THE MANUAL

CUTTING-EDGE MEN'S HEALTHCARE

Australian Prostate Cancer Research

prostatecancerresearch.org.au

Contents

Editorial

The recent federal election and prolonged lead up highlighted the profound importance of Medicare to the Australian people. The labour "Medi-scare" campaign was seemingly very successful in worrying the populous about the survival of Medicare. However, there did not seem to be a basis in fact that Medicare was to be privatised. I have lived and worked in the United Kingdom and the United States and have experienced firsthand their healthcare systems: NHS, Medicaid, Medicare-cisa and insurances like Blue Cross. I have also spent considerable time teaching in Europe, France, Germany, South East Asia, Indonesia, the Philippines, Singapore and India. My view is that we have an excellent health care service for the majority of Australians and the system is very delicately balanced. A shift out of private health insurance by even a small percentage of Australian's would lead to increased difficulty in the public health sector for provision, assuming those who were uninsured would seek treatment in the public system.

Those who work in public health in Australia are well acquainted with the limited resources and the associated problems. However, the system does work. It relies on the dedication of nurses, doctors and allied health professionals. At present we do have an excellent health service and our politicians have had a stern admonishment from the electorate to maintain and improve health provision for Australians.

A new and flourishing Medicare based APCR prostate cancer clinic in North Melbourne, next to the Royal Melbourne Hospital and the VCCC, is an example of what can be achieved in our health system. We have now seen over 1000 patients per month with numbers continuing to increase. The services now involve many disciplines beyond Urology and nursing care. We provide psychology, physiotherapy, exercise physiology and an androgen deprivation clinic, endocrinology, cystoscopy, urodynamics to name just some of our services. At present, this has been achieved with Medicare and philanthropy as a funding base.

APCR has three missions in North Melbourne. The prostate cancer clinic, the national Prostate Cancer education meeting and the basic prostate cancer research program. The basic prostate cancer research program utilises our informatics and prostate cancer tissue bank to allow our scientists to ask the fundamental questions about lethality in prostate cancer.

Ultimately this new clinic in North Melbourne can be used as a blue print for provision of care for men and their most common cancer. We may see similar centres both regionally and nationally based on this model. These centres must be financially viable and self-sustaining in our Medicare/Private health care system. This idea of looking after men and prostate cancer seems long overdue given our well-developed services for breast cancer, women's and children's health and to a lesser extent indigenous health care.

Prof Tony Costello

Prof Anthony J Costello
Executive Editor

Dr Fairleigh Reeves
Editor

Preserving the penis in squamous cell cancer:
Early diagnosis and management is key

David Sofield
Bethesda Hospital and St John of God Hospital
Subiaco, Perth

Squamous cell carcinoma of the penis (SCCP) has been a rare condition in Australia and other affluent populations, but this is changing rapidly. SCCP is strongly associated with Human Papilloma Virus (HPV), particularly subtypes 16, 6 and 18, which are often detected with in situ and invasive carcinomas of the penis, as well as oropharyngeal, anorectal, vulval and cervical SCC [1, 2, 3].

The existence of 2 aetiologically distinct types of penile SCC has been hypothesized: (1) a type with a viral cause and possible sexual transmission that is more likely to occur in younger individuals and (2) another type of unknown cause affecting older individuals [4, 5, 6]. This first group appears to be increasing in prevalence in Australia and is the focus of this update.

A paradigm shift in the management of SCCP has occurred. Traditionally, surgical management of the primary lesion was overly aggressive. The mandated 2 cm margins resulted in mutilating surgery with major psychosocial detriment. Conversely the management of metastatic disease to the groin nodes and beyond has been inadequate. Recognizing this has led to major changes in recent years. The emphasis is now on preservation of the penis wherever possible utilizing small margins and reconstructive techniques. The introduction of dynamic sentinel lymph node biopsy, in conjunction with PET scanning, has also enabled better stratification of risk such that those patients with established nodal metastasis undergo potentially life saving radical node dissection, whilst those free of metastases are spared the significant morbidity of groin dissection (which has been a significant deterrent, particularly to “occasional” operators in this uncommon condition).

Five-year survival of SCCP is approximately 50% in most series. In recent years, the advent of centralized care of SCCP has seen this improve to 85% in centers of excellence [7]. In 2011, the first Australian centralized service for SCCP was established at Fremantle Hospital in Western Australia. We expected an annual caseload of 6-8 patients. In fact over 90 cases have been referred in the first 4 years and referral numbers are increasing.

Early diagnosis and treatment is key to achieving these improved survival outcomes whilst also preserving penile form and function. This relies critically on awareness, vigilance and early referral by primary physicians and dermatologists.

SCCP typically occurs on the glans with 80% of cases occurring in the uncircumcised penis. Most are slow growing but a subset of rapidly progressive (although often well-differentiated) cases do occur. There is often a precursor in-situ (CIS) stage, which may progress after many years to invasive disease.

Signs of SCCP include redness or ulceration of the skin of the glans or foreskin, not responding to topical steroid or antifungal therapy, discharge in the case of the non-retractile foreskin, or a penile mass. Rarely presentation may be as a result of nodal metastasis to the groin with only a very small primary lesion.

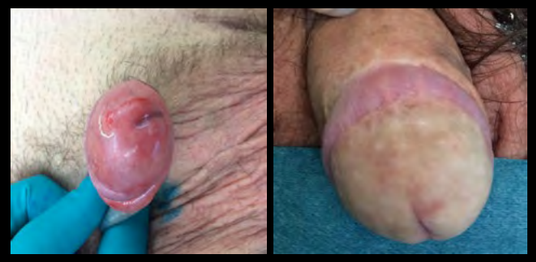
Management options include

- CIS – topical chemotherapy, laser therapy, Moh’s surgery, glans resurfacing with split skin graft
- Invasive SCCP – partial penectomy with glans reconstruction
- Locally advanced SCCP- radical penectomy and perineal urethrostomy formation

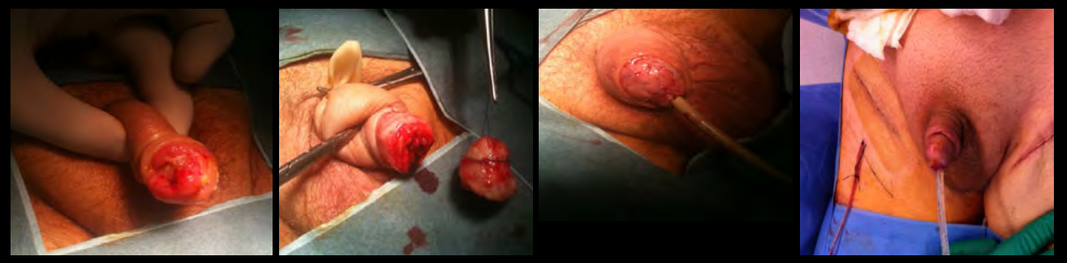
Chemotherapy and radiotherapy both have a selective role to play but surgery remains the mainstay of treatment.

Case Examples:

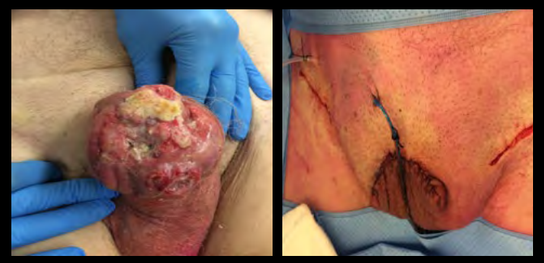
1. Carcinoma in situ – managed with total glans resurfacing with split skin graft



2. Invasive SCCP of glans – glansectomy and neoglans reconstruction with bilateral groin node dissection



3. Rapidly progressive invasive SCC – a 6 week history from normal to locally advanced disease. Managed with radical penectomy, perineal urethrosotomy and inguinal sentinel node biopsy



In summary, penile cancer appears to be increasing in incidence in Australia and to be occurring in a new population of younger, healthier men associated with HPV infection. It is essential that primary care physicians and dermatologists are alert to the possibility that any unusual penile skin lesion may be SCCP. Early referral for biopsy and management to a center of excellence is essential to achieving the twin goals of cure and preservation of penile form and function.

References

[1] Madsen BS, van den Brule AJ, Jensen HL, et al. Risk factors for squamous cell carcinoma of the penis--population-based case-control study in Denmark. Cancer Epidemiology, Biomarkers & Prevention. 2008 Oct; 17(10): 2683-91. **[2]** Scheiner MA, Campos MM, Ornellas AA, et al. Human papillomavirus and penile cancers in Rio de Janeiro, Brazil: HPV typing and clinical features. International Brazil Journal of Urology. 2008 Jul-Aug; 34(4): 467-74; discussion 475-6. **[3]** Kirrander P, Kolaric A, Helenius G, et al. Human papillomavirus prevalence, distribution and correlation to histopathological parameters in a large Swedish cohort of men with penile carcinoma. BJU International. 2011 Aug; 108(3): 355-9. **[4]** Nasca MR, Innocenzi D, Micali G. Penile cancer among patients with genital lichen sclerosus. Journal of the American Academy of Dermatology. 1999 Dec; 41(6): 911-4. **[5]** Rubin MA, Kleter B, Zhou M, et al. Detection and typing of human papillomavirus DNA in penile carcinoma: evidence for multiple independent pathways of penile carcinogenesis. The American Journal of Pathology. 2001 Oct; 159(4): 1211-8. **[6]** Micali G, Nasca MR, Innocenzi D, et al. Penile cancer. Journal of the American Academy of Dermatology. 2006 Mar; 54(3): 369-91; quiz 391-4. **[7]** http://www.europeanurology.com/article/S0302-2838(14)01025-2/abstract/eau-guidelines-on-penile-cancer-2014-update

The role of magnetic resonance imaging in prostate cancer: Changing paradigm

Amila Siriwardana [1,2,3]
Willemien van den Bos [1,2]
Ron Shnier [4], Phillip Stricker [1,2]

1 St Vincent's Prostate Cancer Centre, St Vincent's Clinic, Sydney, Australia

2 Australian Prostate Cancer Research Centre – New South Wales, The Garvan Institute of Medical Research / The Kinghorn Cancer Centre, Sydney, Australia

3 University of New South Wales, Sydney, New South Wales, Australia

4 Southern Radiology, Randwick, New South Wales, Australia

In recent years, magnetic resonance imaging (MRI) technology has improved and MRI is now evolving to have an encouraging role in the diagnosis and management of prostate cancer (PCa). The ability to accurately detect prostate cancer (PCa) and risk stratify patients is central to being able to counsel men about treatment options. Traditionally, the "gold standard" PCa diagnostic pathway combined clinical history, digital rectal examination, PSA testing and systematic random prostate sampling with transrectal ultrasound guidance (TRUS) [1, 2]. This has resulted in substantial overdetection of indolent disease, a proportion of missed or undersampled significant cancer and inaccurate tumour risk stratification. MRI is becoming an increasingly reliable means of obviating these issues. Not only does it have a growing role in cancer detection, but also facilitates targeting of prostate biopsies, monitoring of active surveillance patients, staging, surgical planning and assessment of treatment response to emerging focal therapies [3].

