Podcast
Testicular cancer, TD and MetS
Join the discussion:
www.trendsinmenshealth.com

Testicular cancer: low testosterone and the metabolic syndrome

Mike Kirby, Editor, Trends in Urology and Men's Health

Cure rates for stage 1 testicular cancer are reaching 100%. However, long-term treatment-related side effects pose their own health risks. Regular follow up and monitoring are important for early detection and timely treatment of conditions such as testosterone deficiency and metabolic syndrome.

Testicular cancer (TC) is the most common malignancy in young men, with around 18 000 new diagnoses in Europe each year.[1] While this disease often used to have a lethal outcome, with the main aim being to increase the chance of survival,[2] improved treatments have now resulted in cure rates close to 100% in stage I disease and over 80% in metastatic cases.[3] However, studies have shown that TC survivors are at increased risk of long-term side-effects from the treatments, including testosterone deficiency (TD)[4] and metabolic syndrome (MetS) (see Figure 1),[5] both of which pose their own health risks, as well as decreased fertility, pulmonary toxicity, nephrotoxicity, neurotoxicity and psychosocial problems.[6]

Testicular cancer

TC most commonly affects men between the ages of 15–40 years[3] and around 1 in 215 men in the UK will be diagnosed with it in their lifetime.[7]

At diagnosis, 98–99% of TCs are unilateral and 90–95% are germ cell tumours (GCTs).[8,9] Around 50% of testicular GCTs are non-seminomas and 50% are pure seminomas.[3] Incidence peaks in the third decade of life for non-seminomas and the fourth decade for pure seminomas.[8]

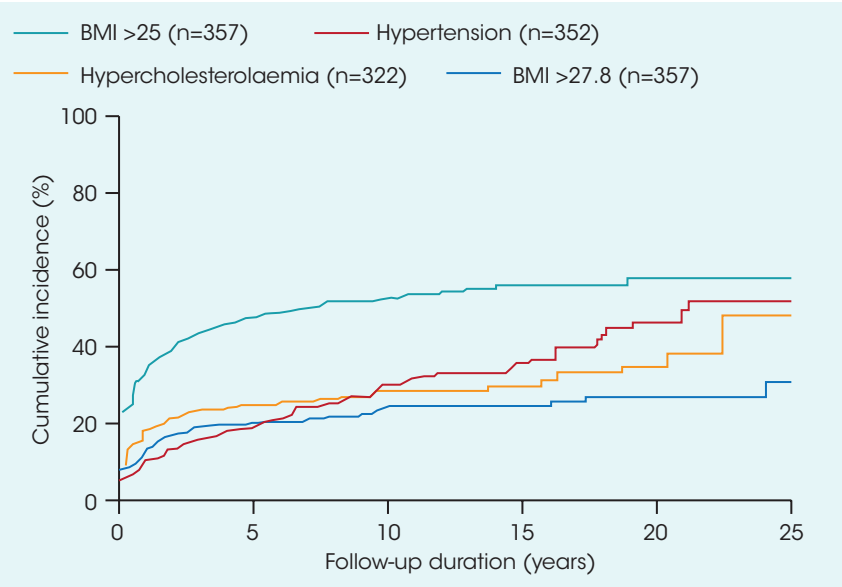

Figure 1. Cumulative risk of cardiovascular risk factors – overweight, hypercholesterolemia, and hypertension – from start of chemotherapy[5]

Although TC incidence is increasing (rates are projected to rise by 12% between 2014 and 2035 in the UK, with up to 10 cases per 100 000), mortality rates are dropping and are projected to fall by 35% between 2014 and 2035 in the UK, to fewer than 1 death per 100 000.[10]

The excellent cure rates for TCs are attributed to careful staging at diagnosis, adequate early treatment facilitated by a multidisciplinary approach, their chemosensitivity (particularly to cisplatin-based chemotherapy), strict follow-up and salvage therapies.[8,11]

The main treatments for TC are surgery (orchidectomy), radiotherapy (RT) and chemotherapy. Orchidectomy is the first step for all TCs, regardless of stage. If the cancer is detected early, orchidectomy may be the only treatment required. In more advanced stages, orchidectomy is usually followed by RT or chemotherapy (typically platinum/platin-based).

