, Fibrinogeno 350). The kidney and hepatic function were normal (Urea, Creatinina, LDH, AST, ALT). Inflammatory reaction due to urinary leakage was present around the necrotic mass. In order to avoid urine leakage and to control the total urine volume, we decided to place a urinary catheter. However, due to the impossibility of placing a catheter, caused by difficulty in finding the urethral meatus, we placed a sovrapubic ultrasound guided catheter. In order to plan a correct treatment approach, we took, under local anaesthesia, a little fragment of the lesion, that turned out to be, at pathological evaluation, a squamous cell carcinoma of the penis (Fig. 2). The patient, then, underwent total body CT-scan, that was negative for lymph node metastasis. However, bone scintigraphy showed metastasis in several bone districts (ribs and lumbar and thoracic vertebrae). Oncological and radiotherapeutic consulting were required, but the patient did not undergo chemotherapy, surgical or radiotherapy treatment, due to a rapid decrease in his general condition (renal and cardiac failure) and he died 45 days later.

Figure 1. Necrotic mass at the pubic with deep central ulceration and a total absence of genitals.



Figure 2. Pathological aspect of squamous cell penile carcinoma.



Discussion

The present case report aimed to underline several important features of penile cancer natural history and patient management. The first point is patient unwillingness to consult physicians about the penile lesion. The reason for this could lie in the fact that the diagnosis of penile cancer can be devastating for a man and his partner and the fear of cancer is heightened by the prospect of penile amputation¹⁷. Soria and co-workers have found, in a large series of penile cancer patients, a long delay before the diagnosis with 13.7% of patients having symptoms which lasted more than a year prior to the initiation of definitive therapy¹⁴. Such a delay stems from ignorance, fear, embarrassment, neglect and guilt, which can be ameliorated somewhat by educating the public about personal hygiene, including the early treatment of phimosis, and about how to recognize early signs of penis cancer^{9,14}. In our case, the patient's unwillingness to consult physician was extreme. It could also have been due to the fact that the patient was homeless and had no family support in acceptance of the disease. Family support should, then, be considered an important factor not only in disease acceptance but also in early diagnosis and management. The second point to be discussed is the uncommon presentation of this case. The frequency of locally advanced penile cancer is nowadays very low, due to the early diagnosis and extremely low incidence of this disease¹⁸. Moreover, this case, to the best of our knowledge, is the first case report that describes a penile cancer patient with an ulcerative mass and a total absence of genitals. Moreover, this case is uncommon due to the presence of bone metastases without lymph nodes invasion. Furthermore, penile cancer has a particular tendency to metastasize

through the lymphatic system and develops mainly through the embolization mechanism instead of lymphatic permeation. Moreover, the best prognostic factors related to survival are, then, the presence of positive lymph nodes, the number and site of positive nodes and extracapsular nodal involvement¹⁹. In addition, in penile carcinoma, the success of therapy is related to lymph node status and treatment²⁰. Distant metastases are, however, very rare and the result of vascular dissemination. The European Association of Urology Guidelines suggest that it is extremely rare to observe patients with positive pelvic nodes or distant metastasis without inguinal lymph-node involvement¹⁹. Our case is, then, extremely uncommon, but this variant should be, however, considered in everyday clinical urological practice. Finally, we would like to underline the fact that there has been little progress over the last decade in the management of advanced penile cancer, especially due to the rarity of this neoplasm in well-developed countries¹⁸.

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Editorial comment

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The author presents a case of penile cancer that have destroyed completely the genitals and had multi focal bone metastasis without clinically infiltration of inguinal nodes.

Unhappily the patient died in 45 days due to rapid disease progression without having chances for systematic treatment.

Some aspects should be pointed out in this discussion:

1. the absence of palpable inguinal nodes does not mean that there were no regional metastasis. It is known that tumors with risk factors have incidence from 20 to 50% of metastatic nodes^{1,6}. Distant metastases to lung, liver or bone are present in only 1 to 10% of patients²; they are a rare phenomenon for patients without lymph node involvement. In this related case the squamous cell carcinoma whose histological findings were not described, had big size and necrotic areas, factors of bad prognosis. The statement that the inguinal regions were free of metastasis possibly can be false despite of physical and images findings. The only way to be sure in situations like this is performing inguinal bilateral lymphadenectomys and histological examination of the matherial³⁻⁶;
2. the possibility of bone metastasis due to prostate cancer cannot be excluded. The age of 75 years and the most frequent tumor in men responsible for bone dissemination became prostate cancer an important hypothesis to explain hot spots found at the bone scan. Serum PSA and biopsy of the metastasis could clarify this doubt;

3. related to the late search for medical care, in undevelopments countries this is very common due to poor education and fear of surgical treatment^{3,5,6}.

In summary this case can not be considered extremely uncommon since there is lack of informations regarding surgical staging and histological diagnosis of the metastasis.

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A return to love without worry

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Introduction

ED has been defined by the National Institute of Health (NIH) as “the inability to achieve and/or to maintain an erection for a sufficiently long period of time so as to permit satisfactory sexual intercourse”¹.