Multiparametric MRI Prostate (mpMRI)

MRI prostate was initially trialed in the 1980's with anatomic T1 and T2 images alone, lacking sensitivity and specificity for significant cancer detection [4]. Modern MRI prostate involves three imaging sequences combining anatomic and functional parameters (Table 1) [5]. The combination of these sequences (T2, DWI, DCE) is named multiparametric MRI (mpMRI), with a full scan taking approximately 30 minutes on 1.5 or 3 Tesla-magnet machines.

Table 1. Parameters for multiparametric MRI (5)

T2-weighted imaging (T2)	Assessment of anatomical prostate zones
Diffusion weighted imaging (DWI)	Tumour detection and characterization including an apparent diffusion coefficient (ADC) map
Dynamic contrast-enhanced imaging (DCE)	Cancer vascularization evaluation following gadolinium contrast administration

PI-RADS Scoring For mpMRI Prostate

Prostate imaging reporting and data system version 2 (PI-RADS v2) is the updated reporting scheme used by radiologists to characterize and assess all suspicious prostate lesions found on mpMRI [6]. It uses a 5-point assessment scale indicating the likelihood that mpMRI findings correlate with the presence of clinically significant PCa at a particular anatomic location. Clinically significant disease is defined as Gleason score >7 (including 3 + 4 with prominent but not predominant Gleason grade 4), and tumour volume >0.5 ml, and/or extraprostatic extension [6].

Table 2. The PI-RADS v2 assessment scoring categories (6)

PI-RADS	Probability of significant cancer	Clinical implication
1	**Very Low**	Clinically significant cancer is highly ***unlikely*** to be present
2	**Low**	Clinically significant cancer is ***unlikely*** to be present
3	**Intermediate**	The presence of clinically significant cancer is ***equivocal***
4	**High**	Clinically significant cancer is ***likely*** to be present
5	**Very High**	Clinically significant cancer is ***highly likely*** to be present

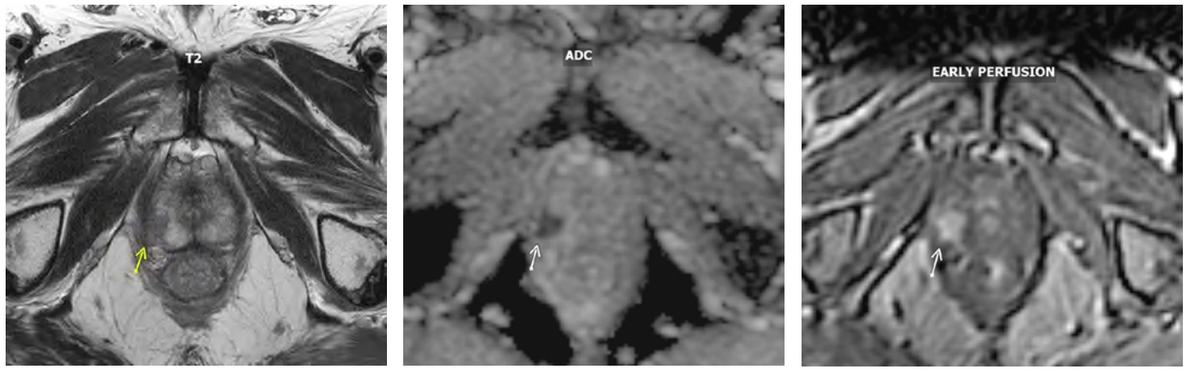


Figure 1. mpMRI of Gleason 9 cancer in right posterolateral apex showing a PI-RADS 4 lesion on a) T2-imaging, b) diffusion-weighted imaging with ADC map and c) dynamic contrast enhanced imaging with early perfusion.

Clinical Applications

Cancer detection

Acknowledging that the traditional diagnostic pathway has limitations, mpMRI of the prostate is proving to be an excellent instrument to aid detection of aggressive cancers within the prostate, while potentially reducing over-detection of insignificant low-grade foci [3, 4]. The reported sensitivity of mpMRI in detection of any significant PCa varies widely (76-96%) and is largely dependent on the experience of the radiologist [3, 7]. However, a recent study at our centre showed a sensitivity of 96% for significant cancer detection and a negative predictive value of 92%, when assessing biopsy-naive men over 40 years with an abnormal PSA or DRE [8].

The role of magnetic resonance imaging in prostate cancer: continued

Targeted biopsy and localization in patients with previous negative biopsy

Currently, there are three ways to use mpMRI to perform targeted biopsies: Cognitive fusion biopsy, MRI/TRUS-fusion biopsy and in-bore MRI-guided biopsy; each are explained in the box below.

Cognitive fusion biopsy:	Surgeon aims to target lesion manually with knowledge of suspicious areas seen on the MRI prostate images
MRI/TRUS-fusion biopsy:	MRI is co-registered with real-time ultrasound images via specialized software to facilitate region of interest sampling
In-bore MRI-guided biopsy:	Prostate biopsies are performed while the patient is undergoing an MRI prostate to ensure absolute concordance with MRI region of interest

Although in-bore MRI-guided biopsy is the most reproducible technique, cognitive fusion and MRI/TRUS-fusion techniques are more cost effective and universally applicable [7].

A recent study by Siddiqui et al. of 1003 men undergoing conventional TRUS biopsy and mpMRI with MRI-targeted biopsy showed that the MRI/TRUS-fusion technique diagnosed 30% more high-grade cancers and 17% less low-grade cancers compared to TRUS [9]. These results are echoed in a recent meta-analysis of MRI-targeted biopsy showing similar overall cancer detection rates to standard TRUS, however, significantly improved detection of significant cancer, reduced detection of insignificant cancer and improved detection of significant cancer in patients with previous negative biopsies [10]. Further studies are required to validate the possibility of replacing systematic biopsy with MRI-targeted approaches.

Active surveillance population

Active surveillance of patients diagnosed with prostate cancer relies on accurate risk stratification of men and a precise means to follow-up patients. mpMRI appears to not only aid in selection of active surveillance patients, but may be a means to monitor patients on active surveillance protocols, decreasing the frequency of follow-up prostate biopsy [11]. Validation studies of this principle are currently being performed.

Staging, treatment planning and role in Focal Therapy

MRI of the prostate was initially introduced as a staging tool for PCa patients, providing information on extra-glandular disease and involvement of the neurovascular bundles, seminal vesicles and lymph nodes. In 2012, the reporting of extraprostatic disease was standardized, and subsequently mpMRI is increasingly used as a decision tool to guide surgical technique such as nerve-sparing intent [5]. Emerging focal therapies for PCa rely on accurate localization to allow planning of limited ablation of the treatment zones, while sparing normal tissue. mpMRI is currently being used in conjunction with transperineal biopsy as a means to help detect appropriate lesions, guide treatment and follow-up patients undergoing focal therapies such as irreversible electroporation, cryosurgery, high-intensity focal ultrasound, photodynamic therapy, radio-frequency ablation and laser-induced interstitial thermotherapy [12].

Limitations and future directions

mpMRI prostate is still evolving, and is not without limitations. There is a significant learning curve of at least 100 cases with mpMRI reporting, and ongoing education is required. Similarly, it is not Medicare rebatable, putting the cost burden on patients. Further research on utility and cost-effectiveness of mpMRI will be essential to establishing its role in the PCa diagnosis and management paradigm. The Urological Society of Australia and New Zealand currently recommends that mpMRI be performed and reported by experienced radiologists, should be ordered and interpreted by urologists, and finally should not yet be considered on its own, but instead in combination with history, examination and biopsy as part of a comprehensive assessment for prostate cancer.

References

[1] Carter HB. American Urological Association (AUA) guideline on prostate cancer detection: process and rationale. BJU International. 2013 Sep; 112(5): 543-7. **[2]** Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. European Urology. 2014 Jan ;65(1): 124-37. **[3]** Futterer JJ, Briganti A, De Visschere P, et al. Can Clinically Significant Prostate Cancer Be Detected with Multiparametric Magnetic Resonance Imaging? A Systematic Review of the Literature. European Urology. 2015 Dec; 68(6): 1045-53. **[4]** Thompson J, Lawrentschuk N, Frydenberg M, et al. The role of magnetic resonance imaging in the diagnosis and management of prostate cancer. BJU International. 2013 Nov; 112 Suppl 2:6-20. **[5]** Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate MR guidelines 2012. European Radiology. 2012 Apr; 22(4): 746-57. **[6]** Barentsz JO, Weinreb JC, Verma S, et al. Synopsis of the PI-RADS v2 Guidelines for Multiparametric Prostate Magnetic Resonance Imaging and Recommendations for Use. European Urology. 2016 Jan; 69(1): 41-9. **[7]** Radtke JP, Teber D, Hohenfellner M, et al. The current and future role of magnetic resonance imaging in prostate cancer detection and management. Translational Andrology and Urology. 2015 Jun; 4(3): 326-41. **[8]** Thompson JE, van Leeuwen PJ, Moses D, et al. The Diagnostic Performance of Multiparametric Magnetic Resonance Imaging to Detect Significant Prostate Cancer. The Journal of Urology. 2016 May; 195(5): 1428-35. **[9]** Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA. 2015 Jan 27; 313(4): 390-7. **[10]** Schoots IG, Roobol MJ, Nieboer D, Bangma CH, Steyerberg EW, Hunink MG. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. European urology. 2015;68(3):438-50. **[11]** Schoots IG, Petrides N, Giganti F, Bokhorst LP, Rannikko A, Klotz L, et al. Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. European urology. 2015;67(4):627-36. **[12]** Donaldson IA, Alonzi R, Barratt D, Barret E, Berge V, Bott S, et al. Focal therapy: patients, interventions, and outcomes--a report from a consensus meeting. European urology. 2015;67(4):771-7.