Testosterone deficiency following testicular cancer

Testosterone deficiency causes significant physical and psychological effects, which can compromise a man's general wellbeing, sexuality and fertility.[12,13] TD has also been strongly associated with MetS,[14] and increased CV and all-cause mortality.[15–19]

Primary TD, characterised by low testosterone and high luteinising hormone (LH) levels, has been reported to affect around 20% of TC

survivors after orchidectomy, with or without chemotherapy.[20]

A systematic review and meta-analysis of 12 studies evaluated the risk of TD in TC survivors based on three different treatment combinations:[4]
1. Orchidectomy plus standard chemotherapy (defined as four cycles of platin-based chemotherapy);
2. Orchiectomy plus non-conventional chemotherapy (defined as platin-based combination chemotherapy with double dose cisplatin, >4 cycles of platin-based combination chemotherapy, or both chemotherapy and infradiaphragmatic RT);
3. Orchidectomy plus infradiaphragmatic RT.

In the included studies, the follow up time varied between two months and 12 years, and the lower reference limit for total testosterone varied from 8 to 12.1nmol/L. The odds ratios for TD were 1.8 (95%; confidence interval [CI] 1.3–2.5; p=0.0007) in subjects treated with orchidectomy plus standard chemotherapy compared with orchidectomy alone; 3.1 (95%; CI 2.0–4.8; p<0.0001) in subjects treated with orchiectomy plus non-conventional chemotherapy compared with orchidectomy alone; and 1.6 (95%; CI 1.0–2.4; p=0.03) in patients treated with orchidectomy plus infradiaphragmatic RT compared with orchidectomy alone.[4]

Steggink *et al*,[20] investigated insulin-like factor 3 (INSL3; a novel marker of Leydig cell function), testosterone and LH levels in TC survivors in cross-sectional and longitudinal cohorts. At a median of seven years after orchidectomy and chemotherapy, TC patients in the cross-sectional cohort (n=79) had higher LH levels, (p<0.001) and lower testosterone levels (p=0.001) versus controls (n=40), but similar INSL3 levels. TC survivors who received orchidectomy alone (n=25) had higher LH levels versus controls (p=0.02), but comparable testosterone and INSL3.

In the longitudinal cohort, TC survivors with normal β-hCG levels (≤5mU/L, n=35) pre-chemotherapy had increased LH levels one year after chemotherapy versus their pre-chemotherapy levels (p=0.001) but no change in testosterone or INSL3. In contrast, TC survivors with high β-hCG levels pre-chemotherapy (n=35) had decreased LH, markedly raised testosterone, and low ISNL3 levels pre-chemotherapy, but increased LH, decreased testosterone and increased INSL3 levels one year later (p<0.001 for all).[20]

These results showed that in chemotherapy-treated TC patients, gonadal endocrine function was disturbed pre-chemotherapy, one year after, and at long-term follow up.[20]

The ongoing multicentre platinum study[21] investigated adverse health outcomes associated with TD after platin-based chemotherapy in 491 TC survivors aged less than 55 years at diagnosis, and low testosterone levels (defined as a serum testosterone ≤3.0ng/ml [10.7nmol/L] or the use of testosterone replacement therapy) were found in 38.5% of subjects.

Subjects who were overweight, obese, or of older age were more likely to have TD, and a genetic abnormality in the sex hormone binding globulin gene appeared to be a predisposing factor in some men, although this needs to be confirmed by larger studies. Subjects who performed vigorous intensity physical activity appeared to have higher testosterone levels. The type of chemotherapy regimen did not correlate with TD.[21]

Compared with TC survivors with normal testosterone levels, those with TD were more likely to take medications for:[21]
- Dyslipidaemia (20% versus 6%, p<0.001);
- Erectile dysfunction (20% versus 12%, p=0.02);
- Hypertension (19% versus 11%; p=0.01);
- Anxiety or depression (15% versus 10%, p=0.06);
- Diabetes (6% versus 3%, p=0.07).

Possible mechanisms for TD following TC

A low testosterone level may be present when TC is diagnosed, or it may follow treatment for the disease. Causes of TD in the presence of TC include:
- Cancer-related damage to the testicular cells that are responsible for the production of testosterone;
- Orchidectomy;
- Chemotherapy/RT-related damage to the remaining testicular tissue;
- Hormonal abnormalities resulting from cancer-related stress.