ED is an underestimated disorder. Discordant data reports range between 12% in men aged 40-65 years old, as described by Furlow, and 52% in men aged 40-69 years according to the Massachusetts Men Ageing Study (MMAS)²⁻⁶.

A large-scale Italian Study published in 2000 reported a prevalence of 12.8% with about 3 Italian million men afflicted with ED⁷.

Drawing upon different data, all published studies confirm that ED prevalence is strongly age-dependent and increases significantly after the sixth decade of life. Current prevalence rate is estimated at 5-10% in the fifth decade of life and increases to 30-50% in the middle of the seventh decade²⁻⁷.

Although ED does not alter life expectancy, it can negatively impact an individual's well-being and quality of life⁸.

Only about 10% of patients seek medical attention and this, only after 1-2 years from the onset of symptoms.

In order to determine whether an ED public educational campaign would be effective in increasing awareness and encourage Italian men to seek medical attention for their condition, the Italian Society of Andrology (Società Italiana di Andrologia, SIA) organized “Return to love without worry”, an ED awareness campaign similar to other campaigns being conducted in other countries throughout the world⁹.

“A Return to Love without Worry” was public information and awareness campaign about erectile dysfunction ED organized by the SIA last spring.

From May 17th until June 30th 2008 Italian men and women had the opportunity to communicate with andrologists by calling a help-line or logging onto a web site.

The aims of this campaign were to make people conscious of the importance of caring for their sexual health and to reassure men that an effective therapy for their sexual problems does exist while emphasizing the role and importance of the andrologist as the referral specialist for,ale sexual dysfunctions.

Another important aim was make people aware that DE could be a symptom of many serious diseases¹⁰.

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The “A Return to Love without Worry” campaign

The “Return to Love without Worry” campaign was founded upon utilizing two channels of communication: a web site and a toll free help line. By calling 800.36.36.77 throughout Italy, it was possible talk directly and anonymously with one of the 100 andrologists of SIA who participated in this campaign. This help line was activated on Sunday May 17th and provided a 24 hour free all day consultation service which was reduced to two hours a day from 8 p.m. to 10 p.m. on Monday through Friday ending on June 30th.

The web site www.amaresenzapensieri.it was created thanks to the assistance of SIA andrologists who provided people with the opportunity to learn all about ED and available therapies. This web site still exists and is considered a reputable source of multimedia information on ED.

The website is both interesting and easy to read and contains all medical aspects of ED including instructions for testing and diagnosing ED and all possible ED therapies. It is divided into three sections: one section contains a five question test with multiple choice answers regarding sexual habits and gives a score for each answer with the final score indicating the level of ED. The second section allows the user to ask personal questions to an andrologist via e-mail who then answers the query. The third section is a “doctor locator” section where the user can find an andrologist closest to his place of residence where he can go and be examined.

“A Return to Love without Worry” was inaugurated with a press conference at the Milan press club on

May 6th.

It was publicized through transmission on 163 public television commercial spots and 729 satellite TV spots and posted on bill boards and on posters in national pharmacies. It was also featured in articles in the most important and popular Italian newspapers and magazines and through the distribution of leaflets in hospitals.

Results

“A Return to Love without Worry” help line gave everyone the opportunity to anonymously discuss sexual problems with a specialized andrologist and proved to be a huge success.

The number of phone calls received on the free help line totalled 14,649 in total with 4,951 received just within the first 24 hours. Andrologists answered 11,109 phone calls and another 1,200 callers hung up before talking to an andrologist perhaps because of shyness and difficulty talking about sexual habits and problems even though the calls were anonymous. Most of the phone calls came from Southern Italy and the Islands. Lombardy, Campania, Lazio and Sicily were the regions with the highest percentages of callers (Fig. 1).

Data on the website here below was updated on September 21th 2008. The total number of visits to the website were a substantial 148,050. The duration of visits to the site and related websites accessed through the principal website revealed that people were interested in further knowledge about ED and sexual healthcare (Tab. I).

Figure 1. Geographic distribution of the phone calls.