Hypogonadism and testosterone replacement

Ada S. Cheung
Department of Endocrinology and Medicine (Austin Health),
The University of Melbourne

Although at times touted to be a "fountain of youth" testosterone supplementation in men is certainly not straightforward, with few good quality studies of significant duration to support benefits of treatment, particularly in aging men. Furthermore, symptoms of low testosterone levels become more common with increasing age, making diagnosis somewhat challenging.

Causes

Hypogonadism may be primary, due to testicular disease (which is associated with elevated luteinising hormone (LH)) or secondary due to pituitary dysfunction, sometimes termed hypogonadotrophic hypogonadism, and associated with low or inappropriately normal LH levels (Table 1). Medical co-morbidities including diabetes, obesity and any acute or chronic illness can also lead to secondary hypogonadism. Testosterone levels do decrease with increasing age [1], also known as late-onset hypogonadism, however it is unclear if testosterone is a cause, or a consequence of pre-existing disease related to accumulation of age-related co-morbidities [2]. There is currently no data that modifying these testosterone levels improve outcomes in older men and there has been some suggestion that this may in fact be harmful [3].

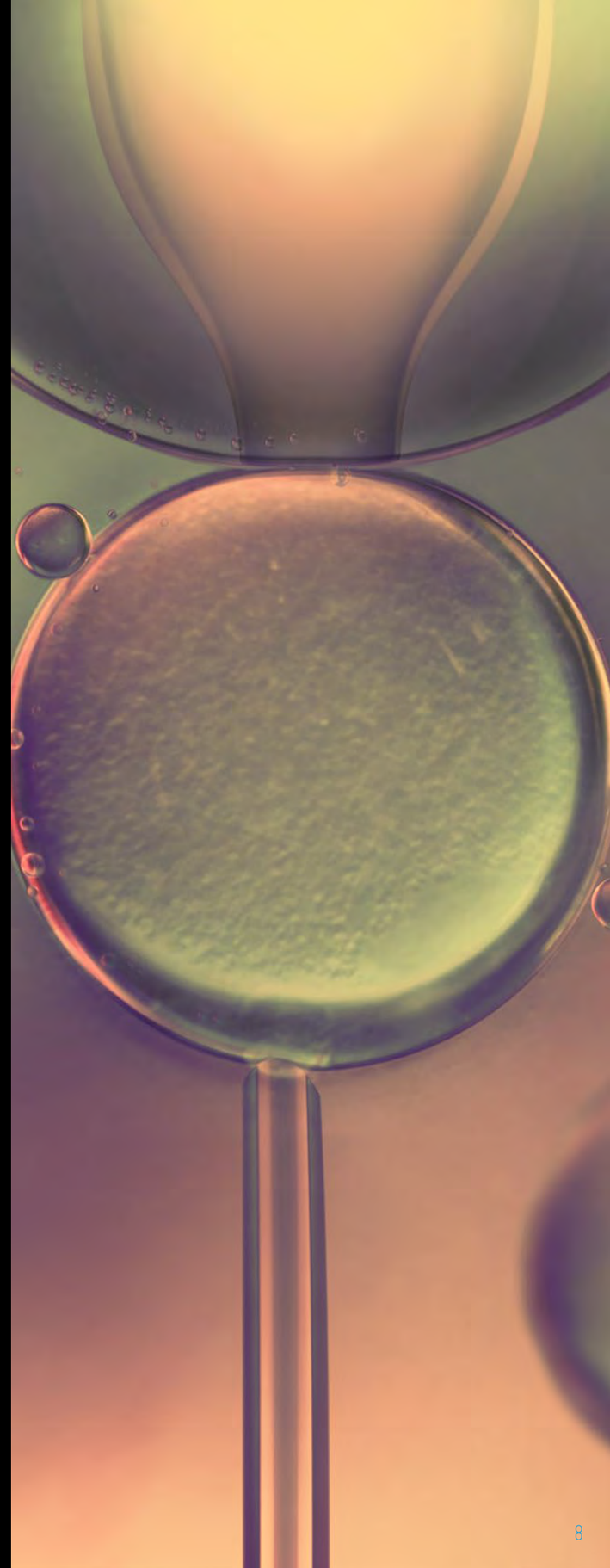


Table 1 - Common causes of hypogonadism in men	
Primary (Testicular Dysfunction) Low Testosterone, High LH	**Secondary (Pituitary Dysfunction)** Low Testosterone, Low or Inappropriately Normal LH
Klinefelter's syndrome	Acute illness
Undescended testes	Chronic illness (i.e. diabetes mellitus, obesity, sleep apnoea, renal disease, pulmonary disease, heart failure, eating disorders or malnutrition)
Orchidectomy	
Orchitis i.e. due to mumps infection	Hyperprolactinaemia
Chemotherapy	Pituitary tumour including prolactinoma
Radiotherapy to testes	Ageing
Testicular trauma	Kallmann's syndrome
Drugs (alcohol, ketoconazole)	Idiopathic hypogonadotrophic hypogonadism
Haemochromatosis	Infiltrative disease (haemochromatosis,

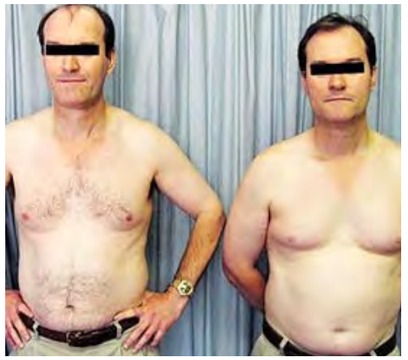


Figure 1.
Subtle signs of hypogonadism are highlighted in these identical twins. The man on the right has hypogonadism related to a pituitary tumour and in contrast to his unaffected identical twin brother (left side), has evidence of central adiposity, gynaecomastia, loss of body hair, nipple pallor, proximal muscle wasting and preservation of scalp hair. Reproduced from; The New England Journal of Medicine 2008; 359(26): 2824. [5]

Adding to the complexity is that symptoms of hypogonadism are non-specific. Symptoms such as decreased sexual function, mobility and energy overlap with many other conditions. The large European Male Aging Study sought to characterise specific symptoms of late-onset hypogonadism and thresholds at which men develop symptoms [4]. The study found that low libido, loss of morning erections and erectile dysfunction were the three best predictors of low testosterone levels and tended to occur when levels were <8 nmol/L. Notably, serum total testosterone should be measured in the fasting state and performed in the early morning between 7am – 11am and if low, confirmed on a separate occasion. LH and FSH levels should be performed to assess for a primary or secondary cause to guide further investigation such as pituitary MRI or prolactin levels. Consideration should be given to investigation for potential long-term consequences of hypogonadism including osteoporosis and metabolic syndrome.

Examine the testes

Often overlooked in the evaluation is the importance of a simple testicular examination. Klinefelter's syndrome, which affects up to 1 in 600 men, can be detected by the identification of pea-sized testicles. Examination may reveal other signs of hypogonadism, which can be subtle (see Figure 1).

Who to treat?

There are multiple considerations to be made when deciding whether to treat an individual with testosterone supplementation. First and foremost is to address the cause and potential for reversibility. For example, dopamine agonists to treat hyperprolactinemia will in turn, potentially normalise testosterone levels. Treatment should be recommended for those with symptoms and confirmed biochemical hypogonadism in whom a reversible cause is not identified. Potential benefits may include improved libido, bone density (however there is no fracture data), decreased fat mass and increased lean mass, and possible effects on mood and cognition [6]. Despite improvements in fat mass, randomised controlled trials have failed to show a benefit in glycaemic control in those with type 2 diabetes [7]. Benefits must be weighed with potential risks of testosterone therapy such as polycythaemia, worsening of obstructive sleep apnoea, mood changes, acne and oily skin [6]. Traditionally, testosterone has been thought to potentially cause pre-existing prostate cancer to progress and worsen prostatic symptoms, however, this is controversial and a recent meta-analysis of 14 clinical trials suggested no deterioration of lower urinary tract symptoms [8]. Recent concerns have also been raised regarding a potential increase in cardiovascular events with testosterone replacement; however, these are mostly retrospective analyses with considerable limitations [9]. Given the uncertainty about long-term risks and to minimise inappropriate use of testosterone, the Pharmaceutical Benefits Scheme now stipulates that for late-onset hypogonadism, treatment can only be reimbursed if total testosterone is <6.0 nmol/L and the patient has an appointment for evaluation with an endocrinologist, urologist or sexual health physician.

What can we learn from the recently published Testosterone Trials?

Given the controversies surrounding testosterone supplementation, in 2003, the US Institute of Medicine (IOM) concluded that there was a lack of definite evidence that testosterone replacement therapy conferred significant benefit, and as such, called for more large, randomised-controlled clinical trials. In response to this, the Testosterone Trials, a series of seven independent but coordinated, multi-centre, double-blind, placebo-controlled trials intended to address outcomes on sexual function, vitality, physical function, cognitive function, anaemia, bone density and cardiovascular events were initiated. In February 2016, Snyder and colleagues published the first results on sexual function, physical function and vitality [10]. Notably, recruited participants had to meet very stringent criteria; to be over 65 years of age and have a serum total testosterone < 9.5 nmol/L. It was difficult to recruit men into this study as relatively few had sufficiently low testosterone levels to qualify. Men enrolled had high baseline rates of comorbidities with 63% obese, 72% having hypertension and 15% had history of myocardial infarction, making it somewhat difficult to generalise findings to the wider population. Despite these stringent criteria, testosterone replacement was certainly not a "fountain of youth" and although demonstrating some improvements in sexual function (Figure 2), these were modest and waned in the later months. The magnitude of improvement was definitely not as robust as that seen for phosphodiesterase inhibitors. Small gains were seen in physical performance and mood, however overall vitality and walking distance was not improved with testosterone replacement.