In Steggink's study, β-hCG-producing tumours were found to affect the gonadal endocrine axis, resulting in increased testosterone and decreased LH levels pre-chemotherapy. The changes in testosterone and LH one year post-chemotherapy were considered largely attributable to successful treatment of the cancer and elimination of the β-hCG stimulus.[20]

In a prospective study of TC patients, almost 40% of those with active disease presented with elevated oestradiol concentrations, compared with only 7% of those without active disease. In the active disease group, there was a very strong correlation between the high oestradiol concentrations and elevated β-hCG concentrations. Pathologically high oestradiol levels interfere with the pituitary gonadal axis and may increase the risk of TD after treatment completion. The source of such high oestradiol levels remains unclear.[22] Oestradiol may be secreted by the tumour itself, or the Leydig cells, in the presence of chorionic gonadotropin.[22,23]

Orchidectomy, of course, immediately halves the number of Leydig cells that produce testosterone in the presence of LH.[20]

Residual Leydig function may be reduced by RT and/or chemotherapy. The testicles are highly radiosensitive and may be damaged by direct or scattered radiation from adjacent tissues, with the degree of damage

dependent on the dose. The degree of gonadal damage resulting from chemotherapy will depend on the type(s) used and cumulative dose(s).[24] The risk of TD appears to be greatest in the most heavily treated patients.[4]

Many patients with cancer will find the experience psychologically stressful. Stress increases cortisol production and may decrease testosterone levels,[25] with secondary increases in serum LH and FSH levels.[26] Increased cortisol and decreased testosterone may, in turn, contribute to increased stress.[25]

An increased risk of accelerated hormonal ageing has been reported in TC survivors over the long term (*ie* 20 years after TC treatment).[27]

Other research has shown that Leydig cell function may recover more than two years after TC treatment,[20] emphasising the importance of regular follow-up and monitoring in these men.

MetS following TC

MetS is a clustering of risk factors for cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). These include abdominal obesity, raised blood pressure, dyslipidaemia (raised triglycerides and lowered HDL cholesterol), and raised blood glucose. Patients with MetS are twice as likely to develop CVD over the next five to 10 years as those without it, and their lifetime risk will be greater still. MetS also confers a five-fold increase in the risk of T2DM.[28]

A study published in 2013[5] investigated the development of MetS after chemotherapy for TC in two studies. Study 1 retrospectively evaluated the development of CV risk factors in 370 TC survivors treated with chemotherapy who were followed up for three or more years (see Figure 1). Study 2 evaluated MetS prevalence and vascular function in 173 of those patients compared with 1085 controls, over 3–20 years (see Figure 2).

In study 1, 24% of TC survivors developed hypercholesterolaemia, 24% became overweight and 30% developed hypertension after a median follow up of 0.9, 1.7, and 5.1 years, respectively. In study 2, 25% of TC survivors had MetS after a median follow up of five years, equating to a 2.2 (95% CI 1.5–3.3) times higher risk than in the general population. MetS prevalence increased with age from 13.3% in TC survivors aged 18–30 years, to around 35% in those aged 40–60 years. The presence of MetS was associated with lower baroreflex sensitivity and increased carotid artery intima-media thickness, which may precede overt CVD.[5]

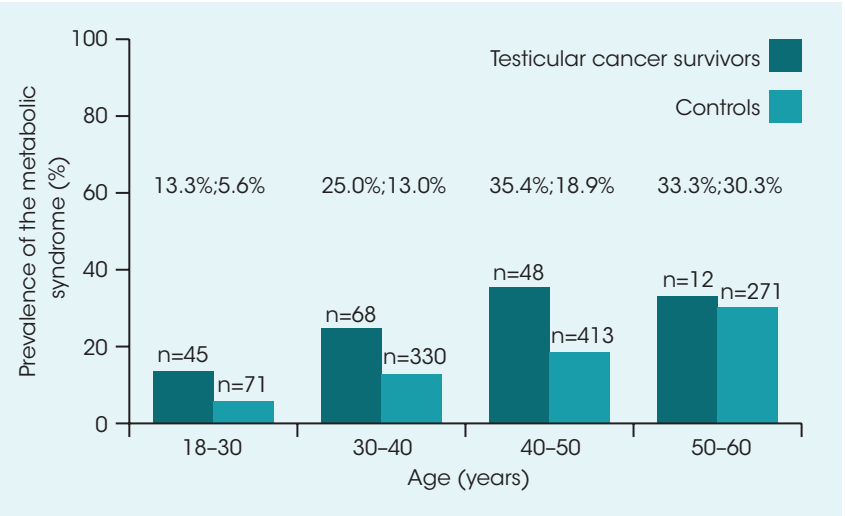

Figure 2. Prevalence of the metabolic syndrome in TC survivors and in controls according to age category[5]

Of the MetS components, (see Table 1) high blood pressure was the most common (affecting 59%), followed by low HDL cholesterol (44%), raised triglycerides (29%), central obesity (17%), and high glucose levels (14%). Overweight and hypercholesterolaemia were detected mainly within the first five years post-chemotherapy, while the risk of hypertension, which may indicate vascular damage, extended beyond a follow-up period of 10 years, highlighting the importance of long-term follow up in these patients.[5]