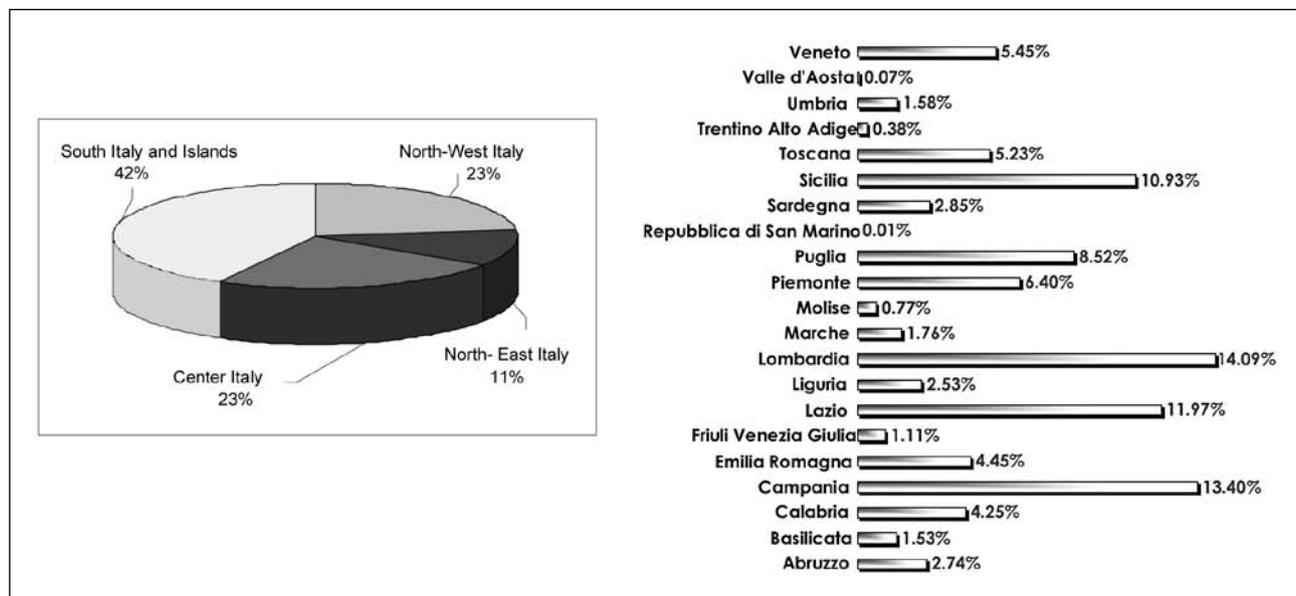


Table I. Data concerning website access.

Total visits	148,050
Daily visits (on average)	1,156
Duration of visits (on average)	7'18"
Total web site links accessed	1,670,336
Web site links accessed in each visit (average)	11.28
Consultancy questions received	> 2000

The "Doctor Locator" section was also visited very frequently with many people searching for an andrologist nearest to them perhaps because they thought they needed an examination by a specialist after consulting the website (Tab. II).

The "A Return to Love without Worry" campaign was reported on by 206 journalists and featured in 106 articles in the most important Italian newspapers and magazines, medical journals, TV and Radio programmes and general Web sites which were read or listened to by 87,753,724 people.

Discussion and conclusions

"A Return to Love without Worry" was created with the intention of facilitating a direct dialogue between andrologists and the general public.

People often undervalue the importance of their sexual life and ignore their sexual healthcare. Sexuality is not often discussed because of shyness and modesty and people don't often revert to an andrologist because they don't think that they need him.

ED is a very common condition with about 13% of men suffering from it and it is often a symptom of more serious illness. The aim of "A Return to love without Worry" was to make people more aware of their sexual healthcare and to overcome shyness and modesty by way of an anonymous help line and web site.

The success of the project and the large number of people involved reveal a public need and desire to be informed and advised on ED and sexual healthcare and confirm that both a toll free phone line and a web site are excellent instruments to bring many otherwise overlooked patients to medical consultation.

Table II. Results concerning the "Doctor Locator" section.

Total visits to Doctor Locator section	25,579
Total searches for local andrologist	51,157

ED has very negative effects not only on a man's sex life but also on his relationship with his partner, his psychological state of mind and on his quality of life in general.

Since many diseases can lead to ED, it should be considered a symptom of specific systemic or related to other disorders which require careful clinical evaluation and knowledge of a patient's history¹¹.

ED may be the first sign of a systemic illness and could possibly signal an atherosclerotic, metabolic, or neurological condition that remains clinically undiagnosed³. Furthermore, it could also represent an early clinical indication of a widespread, largely sub-clinical vascular disorder ("the tip of the iceberg")¹⁰. Public education and information campaigns about erectile dysfunction ED are necessary and useful in increasing public awareness and changing help-seeking behaviour of people.

A very important characteristic of the "A Return to Love without Worry" campaign, which distinguished it from other awareness campaigns was the active participation of specialized andrologists who, through the help line, provided direct, anonymous contact with people to discuss their sexual problems.

The data collected from the campaign will prove useful in the future for the health professional to learn about patients who suffer from ED, their concerns and questions and role the andrologist can play in helping them.

The andrologist can help men with ED to recognize, confront and treat their conditions and this is the message which "A Return to Love without Worry" aims to give to people.

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Methodological bases for systematic reviews

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Summary

Objective. Systematic reviews provide the highest evidence level in Literature. Objective of the present study is to describe their methodological basic concepts.

Material and methods. A PubMed Literature search was performed combining the terms “systematic review”, “methodology”, “evidence-based medicine” “EBM”. Moreover, the Cochrane Collaboration handbooks and learning material were widely used.

Results. Several rigorous rules have to be followed in order to define a review “systematic”. Different basic steps have been identified in the development of systematic reviews: formulation of the question (defining participants, interventions, type of studies, and outcomes), search, selection and qualitative evaluation of the useful studies, reporting and interpreting the results of the systematic review (eventually through meta-analytical techniques). As biases might easily be amplified in this context, every kind of systematic error should be avoided in each of the described steps. A brief description of the most common types of biases (selection, performance, attrition, and detection bias) is reported.