The clinical importance of these results is unclear. Certainly for individuals with testosterone levels greater than 9.5 nmol/L, benefits would be doubtful. Even if benefits were seen, the degree of improvement was limited and long-term safety is still unclear. Whilst an important step in the field, the results from the first three Testosterone Trials do not resolve the controversy regarding possible adverse effects, in particular cardiovascular, and larger, longer studies are needed.

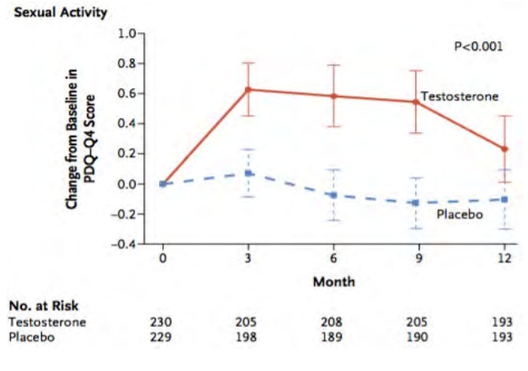


Figure 2. Sexual activity in the testosterone group compared with placebo. Reproduced from Snyder et al. [10]

Testosterone preparations

For those in whom a decision is made to commence testosterone supplementation, options for treatment include intramuscular injections, of which the simplest is long-acting testosterone undecanoate (Reandron®) typically given three-monthly, or daily topical options such as testosterone gel (Testogel®), testosterone transdermal solution (Axiron®), testosterone cream (AndroForte®) or testosterone patches (Androderm®). Treatment should be based on patient preference and tolerability. For intramuscular testosterone undecanoate, it is recommended that dose titration be based on trough levels (aiming for the low-normal range 10 – 15 nmol/L) as well as symptom relief, and the interval of injection may be increased or decreased to achieve this. For daily topical treatments, a fasting testosterone level should be performed with a goal of the normal reference range.

In those seeking fertility, testosterone can suppress spermatogenesis, and referral should be made to a specialised fertility service for consideration of gonadotrophin therapy, ideally prior to commencement of testosterone therapy.

Long-term monitoring

Treatment with testosterone supplementation is often lifelong, and although evidence is inconclusive, monitoring should occur for symptoms of obstructive sleep apnoea and lower urinary tract symptoms in addition to hypogonadal symptoms. Fasting serum testosterone as well as haemoglobin and prostate specific antigen should be performed periodically.

As there is currently little good quality evidence to guide management of hypogonadism, treatment should be reserved for those who are symptomatic and have low serum total testosterone levels and where there is a specific goal for treatment. This may be to relieve symptoms or to improve bone mineral density. Future results from the Testosterone Trials and other clinical studies are eagerly awaited, and in time, will hopefully improve clinical decision making for men with hypogonadism.

References

[1] Yeap BB, Alfonso H, Chubb SA, et al. Reference ranges and determinants of testosterone, dihydrotestosterone, and estradiol levels measured using liquid chromatography-tandem mass spectrometry in a population-based cohort of older men. The Journal of Clinical Endocrinology and Metabolism. 2012 Nov; 97(11): 4030-9. **[2]** Sartorius G, Spasevska S, Idan A, et al. Serum testosterone, dihydrotestosterone and estradiol concentrations in older men self-reporting very good health: the healthy man study. Clinical Endocrinology (Oxf). 2012 Nov; 77(5): 755-63. **[3]** Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. The New England Journal of Medicine 2010 Jul 8; 363(2): 109-22. **[4]** Wu FC, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. The New England Journal of Medicine. 2010 Jul 8; 363(2): 123-35. **[5]** Newnham HH & Rivera-Woll LM. Images in clinical medicine. Hypogonadism due to pituicytoma in an identical twin. The New England Journal of Medicine. 2008 Dec 25; 359(26): 2824. **[6]** Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology and Metabolism. 2010 June; 95(6): 2536-59. **[7]** Gianatti EJ, Dupuis P, Hoermann R, et al. Effect of testosterone treatment on glucose metabolism in men with type 2 diabetes: a randomized controlled trial. Diabetes Care. 2014 Aug; 37(8): 2098-107. **[8]** Kohn TP, Mata DA, Ramasamy R, et al. Effects of Testosterone Replacement Therapy on Lower Urinary Tract Symptoms: A Systematic Review and Meta-analysis. European Urology. 2016 Jun; 69(6): 1083-90. **[9]** Tanna MS, Schwartzbard A, Berger JS, et al. Management of Hypogonadism in Cardiovascular Patients: What Are the Implications of Testosterone Therapy on Cardiovascular Morbidity? The Urololgic Clinics of North America. 2016 May; 43(2): 247-60. **[10]** Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of Testosterone Treatment in Older Men. The New England Journal of Medicine. 2016 Feb 18; 374(7): 611-24.

Popular diets - Fad or fact?

Karen Inge
kareninge.com

The prevalence of obesity in Australian men is a concern with 70% of men over the age of 25 now overweight or obese [1]. Men living in regional areas have a higher incidence (75%) compared with men living in major cities (68%) [1]. Obesity has been associated with increased risk of cardiovascular disease, Type 2 diabetes and certain cancers such as aggressive prostate cancer. The increase in sedentary behaviours and poor diet choices appear to be major contributing factors. The rate of sedentary males has risen from 34% in 2004-05 to over 40% today. Additionally, men appear to be more sedentary when they reach the age of 45 [1]. According to the latest nutrition survey, males aged 31-70 are consuming 36% of their total energy (kilojoule) intake from discretionary foods [1]. Discretionary foods refer to sweet food and beverages, processed meats, pies and pastries, commercial burgers and fried foods and salty snack foods. Alcoholic beverages account for 6% of total energy intake [1]. With the rise of weight loss diets frequently promoted on various media avenues, 17% of men are on a weight loss diet at any given time [2]. Fad diets often boast many health benefits, but it can be difficult to discern the facts from the miraculous claims. The popularity of some of these diets has gained interest in the scientific field; The table on the following page, provides a summary evaluating the pros and cons of some of the latest and most popular weight loss diets.

Summary

Diets come with advantages and disadvantages, but it is crucial for individuals to recognise that although diets may result in weight loss, there is a chance that they will regain the weight if they relapse back into their previous eating habits. Combined with exercise, a nutritionally-balanced diet provides individuals with the necessary nutrients for optimal health. The majority of men are not meeting the Australian Dietary Guidelines: only 3.8% meet the recommended daily serves of vegetables and 44% for the fruits [11]. Although dietary requirements is dependent on size, age and other health factors, the Australia Guide to Healthy Eating recommends the following daily serves for the majority of men aged 19-70 [12]:

- 6 x vegetables and legumes (5 ½ serves for men aged 51-70)
- 2 x fruits
- 6 x grains
- 3 x lean meat/fish/poultry/eggs/seeds/legumes/beans (2 ½ serves for men aged 51-70)
- 2.5 x milk/yoghurt, cheese & alternatives
- 0-2 ½ x of additional serves from the previous five groups/discretionary foods

Key issues to consider when advising on the suitability of the latest diet as recommended by Dietitians Association of Australia:

- Is it backed by science?
- Does it fit with generally accepted nutrition and healthy guidelines?
- Does it come from a professional with recognised nutrition qualifications?
- Can it be adapted to individual lifestyles, while meeting individual nutrition needs?
- Is it designed to be followed in the long term?

In comparison, it is best to steer away from diets that make unrealistic claims and promote unbalanced and unhealthy eating advice, such as avoiding nutritious foods or entire food groups.

For individually tailored weight loss dietary advice, it may be best to refer to an Accredited Practising Dietitian: http://daa.asn.au/

References

[1] Australia Bureau of Statistics. Australian Healthy Survey: Updated Results, 2011-12. cat no. 4365.0.55.033, ABS, Canberra. **[2]** Better Health Channel. Body Image – Men. 2013. [cited May 24 2016]; Available from: https://www.betterhealth.vic.gov.au/health/healthyliving/body-image-men **[3]** Matarese, LE, Pories, WJ. Adult weight loss diets: Metabolic effects and outcomes. Nutrition in Clinical Practice. 2014 Dec; 29(6): 759-67. **[4]** Whyte, J. Today's diets: Do they work? Fact versus fiction. Consultant. 2013; 53(10): 701-04. **[5]** Katz, DL, Meller. S. Can we say what diet is best for health? Annual Review of Public Health. 2014; 35: 83-103. **[6]** Pitt, CE. Cutting through the Paleo hype: The evidence for the Palaeolithic diet. Australian Family Physician. 2016 Jan-Feb; 45(1): 35-8. **[7]** Bellavia A, Tektonidis TG, Orsini N, et al. Quantifying the Mediterranean diet in terms of survival. European Journal of Epidemiology. 2016 May; 31(5): 527-30. **[8]** Kenfield SA, DuPre N, Richman EL, et al. Mediterranean Diet and Prostate Cancer Risk and Mortality in the Health Professionals Follow-Up Study. European Urology. 2014 May; 65(5): 887-94. **[9]** Johnstone A. Fasting for weight loss: an effective strategy or latest dieting trend? International Journal of Obesity. 2015 May; 39(5): 727-33. **[10]** Sheppeard, A. To diet or not to diet? Australian Doctor. 2013 Jun; 6: 19-21. **[12]** Australia Bureau of Statistics. National Healthy Survey: First Results, 2014-15. cat no. 4364.0.55.001, ABS, Canberra. **[13]** Australian Guide to Healthy Eating. Recommended number of serves for adults. [cited 24 May 2016]; Available from: https://www.eatforhealth.gov.au/food-essentials/how-much-do-we-need-each-day/recommended-number-serves-adults