The study data also showed an association between total testosterone levels and MetS. The TC survivors with unsupplemented total testosterone levels <15mmol/L (22%) had an approximately four-fold increased risk of MetS, which was particularly associated with abdominal obesity.[5]

The study authors concluded that TC survivors treated with chemotherapy appear to develop MetS at an earlier age than controls, and this is often accompanied by early signs of atherosclerosis. Low testosterone may play a causal role.[5]

The ongoing platinum study[29] evaluated clinical and genetic MetS risk factors in North American TC survivors (mean age 38.1 years), using matched controls from the National Health and Nutrition Examination Survey. MetS was defined as three or more of the following:

- Abdominal obesity;
- Hypertension;
- Hypertriglyceridaemia;
- Decreased high density lipoprotein cholesterol (HDL-C);
- Diabetes.

TC survivors were significantly more likely to have hypertension than controls (43.2% versus 30.7%; $p<0.001$), elevated LDL cholesterol levels (17.7% versus 9.3%; $p<0.001$), elevated total cholesterol levels (26.3% versus 11.1%; $p<0.001$) and a body mass index ≥25kg/m^2 (75.1% versus 69.1%; $p=0.04$), but they were less likely to have abdominal obesity

(28.2% versus 40.1%; $p<0.001$) or decreased HDL-C levels (23.7% versus 34.8%; $p<0.001$).[29]

The finding of a smaller waist circumference but higher BMI in TC survivors versus controls was surprising, but may be a result of the increased femoral bone and subcutaneous adipose tissue deposition observed in subjects with TD compared with those without.[29,30] The lower prevalence of low HDL-C levels observed in TC survivors versus controls may be the result of reduced androgen levels not suppressing HDL-C, as physiological testosterone levels in normal men suppress HDL-C levels.[29,31]

MetS frequency was similar between both groups overall (21.0% in TC survivors versus 22.4% in controls; $p=0.59$), it did not vary by treatment ($p=0.20$) and it was not related to a single nucleotide polymorphism in rs523349 ($p=0.61$), which has recently been implicated in MetS risk. TC survivors with MetS had a significantly higher prevalence of obesity (60.8% versus 22.7%; $p<0.001$) and TD (46.1% versus 26.8%; $p<0.001$) than those without MetS. A testosterone level ≤3ng/mL (10.7nmol/L) was also significantly associated with MetS (odds ratio 2.06; $p=0.005$).[29]

The metabolic abnormalities observed in TC survivors were thought to suggest possible shifts in fat distribution and metabolism, accompanied by TD and inflammation. The study authors concluded that the high prevalence of CVD risk factors in these patients may not be fully captured by standard MetS criteria, and MetS related to cancer treatment requires further characterisation.[29]

Possible mechanisms for MetS following TC

While previous research has linked low testosterone levels with a higher fat mass, BMI and abdominal fat distribution in TC survivors,[32] the Platinum study found that TC survivors had smaller waist circumferences in comparison to controls.[29]

The aetiology of cancer treatment-related MetS appears to differ from that in the general population, where excess calorie intake and a sedentary lifestyle are the primary causes. Cancer treatment-related MetS is multifactorial and differs between individual patients depending on their cancer diagnosis and treatment. TD and chemotherapy are thought to be the main contributors.[29,33]

While chemotherapy can affect taste and smell, research has shown that impaired taste function was not related to a different dietary intake in TC survivors versus controls, so this is an unlikely contributor to the increased prevalence of MetS.[32]

Testosterone levels <15nmol/L have also been associated with high blood glucose levels, which correlates with the independent association between low to normal testosterone levels and insulin resistance seen in older men.[5,34]

Follow-up and monitoring in TC survivors

Because TC survivors appear to be at increased risk of TD, MetS and CVD,[4,5] careful follow-up and monitoring is important for the early detection and timely treatment of TD and CV risk factors to help reduce CVD risk.

The relatively high prevalence of Leydig cell dysfunction in TC survivors,

		Study I (n = 370)	Study II (n = 173)
Baseline characteristics			
Age at start chemotherapy (years)	Median (range)	28 (16–64)	28 (16–52)
Chemotherapy regimen:			
BEP/EP	n (%)	262 (71%)	159 (92%)
PVB		27 (7%)	0 (0%)
PVB+		42 (11%)	0 (0%)
PVB/BEP		15 (4%)	1 (1%)
Other		24 (7%)	13 (7%)
Follow up data			
Follow up duration (years)	Median (range)	12 (3–29)	5 (3–20)
Age at end follow-up (years)	Median (range)	42 (19–73)	37 (19–59)
Deceased:	n (%)	25 (7%)	not applicable
Death of testicular cancer		14 (4%)	–
CHD:	n (%)	19 (5%)	not applicable
Age at CHD (years)	Median (range)	49 (30–62)	–
Follow-up duration at CHD (years)	Median (range)	15 (0–28)	–