Conclusion. Since they provide the highest level of evidence in medical Literature, caution should be used in calling a review systematic. Moreover, the results of systematic reviews of randomized controlled trials should be carefully interpreted before application in clinical practice.

Keywords

Systematic review • Meta-analysis • Evidence-based medicine • Methodology

Introduction

Evidence-based medicine (EBM) has been defined as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients”, integrating individual clinical expertise with the highest level clinical evidence from research¹. Accordingly, high-quality healthcare implies a practice that is consistent with the best available evidence². According to the Oxford Centre for Evidence-based Medicine, the highest levels of evidence are produced by systematic reviews of randomized controlled trials (RCTs) (level 1a)³.

Different kinds of Literature reviews exist: traditional (even called narrative) reviews are qualitative summaries, usually addressing broad questions. The typical feature of narrative reviews is the use of non reproducible, subjective, and often non-explicitly described methods to collect and interpret studies. The main drawback of these studies is the tendency to confirm preconceived concepts⁴. On the opposite

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side we have the systematic reviews, including comprehensive, exhaustive searches for primary studies on a focused and narrow clinical question, explicitly stating the methods used to select the pieces of evidence, using clear and reproducible eligibility criteria, critical appraisal of the studies' quality, and synthesis of results according to a pre-determined and explicit method ⁵. A particular way of reporting the results of systematic reviews is to perform meta-analyses, in which data from all homogeneous studies are collected to generate summary (pooled) estimates of effects. "Effects" are measures of association between exposure and outcomes (e.g. absolute and relative risk reduction rates, odds ratios, etc.) ⁶.

Founded in 1993 and named after the British epidemiologist Archie Cochrane, the Cochrane Collaboration is the most important international not-for-profit and independent organization dedicated to the production of systematic reviews of healthcare interventions. Published quarterly as part of The Cochrane Library, the Cochrane Database of Systematic Reviews has become in the last 20 years the benchmark for Evidence-Based Medicine (EBM) supporters. Moreover, hundreds of systematic reviews are monthly published in the world Literature, but only few of them meet the criteria to be really considered systematic ones. In order to improve the quality of reporting meta-analyses, a conference statement has been generated by the Quality of Reporting of Meta-analyses (QUOROM) group ⁷, but only a minority of the readers knows the methodology that has to be used conducting a systematic review.

Objective of the present study is to provide an overview on the methodological bases of systematic reviews.

Material and methods

A PubMed Literature search was performed combining the terms "systematic review", "methodology", "evidence-based medicine" "EBM". Moreover, the Cochrane Collaboration handbooks ⁶ and learning material ⁸ (available on www.cochrane.org) were widely used.

Steps for conducting a systematic review

There are several rules to be taken into account when performing a systematic review. In this section we analyze step by step the different moments of the methodology for systematic reviews.

Formulating the question

The first step in a systematic review is to exactly de-

fine the question to be answered. A not well-defined question brings to uncertainty whether to include or not a given study, and to unsure, undefined or even wrong results.

The objective of the review depends upon several factors, such as the relevance or impact of the topic, the support of theoretical, biological or epidemiological information, the potential generalizability and validity of answers to the question, the availability of resources, etc.

The question addressed by the review might be narrow or broad in its formulation. For example, a review might assess the efficacy of 5-phosphodiesterase inhibitors in improving erectile function (broad issue) or, more specifically, address the effect of sildenafil in improving the percentage of successful intercours in patients with erectile dysfunction after nerve-sparing radical prostatectomy. There are several issues to be taken into account in formulating the wideness of a question: broad questions are more generalizable to multiple settings, include all relevant studies of a given topic, but usually are more difficult to be performed, and the results might be biased by the presence of too heterogeneous populations, rendering the results poorly significant. On the contrary, narrow questions might be biased by the exclusion of some relevant study, are poorly generalizable, but often provide sharp answers in peculiar clinical topics.

Subdividing the question in its main components might help to correctly build the review. The key components of a question are the following.

Participants

This component is the answer to the question: which types of people has to be involved in the studies of the systematic review? In order to identify these people, firstly a disease object of the review has to be identified; secondly, a population with the given disease has to be defined. This means that the Authors have to strictly define the criteria to identify the presence of a disease, and they have to decide if they are interested in a special setting of patients (according to age, sex, risk factors, comorbidities, social, economic, or community issues, or whatever else). Any restriction with respect to specific population features should be based on sound evidence. For example, focusing a review of the effectiveness of PSA screening for prostate cancer on men older than 50 years should be justified on the basis of biological plausibility, previously published high-level evidences and existing controversies. Selecting a population on the basis of personal interests or

beliefs without any scientific population should be avoided.