DIET	PREMISE	PROS	CONS	ADVICE
LOW CARB, HIGH-FAT	**Diet:** meat (including the fat), fish, eggs, full-fat dairy, nuts and non-starchy vegetables, fats & oils including coconut oil **Restrictions:** starchy vegetables, grains & grain products, legumes and most fruits, sugar + other sweetened foods & beverages	• Reduction in energy-rich, poor nutrient foods • Favours vegetables and other unprocessed foods • Rapid initial weight loss [3] • Lowers cardiovascular disease and all-cause mortality - Greater health benefits for those who reduce their fat and protein intake by choosing vegetable sources [4]	• Lack of fibre without grains can cause constipation [3] • Halitosis from ketone production [3] • People with diabetes must adjust insulin for reduction in body weight and carbohydrate intake [3] • Can lead to weight gain if one does not strictly follow kilojoule restrictions [5]	• Differentiate between nutritious and non-nutritious carbohydrate-rich foods • Be wary of eating foods high in saturated fat like fatty meat such as bacon, salami and other processed meats + using saturated fats like butter, cream and coconut oil => saturated fat compromises heart health & processed meats increase the risk of bowel cancer
PALAEOLITHIC (PALEO)	Eating like our Stone Age ancestors – modern adaptation **Diet:** lean meat and poultry, fish, seafood, eggs, vegetables, fruit, nuts, seeds **Restrictions:** dairy, grains, chickpeas, lentils	• Emphasis on natural, unprocessed foods • Increased satiety [6] • Positive results in short-term studies: weight loss, improved blood pressure and glucose tolerance, ⇧ insulin secretion, ⇩ insulin sensitivity and improved lipid profile [5,6]	• Many of the plants our ancestors ate no longer exist [5] • Whole grains and legumes are important sources of energy-giving carbohydrates and fibre (soluble, insoluble and resistant starch) ⇨ lack of fibre can lead to constipation and other bowel issues [6] • Dairy is a major source of calcium ⇨ inadequate calcium in diet increases risk of osteoporosis • Over-hyped and under-researched ⇨ limited number of controlled clinical trials comparing the Paleo diet to accepted diets such as the Mediterranean Diet [6]	• Ignore Paleo marketing fads and snack foods, such as such as Paleo cookies or brownies, which are high in saturated fat and kilojoules • Follow Paleo Plus diet – Paleo + dairy & grains
VEGETARIAN / VEGAN	**Diet:** grains, legumes, fruit, vegetables, nuts, seeds **Restrictions:** dairy, eggs, all foods containing any animal-derived ingredient **Pescatarian:** includes fish but not red meat or poultry **Lacto-ovo:** permits dairy products and eggs	• A nutritionally-balanced vegan diet has benefits related to ⇩ inflammation, ⇩ cancer risk, improvements in body composition & insulin sensitivity [5] • Ample evidence suggests: - ⇩ risk of cardiovascular disease, hypertension and Type 2 diabetes - lowers cholesterol levels and blood pressure [4]	• Deficiency risks: vitamins B12 and D, iron, calcium, zinc and long chain omega-3 fatty acids ⇨ however, dietary deficiencies not as common today due to fortified products and meat substitutes [4] • Very high fibre may cause gastrointestinal symptoms	• Vegans need regular blood tests to monitor nutrition status • Important to include protein alternatives: tofu, tempeh, legumes, nuts and seeds – these are also sources of iron, zinc and calcium • Iron-rich foods: leafy greens, legumes, nuts, seeds • Need to include Vitamin-C rich foods, like citrus and tomatoes, to help iron absorption • Be wary of vegetarian dishes when eating out as kilojoule intake may be excessive due to large portions and hidden fats
MEDITERRANEAN	Adapting the diets of societies around the Mediterranean Sea **Diet:** High intake of plant foods - vegetables, fruits, nuts, olive oil, legumes, herbs & spices; moderate intake of red wine; low consumption of milk and dairy products primarily from yoghurt and cheese; and limited consumption of red meat (with emphasis on fish as meat)	• Centred around plant foods • No banned food groups • Wine in moderation • Rich in healthy unsaturated fat from olive oil, oily fish and nuts • Includes moderate portions of nutritious carbohydrates • Favourable effects on body composition, insulin resistance and metabolic syndrome • Heart health benefits in lipoprotein levels, endothelium vasodilation, myocardial and cardiovascular mortality, and cancer incidences in obese patients [4,5] • Rich in antioxidants and anti-inflammatory properties [7] • Studies show it reduces the risk of some cancers [7] • Reduced mortality for men diagnosed with nonmetastatic prostate cancer [8]		• Easy to follow • Tastes delicious • Need to exert caution with portion of healthy foods • Be wary of excessive wine consumption –Mediterraneans tend to drink during mealtimes with family, friends, neighbours
INTERMITTENT FASTING 5:2 "THE FAST DIET"	Fasting two non-consecutive days a week => on fasting days, women, 500 calories (2000 kJs); men, 600 calories (2400 kJs) Non-fasting days: follow healthy eating guidelines **Restrictions:** alcohol on fasting days	• No banned foods • Initial research suggests it may be effective for weight loss and coronary heart risk reduction in obese adults [9] • Preliminary studies indicate that this diet is effective for normal-weight and overweight individuals wishing to lose a moderate amount of weight (5-6kg) within a relatively short period of time (12 weeks) [9] • Although additional research is required, this diet may be as efficacious as daily kilojoule restrictions in improving certain indices of risk of Type 2 diabetes and cardiovascular disease [9]	• Difficulties sleeping, bad breath, irritability, anxiety, dehydration, daytime sleepiness [10] • Likely to be very hungry and have less energy [10] • Risk of overindulging/binging on non-fasting days [10] • Long-term effects on human unclear [9]	• Not recommended for people: already underweight, children and teenagers, people with Type 1 diabetes or on insulin therapy, pregnant or breastfeeding mothers, people recovering from surgery [10]

Looking for new twists in Peyronie's disease


Uros Milenkovic, Wouter Everaerts
UZ Leuven, Belgium

Peyronie's disease (PD) is an incurable and sexually debilitating medical condition, named after the French surgeon Francois Gigot de la Peyronie. In 1743 he described an abnormality of the penis typified by indurations of the corpora cavernosa associated with penile deformity. Indeed, PD is a connective tissue disease affecting the tunica albuginea, causing aberrant tissue healing after (minor) penile trauma. Formation of disarranged collagen and elastin depositions constitutes a fibrous plaque, which impedes the expansion of the tunica during erection, resulting in shortening, penile bending, indentation and often pain. Two distinct stages can be discriminated. The initial (active) stage, with inflammation and plaque formation, is associated with painful erections and changing deformity of the penis. After this initial phase, the plaque retracts and calcifies, resulting in a stable and usually painless deformity of the penis (chronic stage).

Several pathological processes occur in a temporal fashion; (micro) traumata, fibrin deposition, inflammation, myofibroblast formation, extracellular matrix formation, contraction, stabilization and finally calcification [1]. The interrelation between the various stages and the signals that regulate these processes are ill defined. Due to its relative sparsity and the uncommon need for resection of plaque tissue, especially in the active phase of the disease, the human phenotype of PD has been understudied. Some lessons can be learnt from a highly similar disease in the palmar fascia, Dupuytren's contracture, which is more common. The co-occurrence of Dupuytren's contracture, Ledderhosen (plantar fascial fibromatosis) and PD suggests a genetic background.

PD presents with either a penile curvature, waist or more complex deformity, often resulting in severe and difficult-to-treat erectile dysfunction [2]. Moreover, it can lead to coital fracture and significant psychological distress for patients as well as their partners [2]. Although the exact prevalence is unknown, it is estimated between 1 and 3% in Western populations [3]. PD most often occurs in older men (mean age 53), although nearly 10% of patients experience symptoms before the age of 40. Recent trauma is the most commonly associated event, but the majority of men have no recollection of any trauma.

Evaluation of patients with PD consists of a focused medical history and physical examination looking for signs of coexistent Dupuytren and/or Ledderhosen disease, a subjective erectile function questionnaire, and induction of an artificial erection to objectively measure penile curvature and document plaque characteristics with penile duplex Doppler ultrasound (PDDU). Since the latter is rarely readily available, a photograph of the patient's phallus in full erection may serve as an alternative assessment tool for penile deformity. Finally, the psychological and emotional impact of PD on the patient's personal life should be assessed. Standardized questionnaires, such as the International Index of Erectile Function (IIEF) and the Peyronie's Disease Questionnaire can be used to follow up disease progression and treatment effects over time.

Several treatment options are available, depending on disease severity (erectile status, invalidating symptoms, psychological impact), patient preference, and experience of the treating physician. It is important that patients have realistic expectations about the proposed therapies to minimize disappointment and physiological distress. Medical therapies are utilized in early stage PD, whereas surgical interventions and intra-lesional injections are reserved for patients with a stable curvature or plaque for more than 6 months (chronic phase).

A myriad of agents have been proposed as oral treatment for PD, including vitamin E, tamoxifen, colchicine, carnitine, antioxidants and phosphodiesterase (PDE) 5 inhibitors. Although these drugs are more appealing to patients than intra-lesional injections or surgery, none of these agents have documented long-term efficacy and their use is not supported by the International Consultation on Sexual Medicine [4].

Surgical procedures to the tunica albuginea offer a fast and effective solution to obtain a functionally straight penis, but often lead to shortening of the penis and impose a high risk of worsening the already present erectile dysfunction. Alternatively, intra-lesional injections of collagenase improve plaque size and penile deformity, but can be accompanied with pain, corporal rupture and allergic reactions [5]. Both interventions rely on the ability to resume sexual intercourse by straightening the penile curve, but don't focus on the inherent pathophysiological process leading to PD. As such these interventions should be considered as symptom management rather then an actual causative treatment.

Therefore, there is an unmet need for novel and improved therapeutic options for PD patients. Tackling the disease in an early stage, before irreversible plaque formation, could lower treatment costs and decrease the number of patients needing surgery.

Recent advances in regenerative medicine offer new perspectives in the treatment of PD. Recent studies have explored the potential for adipose tissue-derived stem cells (ADSC) to treat PD in animal models. ADSC possess anti-fibrotic, immunomodulatory and extracellular matrix-modifying paracrine properties and have been used successfully in fibrotic disease models including kidney, liver and lung fibrosis [6]. Injection of transforming growth factor beta (TGF-b1) in the dorsal tunica albuginea induces PD-like plaques in rodents. Interestingly, injection of ADSCs 24 hours after injection of TGF-b1 (acute phase) was able to prevent penile plaque formation and improve erectile function [6, 7]. Several trials using ADSC to treat PD in humans have recently been initiated. Results of these trials are eagerly awaited to see if ADSC can really twist the future for patients with PD.