Interventions

This key component means that the Authors have to clearly select the interventions of interest. With the objective to answer the question “Is a given intervention efficacious to treat a given disease?”, the given intervention almost always needs to be compared to a control group. The control group might receive another existing treatment with proven efficacy (active treatment), or a placebo, a sham treatment or no treatment at all. The choice to use a control group with an active comparator or not depends on practical, medical, and ethical issues, evaluating the kind of disease, the risk to delay an active treatment and the efficacy of the existing therapies.

Outcomes

Another key component is the outcome to be evaluated. Every disease and every intervention has specific outcomes that can modify the results of the review. Selecting the most important outcome is a fundamental task that can provide the reader the right data concerning cure of a disease, while wrong or minor outcomes can confound the reader with high volume data that worsen the readability of the review. Generally, a systematic review has to report all outcomes that are likely to influence the healthcare diagnostic or therapeutic process of the selected disease. Specifically, all the outcomes that need to be considered should be specified, even though the Authors think to have low probabilities to find data on those outcomes. As reported by the Cochrane handbook⁶, the most classical example in this issue is the quality of life of patients undergoing chemotherapy for advanced cancer. Although quality of life is the most important outcome for these patients, incorrectly most studies only report survival data. Finally, all the adverse events should be taken into account in the review, specifying and extrapolating those requiring a treatment withdrawal. When an article appears to be relevant for the population and interventions, but the results are reported in an incomplete or inadequate form to be used in the review, the Authors should be contacted in order to ask them appropriate clarifications before excluding the study from the analysis.

Types of studies

In 1998, the Oxford Centre for Evidence-based Medicine categorized the evidence levels in order to assess which was the best study design in order to

answer a given clinical question³. While randomized clinical trials are the referral points when assessing the efficacy of a treatment, other study designs are best used to answer different questions. For example, epidemiological problems are best addressed through cohort or case-control studies. Considering the systematic reviews of treatment efficacy (and consequently RCTs as gold standard studies), other features have to be taken into account. Mainly, follow-up should be adequate to evaluate the outcome: short term studies are more useful to address acute diseases or acute adverse events; long term studies are needed to answer survival issues or questions concerning chronic diseases. Moreover, the control group should be carefully chosen: placebo controlled studies might be non-ethical in life-threatening diseases, active drug comparisons might be non-appropriate if the active comparator efficacy have not been clearly proven.

Looking for all the relevant studies

According to what we have previously established, systematic reviews on the effect of a healthcare intervention are usually focused on RCTs. A comprehensive, thorough, and complete search is the basic step in order to define our review “systematic”. Currently, most searches are performed through electronic databases, but a simple search in a single electronic database is not sufficient. In fact, published data show as only 30-80% of RCTs can be retrieved by searching a single electronic database (MEDLINE). Accordingly, at least 3 electronic databases should be used, adding studies through hand-searching and contacting experts and colleagues for unpublished studies⁹. Selecting all relevant studies is important not only to provide as complete data as possible, but also to minimize selection bias.

Electronic databases

One of the most important scientific revolutions coming from the advent of the internet was the introduction of shared electronic databases available for all scientists. Such databases allow performing easy and not time-consuming searches. Currently, the three databases usually considered the richest sources for RCTs are PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (“CENTRAL”).

PubMed is published free by the U.S. National Library of Medicine, including over 18 million citations from MEDLINE and other life science journals for biomedical articles back to the 1950s. Usually considered the European counterpart to MEDLINE, EMBASE (pub-

lished by Elsevier's Excerpta Medica) is estimated to contain a slightly lower number of records. Although performing searches in the two databases produces similar number of references, the overlapping references retrieved range between 2-75% of cases¹⁰⁻¹³. Finally, the CENTRAL database was born with the specific intent of collecting and making accessible clinical trials (randomized or not) potentially useful for systematic reviews. This database collects trials published in several languages, available only as conference proceedings or in other sources difficult to access, or not indexed in other databases¹⁴.

Several other electronic databases are currently available for use (Web of Science, Scopus, Google Scholar, and CancerLit), but their diffusion is slightly more limited.

In most databases, searches can be performed according to two different protocols: free text strategies or Medical Subject Headings (MeSH) strategies. The free text searches are classically performed through the keywords selected by the Authors and combined according to their needs. Usually, a good way to perform the free text searches is to use the terms that define a given question (population, intervention, outcome, study design), and subsequently combine them in a non-selective manner through the Booleans operators. Initially, the search should be performed using the operator OR (that includes in a search all the references including at least one of the terms used), and subsequently refined with the operator AND (that includes only the references that include all the terms used). No limits should be used in the search (for publication time, languages, kind of study, or other limits). On the contrary, MeSH searches are performed through terms already introduced by the PubMed administrators. A given MeSH search provides results coming from a combination of searches of different pre-established terms. To have a more precise idea, a MeSH search provides more precise results than a single term free-text strategy. On the other hand, well performed free-text searches usually are more sensitive and retrieve more articles than MeSH ones do. An example: on November the 10th 2008, a PubMed free-text search and a MeSH one of the terms "erectile dysfunction" produced 14265 and 12311 results, respectively.

Handsearching

Healthcare journals handsearching is a fundamental step in good quality systematic reviews. It has been shown that up to 52% of RCTs can be missed by PubMed searches and retrieved only by handsearching¹⁵. In fact, not all trials are published in in-

dexed journals, and not all journals provide the correct keywords for easy identification. Reference lists of other studies or of other reviews should be used to complete the identification of published records. Moreover, conference proceedings are usually not included in electronic databases, and this kind of grey Literature is reported to contain more frequently "negative" results than published studies¹⁶. Consequently, missing conference proceedings might significantly affect the results of a systematic review. On the other hand, indeed, conference proceedings often report incomplete or not usable data, making them difficult to be used in systematic reviews.

Finally, retrieving unpublished studies is another challenging step. Lots of completed studies will never be published, because of several reasons, such as negative results, lack of funds, low interest, bad reporting, and so on. Colleagues, friends, or experts in a given field can be contacted to collect information about known ongoing or just-ended studies. Moreover, several databases exist registering all the ongoing clinical trials. The most common are from USA (www.clinicaltrials.gov) and European authorities (www.eudract.emea.europa.eu).

Documenting the search

One of the most important features of systematic reviews is that the search should be reproducible. With this aim, the search methodology and strategy should be accurately detailed, specifying all the information needed to replicate the search. In particular, the Authors should mention the databases used, the dates when the searches were performed, the years covered by the search, the (eventual) limits used, and all the single steps including all the terms and the Booleans operators used in the search. Moreover, the methods used to perform handsearching should be detailed specifying journals, congress proceedings, reference lists and personal communications used.

Selecting relevant studies

The circumstances of inclusion or exclusion of the studies should be described in details. In a first stage, the results of the electronic search should be screened by at least two Authors, as there is evidence that increasing the number of "reviewers" decreases the risk for including non relevant articles or excluding relevant ones¹⁷. If the title or abstract do not provide enough information for the decision, the text should be retrieved and screened. Disagreement between the Authors is generally solved by open discussion. A point of high attention should be to avoid duplicated publications,

including several times studies coming from the same patient series published in different time-sets or under different viewpoints. The number of articles selected or excluded should be carefully reported, as well as the reasons for exclusion. A generally accepted criterion to define a search sensitive enough is the selection of no more than 5% of the retrieved articles. When more than 5% of the retrieved abstract is considered useful for the review, we have an increased possibility to have articles missed by our search ⁶.

Evaluating the quality of the selected studies: “garbage in, garbage out” ¹⁸

Quality assessment of the studies selected for the review is a necessary step in order to correctly evaluate the results of a review. Validity and applicability (or external validity or generalizability) of a certain study are the most important criteria to assess the quality of a study. Therefore, they should be carefully evaluated before including a trial in a systematic review. In systematic reviews, the validity of a study is the extent to which its design and conduct are likely to prevent systematic errors or biases ¹⁹. Studies with a non rigorous design, in fact, might underestimate or overestimate the efficacy of a treatment, invalidating the results of the review. Systematic errors are typically classified into 4 different categories: selection, performance, attrition, and detection bias.

Selection bias

One of the most important factors able to distort the results of a study is the selection of the population included. Once strict inclusion/exclusion criteria have been established, in an ideal study there should not be the possibility to influence the patients' allocation to one arm or to the other of intervention. Hence, two steps should be run: 1) a true randomization process should be performed and detailed, possibly through a central electronic (or using numeric random tables) management; 2) a complete concealment of the treatment should be organized for the providers organizing the treatment, so as they cannot recognize and influence the selection for the treatment arm. Sometimes, concealment is not applicable: comparing surgical and medical therapies or different surgical treatments does not allow medical blinding, while analysts should always be blinded. Studies demonstrated that concealment biases provide worse effects than true allocation biases do ²⁰.

Performance bias

Differences in providing health care interventions in two different arms of a trial set the case for per-

formance bias. Blinding patients is the procedure that mostly avoids unintended differences. Patients who are aware of their treatment status more easily complain of a given symptom in case of placebo arm or are cured by the interventional treatment. Moreover, contamination (i.e. providing intervention to the control arm) and co-intervention (i.e. providing additional healthcare to one of the arms) may lead to additional biases. An unbiased design should be the one answering no to the following question: “were the patients or the doctor providing healthcare aware of the treatment?”

Attrition bias

The management of the patients lost during a study is fundamental to interpret the results. Attrition bias is the systematic error due to the incorrect exclusion of the patients that not finish a study. Withdrawals, dropouts, lost to follow-ups, and protocol deviations should always be considered as participants in intention-to-treat analysis protocols.

Detection bias

This last systematic error is due to biases in the assessment of outcomes. Firstly, blinding procedures in the evaluation prevent influencing the outcomes, and particularly the subjective ones (such as pain, symptoms, and questionnaires). Secondly, the outcomes to be reported have to be established per protocol, before the assessment begins. Reporting partial outcomes or only the significant ones are typical strategies affected by detection bias.