References

[1] Gonzalez-Cadavid NF. Mechanisms of penile fibrosis. The Journal of Sexual Medicine. 2009 Mar; 6 Suppl 3: 353–62. **[2]** Langston JP, Carson CC 3rd. Peyronie's disease: review and recent advances. Maturitas. 2014 Aug; 78 (4): 341–3. **[3]** Sommer F, Schwarzer U, Wassmer G, et al. Epidemiology of Peyronie's disease. International Journal of Impotence Research. 2002 Oct; 14(5): 379–83 **[4]** Ralph D, Gonzalez-Cadavid N, Mirone V, et al. The medical management of Peyronie's disease: evidence-based 2010 guidelines. The Journal of Sexual Medicine. 2010 Jul; 7(7): 2359–74. **[5]** Hatzimouratidis K, Eardley I, Giuliano F, et al. EAU Guidelines on Penile Curvature. European Urology. 2012 Sep; 62(3): 543-52. **[6]** Castiglione F, Hedlund P, Van der Aa F, et al. Intratunical injection of human adipose tissue-derived stem cells prevents fibrosis and is associated with improved erectile function in a rat model of Peyronie's disease. European Urology. 2013 Mar; 63(3): 551–60. **[7]** Gokce A, Abd Elmageed ZY, Lasker GF, et al. Adipose tissue-derived stem cell therapy for prevention and treatment of erectile dysfunction in a rat model of Peyronie's disease. Andrology 2014 Mar; 2(2): 244–51.

The role of physiotherapy in the management of male chronic pelvic pain


Shan Morrison [1]
Rachel Heerey [1,2]
1 Women's & Men's Health Physiotherapy, Melbourne,
2 APCR Prostate Cancer Centre Melbourne

What is chronic pelvic pain syndrome?

Chronic pelvic pain syndrome is a common and disabling condition. It is any pelvic pain that lasts for more than 6 months, and is estimated to affect 1 in 10 men. An Australian study reported a prevalence of 8% [2]. It is the 3rd most common diagnosis of men under 50 years of age presenting to urologists. Symptoms significantly diminish quality of life and impair physical and psychological function.

It presents as pain or discomfort in the lower abdomen, perineum (between testes and the anus), the penis, testes, anus, low back, buttock or the tailbone. Bladder, bowel and sexual pain and changes in function of these organs are common. It is often diagnosed as prostatitis and treated with antibiotics, however 90% of cases do not respond to this management. This leaves sufferers experiencing pain that impacts their whole life – especially their ability to sit, concentrate at work, sleep, exercise and to have sex, negatively impacting relationships, work productivity, enjoyment of daily activities and their mental health.

What causes chronic pelvic pain syndrome?

The current understanding of the cause of chronic pelvic pain is that it most commonly begins with local injury to the urinary tract or surrounding tissues, such as infection or trauma. This then leads to local inflammation, and spasm and ischemia of the pelvic floor muscles and/or bladder neck. In certain susceptible / predisposed individuals, this subsequently leads to changes in the peripheral and central nervous systems, leading to the development of a chronic systemic neurological condition [4].

The original cause of the pain has often resolved, but the pain continues. This is why most investigations come back negative. New pain generators develop in surrounding tissues (i.e. muscles) and nerves transmitting sensations from painful areas can become excessively sensitive. Men with chronic pelvic pain have been found to have functional and anatomical brain changes suggestive of central sensitisation on functional MRI [1].

Stress, anxiety or depression are often part of the vicious cycle of pain. Due to the mind - body connections, pelvic pain can become all-consuming, affecting sleep, concentration, mood, gut and energy levels.

UPOINT classification of chronic pelvic pain syndrome

Historically, chronic pelvic pain has been difficult to treat and poorly managed. Treatment has traditionally consisted of monotherapies, such as medications including antibiotics or anti-inflammatories, isolated psychological intervention, or alternative therapies such as acupuncture. However, due to the diverse aetiology and clinical presentations of men with chronic pelvic pain, monotherapy is often ineffective.

The UPOINT classification system was developed by Dr Daniel Shoskes in 2008, a Urologist in Cleveland, USA. It is a 6-point clinical phenotyping system for men with chronic pelvic pain [7]. The aim of the system is to use directed multi-model therapy to achieve improved treatment outcomes.

The 6 UPOINT domains are Urinary, Psychosocial, Organ Specific, Infection, Neurologic/Systemic, and Tenderness. Urinary is positive if the patient has bothersome urinary symptoms or high post-void residual, psychosocial is positive in the presence of clinical depression or catastrophising, organ specific is positive if there is specific prostate tenderness on examination or other organ specific findings, infection is positive if there is evidence of infection on pathology testing, neurologic / systemic is positive if there is pain outside the abdomen and pelvis or a concurrent diagnosis of fibromyalgia, chronic fatigue syndrome or irritable bowel syndrome, and tenderness is positive if there is palpable muscle spasm or trigger points in the pelvic floor muscles or abdomen. Each positive domain is then treated appropriately via referral to other members of a multidisciplinary team, such as a pelvic floor physiotherapist and psychologist.

Men with more positive domains on the UPOINT classification system have been shown to have higher symptom severity and longer duration of symptoms. Additionally, pain severity was most commonly associated with positive psychosocial, neurologic/systemic, and tenderness domains [5].

Shoskes et al, evaluated the UPOINT system, studying outcomes of 100 patients with chronic pelvic pain syndrome treated with multi-modal therapy offering specific therapy for each positive UPOINT domain [6]. It was found that 84% of men had a clinically significant improvement in symptoms and quality of life, maintained 6-12 months after treatment. This is a very promising outcome, given the previously published poor outcomes for men with chronic pelvic pain syndrome.

Physiotherapy management of chronic pelvic pain syndrome

It is essential that men with chronic pelvic pain are treated by a multi-disciplinary team of health care professionals to enable a thorough assessment and an individualised treatment plan. This team will often include a urologist, a pelvic floor physiotherapist, a psychologist, and a pain medicine specialist.

Pelvic floor physiotherapists are an integral part of this multidisciplinary team. Their primary role is to treat the 'Tenderness' UPOINT domain: tenderness in the pelvic floor muscles or surrounding muscles of the pelvis. Tenderness in the pelvic floor muscles is present in around 80% of men with chronic pelvic pain syndrome [8]. This is caused by spasm of these muscles, which in turn leads to tissue ischemia, and irritation of the pelvic nerves.

Treatment for pelvic floor muscle spasm often involves internal myofascial release, and teaching men how to relax their pelvic floor muscles. Internal myofascial release of the pelvic floor muscles is a common treatment technique, and has been found efficacious in this patient population [3]. The pelvic floor physiotherapist will also explain the science of chronic pelvic pain, which can give sufferers hope that pelvic pain can be changed for the better.

Shan Morrison and Rachel Heerey are pelvic floor physiotherapists with a special interest in chronic pelvic pain, practising at Women's and Men's Health Physiotherapy in Melbourne. Rachel also runs the Pelvic Pain Program at the APCR Prostate Cancer Centre in Melbourne. Further information on male chronic pelvic pain syndrome can be found at www.pelvicpain.org.au

References

[1] Farmer MA., Chanda ML, Parks EL, et al. Brain functional and anatomical changes in chronic prostatitis/chronic pelvic pain syndrome. The Journal of Urology. 2011 Jul; 186(1): 117-24. **[2]** Ferris JA, Pitts MK., Richters J, et al. National prevalence of urogenital pain and prostatitis-like symptoms in Australian men using the National Institutes of Health Chronic Prostatitis Symptom Index. BJU International. 2010 Feb; 105(3): 373-9. **[3]** Fitzgerald MP, Anderson RU, Potts J, et al. Randomized multicenter feasibility trial of myofascial physical therapy for the treatment of urological chronic pelvic pain syndromes. The Journal of Urology. 2013 Jan; 189(1 Suppl): S75-85. **[4]** Pontari M. Eitology of chronic prostatitis / chronic pelvic pain syndrome; psychoimmunoneurendocrine dysfunction (PINE syndrome) or just a really bad infection? World Journal of Urology. 2013 Aug; 31(4): 725-32. **[5]** Shoskes DA, Nickel JC, Dolinga R, et al. Clinical phenotyping of patients with chronic prostatitis/chronic pelvic pain syndrome and correlation with symptom severity. Urology, 2009 Mar; 73(3): 538-42; discussion 542-3. **[6]** Shoskes DA, Nickel JC, Kattan MW. Phenotypically directed multimodal therapy for chronic prostatitis/chronic pelvic pain syndrome: a prospective study using UPOINT. Urology. 2010 Jun; 75(6): 1249-53. **[7]** Shoskes DA, Nickel JC, Rackley RR, et al. Clinical phenotyping in chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis: a management strategy for urologic chronic pelvic pain syndromes. Prostate Cancer and Prostatic Diseases. 2009; 12(2): 177-83. **[8]** Zermann DH, Ishigooka M, Doggweiler R, et al. Neurourological insights into the etiology of genitourinary pain in men. The Journal of Urology. 1999 Mar; 161(3): 903-8.

Reducing the impact of cardiovascular toxicity of cancer therapies

Ben Costello[1, 2]
1 Baker IDI Heart and Diabetes Institute
2 Alfred Hospital

In the last few years, cardio-oncology has been a hot topic in both cardiology and oncology circles. As cancer survivorship has improved with advancing therapies, late cardiovascular (CV) side effects have become an important management issue, particularly in childhood cancers, lymphoma and breast cancer. For example, CV disease is now the major cause of mortality in patients diagnosed with early stage breast cancer, as these patients have longer cancer free survival, are older at diagnosis, and develop chemotherapy specific side effects [1].

Not only are there CV side effects from the traditional chemotherapy agents (in particular anthracyclines) but newer targeted therapies such as Herceptin (trastuzamab) and tyrosine kinase inhibitors are being noted to have CV side effects not necessarily predicted by the mechanism of action. Anthracyclines have tended to cause irreversible (Type I) cardiac myocyte damage, while myocyte injury from targeted therapies is more reversible (Type II), though there is considerable overlap. Detection of cardiotoxicity and prevention of progression is critical to avoid interruption to potentially curative cancer treatments.