Quantification of the quality of the studies

Different approaches can be used to assess the validity of a study, as the components of the “quality” of a study might be evaluated a single ones or in groups. Specifically, a single component could be classified as “adequate”, “inadequate”, or “unclear”. In the case where all the components are adequate, a low risk for bias can be identified. Whenever at least a criterion is unclear or inadequate, the risk becomes moderate or high ^{6 17}.

On the other hand, groups of components can be assessed through checklists or scales. In checklists the components are evaluated separately, without any numerical score, while in scales each item has a specific score that is combined with the others in an overall quality score. In a well conducted systematic review, Moher et al. identified 9 checklists and 25 scales. Among them, only the Jadad scale had been developed according to established methodological procedures ²¹.

Jadad score is a very simple one, assigning 1 point if the trial is either randomized or double-blinded, or in the case of an accurate description of the drop-out patients. Further points are given if randomisation and blinding procedures are appropriate, whereas points are subtracted in the case of inappropriate descriptions of the same procedures. An overall score > 1 indicates a good-quality study¹⁹. Once assessed, study validity might be used with a threshold to include studies in a review, as weights in statistical analysis, in sensitivity analyses, in the interpretation of the results.

Calculate, combine, and report the results: hints

This is the most complex aspect of a systematic review. Even though a single paragraph cannot be exhaustive for this topic, some hints are given to improve the understanding of a systematic review.

After the selection of the studies, the Authors should extract data to analyse them. Data extraction is usually performed on appositely developed forms or databases after pilot testing. Information concerning the study features, quality and outcomes are collected and evaluated. The outcomes reported in systematic reviews depend on the type of study in-

cluded. When RCTs are included, the outcomes are usually expressed as Risk Ratios, Odds Ratios, or weight differences between means (for continuous outcomes).

Following, the Authors have to decide how to report them. Tabulation is the easiest form of reporting the results of systematic reviews, expressing in columns the features (e.g. year, number of participants, setting, study design, quality) and the outcomes (e.g. main outcome, secondary outcomes, adverse events) of the single studies. An example from an already published systematic review is given in Table I²². When several studies are analysed with homogeneous population, similar study design, treatment arms, and main outcomes, appropriate meta-analytic statistic software (such as the freely available RevMan from the Cochrane Collaboration) might be used to combine the results of the single studies in a single result. The classical graphical representations of meta-analyses are forest plots, displaying effect estimates from each study with their confidence interval (CI), and providing a visual summary of the data. The results of each component study are shown as boxes centered on the point estimate, with the horizontal line representing the CI. The pooled estimate is usually displayed at the bottom of the

Table I. Example of results reporting in a non meta-analytic systematic review on the efficacy of anticholinergic drugs in patients with bladder outlet obstruction and Low Urinary Tract symptoms (modified from²²).

AUTHORS	STUDY DESIGN	CASES	DURATION (MO.)	MAJOR FINDINGS
Saito et al.	RCT: Tamsulosin vs. tamsulosin + propiverine	134	1	Improvements were shown in daytime frequency (29.6% in tamsulosin and 44.7% in combination therapy arms), nighttime frequency (22.5% in tamsulosin and 44.4% in combination therapy arms), and urgency symptoms (18.2% in tamsulosin and 22.2% in combination therapy arms)
Athanasopoulos et al.	RCT: Tamsulosin vs. tamsulosin + tolterodine	50	3	Combination therapy increases Qmax (+ 1.2 ml/s); decreases in PdetQmax (- 8 cm H2O); improves quality of life score
Lee et al.	RCT: Doxazosin vs. doxazosin + propiverine	211	2	Combination therapy improves urinary frequency (p = 0.004), average micturition volume (p = 0.004), scores on items 2, 4, and 7 of IPSS (p = 0.029). Patients' satisfaction was higher in the combination therapy group (odds ratio 2.34)
Abrams et al.	RCT: Tolterodine vs. placebo	222	3	Tolterodine does not reduce significantly Qmax (- 0.7 ml/s) and PdetQmax (- 7 cm H2O); increases volume to first detrusor contraction (+ 59 ml, p = 0.0026), maximum cystometric capacity (+ 67 ml, p = 0.0001), and decreases BCI (- 10, p = 0.0045) and voiding efficacy (- 7%, p = 0.018)

plot as a diamond. Figure 1 shows an example of forest plot of a published meta-analysis ²².

Following, the effect measures have to be pooled across studies, that is to be weighted according to their sample sizes. Pooling is accomplished using two statistical models: the random effects model (assuming that the analysed studies are only a random part of the possible studies on a given topic) or the fixed effects model (assuming that the studies in the meta-analysis are representative of the “true” effect, that is fixed, and differences between the studies are due to chance) ⁵. The former model is preferred when the data are heterogeneous and the evaluated studies report highly different results, providing a more conservative estimate with a wider confidence interval; in absence of heterogeneity both models produce similar results ⁵.

Another crucial point of a well-conducted meta-analysis is the evaluation of publication bias, that is a reporting bias consisting in the higher probability for a certain kind of studies to be accepted for publication due to their positive results (publication bias), their language (language bias), the rapidity of publication (time-lag bias) or the possibility to be cited more often (citation bias). Reviewers can check for the presence of publication bias using graphical methods (e.g. funnel plots), and statistical tests (e.g. Egger test) ²⁴.

Last but not least, the interpretation of the results has to provide a clinical application of the results of the systematic review whenever possible, highlight-

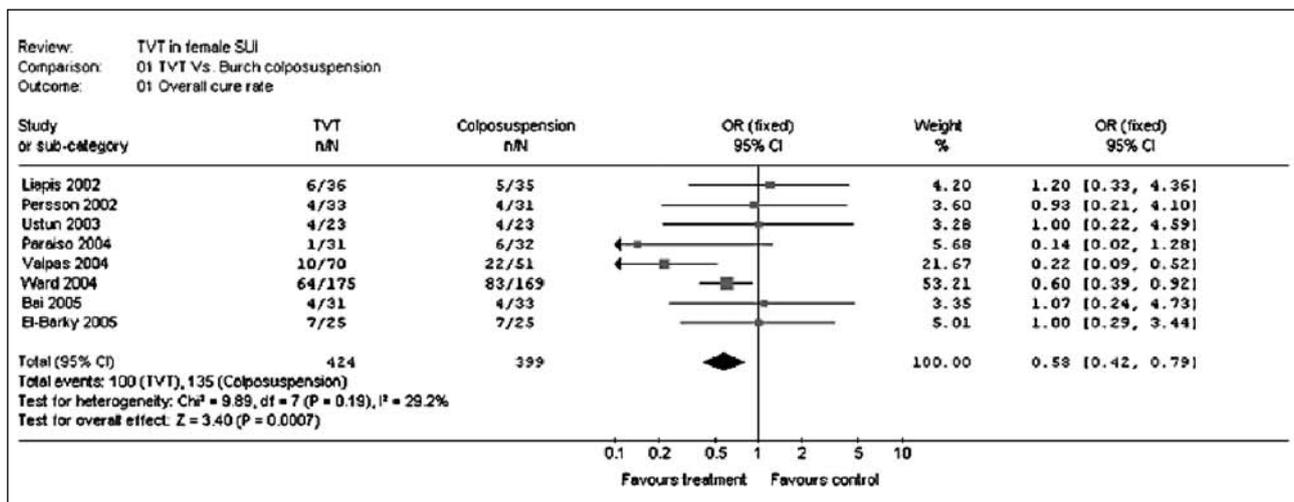
ing the limits of the included Literature and the limits of the review or meta-analysis itself. A classical example of incorrect results coming from a systematic review in andrological Literature is the Cochrane article on the effects of varicocele treatment in improving pregnancy rates in subfertile men ^{25 26}. According to their review, the Authors conclude that three is not sufficient evidence justifying varicocele treatment in subfertile patients. The Italian Society of Andrology (SIA), indeed, recently published a contrary opinion, highlighting the biases of this review, not only in the included studies (heterogeneous inclusion criteria and clinical characteristics), but also in the results provided and in their interpretation ²⁷.

As far as possible, the manuscript of a systematic review (mainly concerns meta-analyses) should be written following the advices and guidelines of the QUOROM statement ⁷.

Conclusions

Systematic reviews and meta-analyses of randomized controlled trials are the cornerstones of evidence based medicine. Several rigorous rules have to be followed in order to define a review “systematic”. As biases might easily be amplified in this context, every kind of systematic error should be avoided in the formulation of the question, in the search and selection of the useful studies, in their qualitative evaluation, and in reporting and interpreting the results of the systematic review.

Figure 1. Example of forest plot showing meta-analysed data of efficacy comparing interventions (TVT vs. Burch colposuspension) in patients with stress urinary incontinence. The odds ratios of the single studies’ results are shown in squares, with the horizontal lines as confidence intervals (CI); the meta-analysed data is shown as a diamond, whose lateral angles represent the CI. All the results on the left of the equivalence line are in favour of TVT, all the results on the right favour the colposuspension. When CI lay across the equivalence, no significant result is obtained 23 (permission for reproduction requested)



Since they provide the highest level of evidence in medical literature, caution should be used in calling a review systematic. Moreover, the results of systematic reviews of randomized controlled trials should be carefully interpreted before clinical practice application.

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Journal of Andrological Sciences (JAS) is a young journal. One of the purposes of ours is to provide our readers with articles which might improve the scientific quality of their literature contributions.

The article of Dr. Antonio Galfano is the first of a series of papers which will evaluate all the issue related to the production of a good clinical paper step by step. At the end, we could collect all the papers in a monography evaluating how to write and how to read scientific articles.

I charged with the task to write the first paper two young co-

workers of mine, whose contribution has been precious for the development of the scientific activity at the urology clinic of the university of Verona at first and, currently, at the university of Padua.

The paper is of excellent quality and I believe it will be useful for all who are interested in a significant scientific production. In the meanwhile, the text provide several hints to learn how to read the available systematic reviews of the literature, evaluate their quality and appreciate the quality or, if needed, highlight the shortcomings.

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