AC (anthracycline) chemotherapy has been the mainstay of treatment for both haematologic malignances (aggressive lymphoma, leukaemia) and solid tumours (breast, sarcoma). There is correlation between the cumulative dose of AC and the incidence of cardiac failure, mediated by iron-dependent generation of reactive oxygen species and subsequent widespread oxidative damage. In trial settings, symptomatic heart failure occurs in 2-5% of patients treated with AC, which may be up to 20% in the real world with longer term follow up [2]. When advanced AC cardiomyopathy occurs, it is serious, with a two year mortality approaching 60% [3]. Treatment of AC cardiotoxicity is the same as other cardiomyopathies, with angiotensin converting enzyme inhibition (ACEI) and beta blockade the mainstay of cardioprotective strategies.

Cardiotoxicity from targeted therapies was originally noted with the use of Herceptin (trastuzamab) in aggressive breast cancers, over expressing the growth factor receptor gene HER2 (HER2+ cancers). The HER2 receptor is expressed in the cardiac myocyte and is involved in cell repair, particularly in vulnerable myocytes. When Herceptin is used in conjunction with AC chemotherapy the risk of cardiotoxicity is increased and cardiac dysfunction is noted in up to 40% of patients.

Other targeted therapies include tyrosine kinase inhibitors and other growth factor inhibitors, which are used in many cancers. Their CV effects vary, including increasing pleural effusions (dasatinib), vascular events (nilotinib) and hypertension (sorafenib, bortezomib), as well as potential direct cardiac toxicity.

Thus, an important part of the management of patients with cancer is the prevention and detection of chemotherapy related cardiotoxicity. Traditional risk factors for CV disease (hypertension, diabetes mellitus, smoking) and known ischaemic heart disease increase the risk, and the presence of such risk factors should be used to modify chemotherapy regimes. Monitoring and early detection of cardiotoxicity is important, and traditionally left ventricular ejection fraction (LVEF) is the mainstay of surveillance.

Patients planned for potentially cardiotoxic therapies should have baseline imaging with echocardiography or gated heart pool scans, with follow up dependent on the type and dose of chemotherapy. However LVEF is neither sensitive nor specific for the diagnosis of cardiac dysfunction and the 95% confidence intervals of measured LVEF are ±11%, which is far greater than the difference between a normal heart and a potentially damaged heart. Thus there is considerable interest in more sensitive methods to detect patients with structural disease prior to the development of signs and symptoms of heart failure. Biomarkers such as troponin and BNP, and advanced imaging techniques have the potential to detect cardiotoxicity earlier than LVEF alone.

A number of studies at the Baker IDI Heart and Diabetes Institute in Melbourne are investigating novel techniques to detect cardiotoxicity, and evaluating the effects of early intervention to prevent progression. The studies involve novel echocardiography techniques, cardiac magnetic resonance imaging (CMRI) and exercise.

Echocardiography

Echocardiography has been used in surveillance of cardiotoxicity, largely using a change in the 2D LVEF. This has drawbacks of reduced reproducibility and insensitivity to early changes in cardiac function. The SUCCOUR trial is a multi-centre study using global longitudinal strain (GLS) to detect cardiac injury and guide treatment. GLS is a measure of heart muscle deformation, and has been shown to identify LV dysfunction earlier than conventional echocardiographic measures in patients treated with chemotherapy [4]. What is unclear is whether early detection of subclinical dysfunction by GLS and subsequent instigation of heart failure therapies (ACEI, beta blockers) will influence CV outcomes. Over thirty centres worldwide are enrolling participants, with the long-term aim of limiting the development of LV dysfunction and heart failure symptoms, and prevention of interruptions to planned chemotherapy.

CMRI

CMRI is considered the gold standard for non-invasive assessment on cardiac size and function and is incorporated into guidelines to support other imaging methods of assessing ejection fraction [5]. Newer CMRI sequences have been developed to detect diffuse myocardial fibrosis (T1 mapping) and oedema and inflammation (T2 mapping). These techniques are being investigated on the Baker IDI's research 3T MRI scanner to assess whether:

i. T2 mapping can identify myocardial oedema as a marker of myocardial injury and be used as a predictor of cardiac dysfunction in patients undergoing chemotherapy, and
ii. There is a relationship between CMR tissue characterization of myocardial inflammation, oedema, and fibrosis with sensitive markers of subclinical myocardial dysfunction such as myocardial strain.

Exercise

In a healthy heart, cardiac function augments with exercise so that it can match the increased metabolic requirements of the exercising muscles (the so-called "cardiac reserve"). The ability to detect a reduction in cardiac reserve when resting measures are normal could be a useful method of detecting cardiotoxicity. Researchers at the Baker IDI have recently developed a novel method in which magnetic resonance imaging (CMR) is used to measure cardiac function during exercise with unprecedented accuracy and reproducibility [6].

To test this method, exercise CMRI is being performed in patients with breast cancer pre and post AC chemotherapy, with half the subjects assigned a supervised exercise program through the course of treatment. The aims of this study are to assess whether a reduction in cardiac reserve is a sensitive method of detecting myocyte injury and to consider the protective effects of exercise through the treatment process. This trial has the additional benefits of focussing on long-term outcomes rather than more fatalistic short-term oncologic goals, as well as providing an outlet with exercise. There is also the additional question of whether exercise training may have a positive tumour effect, with preliminary data suggesting exercise may act synergistically with chemotherapy to improve local control of cancer and prevent dissemination.

In summary, with improved cancer survival, attention must turn to managing the potential long-term adverse effects of cancer therapies. Chemotherapy related cardiac toxicity is a potentially serious condition and accurate diagnosis of myocyte injury is critical. As novel pharmacological approaches to the treatment of cancer are developed, early detection of CV side effects is vital. Currently accepted methods have drawbacks, and with time more sensitive imaging techniques using echocardiography and CMRI, and incorporating exercise training into therapy, may further improve patient outcomes.

References

[1] Patnaik JL, Byers T, DiGuiseppi C, et al. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Research. 2011 Jun 20; 13(3): R64. **[2]** McArthur HL, Chia S. Cardiotoxicity of trastuzumab in clinical practice. The New England Journal of Medicine. 2007 Jul 5; 357(1): 94-5. **[3]** Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. The New England Journal of Medicine. 2000 Apr 13; 342(15): 1077-84. **[4]** Hare JL, Brown JK, Leano R, et al. Use of myocardial deformation imaging to detect preclinical myocardial dysfunction before conventional measures in patients undergoing breast cancer treatment with trastuzumab. American Heart Journal. 2009 Aug; 158(2): 294-301. **[5]** Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society Echocardiography. 2014 Sep; 27(9): 911-39. **[6]** La Gerche AL, Claessen G, Van de Bruaene A, et al. Cardiac MRI: A New Gold Standard for Ventricular Volume Quantification During High-Intensity Exercise. Circulation Cardiovascular Imaging. 2013 Mar; 6(2): 329-38.

Physiology and management of erectile dysfunction

Darren J Katz [1], Christopher Love [1], Eric Chung [2]
1 Men's Health Melbourne (www.menshealthmelbourne.com.au)
2 Androurology (www.androurology.com)

Anatomy and Physiology

The physiology of erections is a complex interaction between the penile anatomical compartments, vessels and nerves. The penile anatomical compartments involved in erections are principally the corpora cavernosa. These are paired cylinders of smooth muscle encased in the tunica albuginea which function as the erection chambers and are separate from the glans penis (see Figure 1). The blood supply comes from the internal pudendal artery which separates into 3-4 branches into the penis. Just beneath the tunica albuginea is the subtunical venous plexus which drains into emissary veins and eventually forms the dorsal veins of the penis. The autonomic nervous system plays an integral role with parasympathetic nerves involved in tumescence and the sympathetic nerves controlling detumescence.

The key steps involved are (see Figure 2):

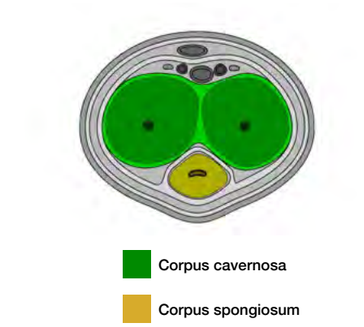
1. Sexual stimulation triggers release of neurotransmitters (nitrous oxide)
2. Dilatation of arterioles within the corpora
3. Engorgement of corpora with compression of subtunical venous plexus thereby "trapping" blood in the penis
4. Detumescence occurs when there is arteriolar contraction which results in the venous plexus "opening up" and blood effluxes from the penis

Epidemiology

The Massachusetts Male Aging study demonstrated an overall prevalence of erectile dysfunction (ED) of 52% in men aged 40-70 in the Boston Area [1]. An Australian study demonstrated that 1 in 5 men over the age of 40 had ED with 10% being completely unable to attain an erection [2]. In another study, it was found that one in four men first sought medical help for ED when they were aged less than 40 yrs old.

Classifications/causes

The aetiology of erectile dysfunction is broad and can very often be multifactorial (Figure 3).



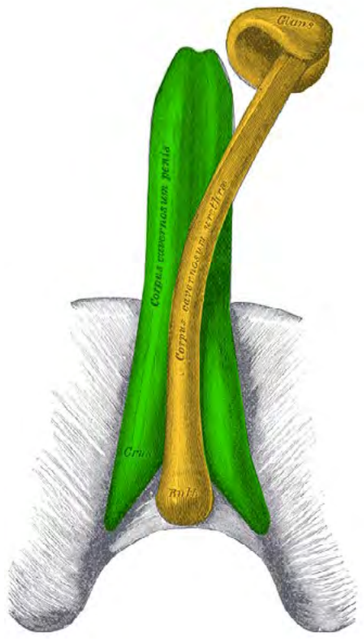


Figure 1. Accessed from: https://en.wikipedia.org/wiki/Corpus_cavernosum_penis#/media/File:Gray1154.png

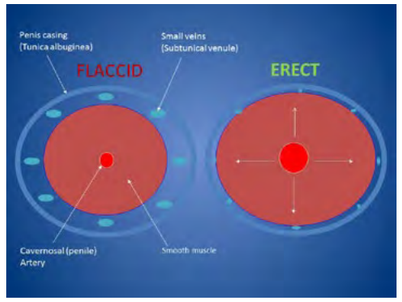


Figure 2: Steps involved in an erection: Engorgement of smooth muscle with blood swells and compresses small veins against penis casing. Blood is trapped.

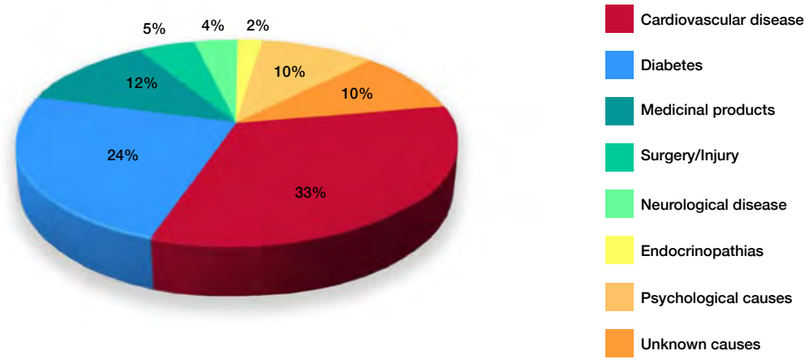


Figure 3: Aetiology of ED:
Sourced from: http://www.for-us-2.com/en/erectile-dysfunction/causes-of-erectile-dysfunction/

Management of ED

History

Much can be ascertained from a complete medical and sexual history and this is the first key step in management. It is preferable if the partner is available and willing to be present at the consultation. Validated questionnaires such as the SHIM (Sexual Health Inventory of Men) can be very useful to assess baseline function and also response to treatment [3].

Examination

Given the multiple aetiologies and various systems that can be involved in ED, the physical examination should be focused, yet must take into account the relevant genitourinary, vascular, endocrine and neurological areas. Measuring testis size with an orchidometer is useful. The presence of penile plaques (Peyronie's disease), androgenisation (or lack thereof) and blood pressure is important to note.

Investigations

General

Depending on the patient's age, risk factors and physical examination findings, testing can be individualised. However, most men should be screened for hypogonadism (morning testosterone), diabetes (HbA1c or fasting blood glucose) and dyslipidaemia.

Specialised

Most patients will not need specialised investigations. For patients for which the aetiology is unclear, or first/second line treatments have not worked, consideration should be made of a penile duplex Doppler ultrasound [4]. This should be done with an intracavernosal vasoactive agent and can help to classify the aetiology of ED and may help direct if further sub-specialised tests are needed. A penile duplex Doppler ultrasound may also predict which treatments may be beneficial. If arteriogenic ED is diagnosed, consideration of referral to a cardiologist for assessment of occult ischemic heart disease is warranted.

Treatment of Erectile dysfunction

The different steps in treatment are shown in Table 1

If there is any type of reversible cause identified in the assessment, this should be treated initially (sometimes in combination with first line therapy).Typical reversible causes include hormonal imbalance (e.g. low testosterone), medication induced ED and psychogenic ED. Modifiable risk factors such diabetes, hypertension, smoking and dyslipidaemia should be optimised as well. This should be performed in consultation with a general practitioner. Rare treatable causes include internal pudenal artery stenosis.

Table 1: Step wise approach to ED treatment*

Step	Options	Notes
1	Treat reversible causes Optimise modifiable risk factors	May augment with drug therapy
2	First line therapies	PDE5 Inhibitors
3	Second line therapies	Penile injections Vacuum erection devices External Shock Wave lithotripsy
4	Third line therapies	Penile prosthesis

*At each step consider psychological support/referral

Psychological support

Not only can ED be caused by psychological problems, ED is a condition which can cause psychological distress in its own right to both the patient and the partner. This can create a negative feedback loop whereby it exacerbates the ED. This needs to be screened for at each consultation and a referral to a qualified allied health professional (ideally with an interest in sexual dysfunction) should be made if necessary.

First line therapy

The most common first line therapy is PDE5 inhibitors. The commercially available drugs in Australia are Sildenafil (Viagra®), Tadalafil (Cialis®) and Vardenafil (Levitra). Key differences between the drugs are shown in Table 2. The side effect profile is outlined in Table 3. All side effects cease with cessation of medication. Occasionally, with frequent daily administration (especially 5mg Tadalafil), the side effects can resolve.

The choice of which PDE5 inhibitor to use takes into account several variables: frequency and timing of intercourse, cost (Sildenafil is the cheapest as it is "off patent"), side effect profile, spontaneity required, previous use etc. There are no large scale good quality comparative studies of these drugs. Because of its prolonged half-life Tadalafil can maintain efficacy for up to 36 hours and hence a daily dose of 5mg will allow for constant blood levels. Tadalafil has also been shown to improve lower urinary tract symptoms (LUTS) and hence may be useful in men who have ED and LUTS.

Contraindications include patients on topical nitrates, severe CCF, unstable angina (or angina with sexual intercourse), resting hypotension, recent stroke or myocardial infarction.

Before classifying a patient as "non-responsive to PDE5 inhibitors", a discussion with the patient should be had to clarify if:

- The medication was sourced from accredited pharmacy (ie not online, overseas etc)
- Taken on empty stomach (Sildenafil, Vardenfail)
- Adequate duration until sexual stimulation
- Sexual stimulation attempted
- Taken maximum dose
- Tried at least 3 times
- Trialled at least 2 PDE5 inhibitors

Table 2: Comparison of the 3 commercially available PDE5 Inhibitors in Australia

	Sildenafil	Tadalafil	Vardenafil
Dosage	25mg, 50mg, 100mg	5mg, 10mg, 20mg	5mg, 10mg, 20mg
Administration	On demand	On demand or daily	On demand
Absorption affected by fatty meal	Yes	No	Yes
Effective from	30-60 mins	30 mins	30 mins
Tmax (approx.)	1 hour	2 hours	1 hour
T 1/2 (approx.)	3 hours	18 hours	4 hours
Off patent	Yes	No	No
Improve avoiding symptoms	Not assessed	Yes (daily dose)	Not assessed

Adapted from European Guidelines on Male Sexual Dysfunction 2015 [5].

Table 3: Comparison of side effects the 3 commercially available PDE5 Inhibitors in Australia

	Sildenafil	Tadalafil	Vardenafil
Headache	13%	15%	16%
Flushing	10%	4%	12%
Dyspepsia	5%	12%	10%
Nasal congestion	1%	4%	10%
Abnormal vision	2%	0%	<2%
Back pain	Not assessed	7%	Not assessed
Myalgia	Not assessed	6%	Not assessed

Adapted from European Guidelines on Male Sexual Dysfunction 2015 [5].

If the previous points have been determined regarding administration of PDE5 inhibitors and the patient does not achieve an adequate response, second line therapies should be instituted.

Second line therapies

Vacuum erection devices (VED)

These devices draw blood into the corpora and an occlusion ring is placed at the base of the penis to sustain the erection. A certain level of dexterity is needed to use a VED however, when used in the correct fashion, an erection suitable for penetration is often the result. Most men cease using a VED in the long term because of the potential side effects such as pain, inability to ejaculate, bruising, "hinging" and paraesthesia.

Penile injections

Penile injections can be a useful treatment for non-responders to PDE5 inhibitors. It allows a "natural" erection to occur within 10-15 mins of administration and, with correct dosage, should last less than 1 hour. There is only one widely available commercial product in Australia (Caverject®) which is Alprostadil. It can be administered in dosages of 2.5-20 mcg. It does not need to be refrigerated and is available in "all-in-one" package (ie drug, needle, alcohol swab). Caverject is expensive (~$20 AUD per injection) and cheaper options can be sourced via compounding pharmacies. However, many of these compounded medications do need to be refrigerated.

Structured training of patients in how to administer penile injections (especially with compounded medications) and monitoring for efficacy and side effects can help increase the success of penile injection therapy.

The side effects of penile injections include pain (10% - especially with alprostadil), prolonged erections (5%) and fibrosis (2%).

Low Intensity External Shock Wave Lithotripsy (LiESWL)

Li-ESWL applied to the penis has recently been shown to have short term efficacy in up to 50% of patient who were non-responders to PDE5Is [6]. The mechanism of action is still debated and may involve recruitment of stem cells and/or angiogenesis. The results to date have involved small numbers of patients and many of the trials have been industry sponsored. However, this is a treatment with no known side effects and so some patients are keen to "give it a shot" even though the evidence for its use is not very strong.

Third line therapies

Penile prosthesis

Penile Prostheses (penile implants) are a concealed, surgically implanted device, generally reserved for patients who have failed other conservative therapies. Penile prostheses offer patients a permanent solution to their ED. For this reason, and combined with a low complication rate seen in high volume penile implant surgeons, the patient satisfaction rate for this procedure is >90% [7].

Summary

ED has a complex multifaceted pathophysiological mechanism. Assessment should be focused on determining the cause and any modifiable risk factors. For most patients, simple testing will suffice, but occasionally a penile duplex Doppler ultrasound can help to direct treatment options. There is a well-established step-wise approach to ED treatments. Involvement of allied health professionals can help with managing the psychological impacts of ED on patient and partner.

References

[1] O'Donnell AB, Araujo AB, McKinlay JB. The health of normally aging men: The Massachusetts Male Aging Study (1987–2004). Experimental Gerontology. 2004 Jul; 39(7): 975–84. **[2]** Pinnock CB, Stapleton AM, Marshall VR. Erectile dysfunction the community: a prevalence study. The Medical Journal of Australia. 1999 Oct; 171(7): 353-7. **[3]** Cappelleri JC & Rosen RC. The Sexual Health Inventory for Men (SHIM): a 5-Year Review of Research and Clinical Experience. International Journal of Impotence Research. 2005 Jul-Aug; 17(4): 307-19. **[4]** Berookhim BM. Doppler Duplex Ultrasonography of the Penis. The Journal of Sexual Medicine. 2016 Apr; 13(4): 726–31. **[5]** Hatzimouratidis K, Eardley I, Giuliano F, et al. EAU Guidelines on Male Sexual Dysfunction: Erectile dysfunction and premature ejaculation. 2015 Mar; Page 16 **[6]** Kitrey ND, Gruenwald I, Appel B, et al. Penile Low Intensity Shock Wave Treatment is Able to Shift PDE5i Nonresponders to Responders: A Double-Blind, Sham Controlled Study. The Journal of Urology. 2016 May; 195(5): 1550-5. **[7]** Chung E, Van CT, Wilson I, et al. Penile prosthesis implantation for the treatment for male erectile dysfunction: clinical outcomes and lessons learnt after 955 procedures. World Journal of Urology. 2013 Jun; 31(3): 591-5.