CHD = coronary heart disease. Chemotherapy regimen: BEP = bleomycin, etoposide, cisplatin; EP = etoposide, cisplatin; PVB = cisplatin, vinblastin, bleomycin; PVB+ = PVB followed by maintenance therapy with cisplatin and vinblastin; PVB/BEP = alternating courses of PVB and BEP; Other = CEB (carboplatin, etoposide, and bleomycin), or BOP/VIP (bleomycin, vincristin, cisplatin/etoposide, ifosfamide, and cisplatin)

Table 1. Baseline characteristics and follow up data of testicular cancer patients[5]

implies that hormonal status should be regularly assessed.[6] This may also help identify men at high risk of MetS and CVD.[2] Testosterone replacement therapy should be considered in the presence of biochemical evidence of TD and persistent clinical symptoms.

Annual follow-up would therefore seem appropriate, including CVD risk factor screening and measurement of BP, waist circumference, height, weight and BMI, HBA_{1c} and testosterone levels. Lifestyle advice should include the importance of smoking cessation, regular physical activity and the consumption of a healthy, balanced diet.

It is worth bearing in mind though, that current MetS criteria were originally developed for the general population, so they may not cover the full spectrum of metabolic abnormities seen in TC survivors.[29]

The fact that cisplatin may remain detectable in plasma up to 20 years after chemotherapy for TC,[5,35] and may still be partially reactive,[5,36] highlights the risk of long-term toxicity and the importance of extended follow-up in these patients, to monitor possible adverse effects.

In TC survivors, long-term, persistent treatment-related side effects are associated with both impaired physical and mental quality of life.[3] If patients are warned about the potential long-term toxicity of their cancer therapy it may facilitate early identification and reporting of any treatment-associated health problems, and help prevent MetS and CVD from occurring.

Other long-term effects of TC treatment include decreased fertility, pulmonary toxicity, nephrotoxicity, neurotoxicity and psychosocial problems. Their incidence and time of onset will vary according to treatment type and intensity.[6]

Conclusion

TC survivors may be at risk of various long-term treatment-related adverse effects, including TD and MetS, which can compromise health and wellbeing. TC commonly affects younger men, and with survival rates increasing, these men may suffer the effects of such chronic conditions over an extended length of time. Primary care practitioners need to be alert to the risks following TC and employ careful, regular follow-up in patients who have received treatment for this disease.

Declaration of interests

Mike Kirby has received funding from the pharmaceutical industry for research, conference attendance, lecturing and advice.

References

1. Znaor A, Lortet-Tieulent J, Jemal A, *et al*. International variations and trends in testicular cancer incidence and mortality. *Eur Urol* 2014;65(6):1095–106.
2. Bogesfors C, Isaksson S, Bobjer J, *et al*. Hypogonadism in testicular cancer patients is associated with risk factors of cardiovascular disease and the metabolic syndrome. *Andrology* 2017;5:711–7.
3. Oldenburg J, Fossa SD, Nuver J, *et al*. Testicular seminoma and non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24(Suppl 6):vi125–vi132.
4. Bandak M, Jørgesen N, Juul A, *et al*. Testosterone deficiency in testicular cancer survivors – a systematic review and meta-analysis. *Andrology* 2016;4:382–8.
5. de Haas EC, Altena R, Boezen HM, *et al*. Early development of the metabolic syndrome after chemotherapy for testicular cancer. *Ann Oncol* 2013;24:749–55.
6. Haugnes HS, Bosl GJ, Boer H, *et al*. Long-term and late effects of germ cell testicular cancer treatment and implications for follow-up. *J Clin Oncol* 2012;30:3752–63.
7. Cancer Research UK. Testicular Cancer risk (www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/testicular-cancer/risk-factors#heading-Zero; accessed 28 November 2019).
8. European Association of Urology (EAU). Testicular Cancer (https://uroweb.org/guideline/testicular-cancer/#1; accessed 28 November 2019).
9. La Vecchia C, Bosetti C, Lucchini F, *et al*. Cancer mortality in Europe, 2000–2004, and an overview of trends since 1975. *Ann Oncol* 2010;21:1323–60.
10. Cancer Research UK. Testicular Cancer statistics (www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/testicular-cancer#heading-Zero; accessed 28 November 2019).
11. Hoffmann R, Plug I, McKee M, *et al*. Innovations in health care and mortality trends from five cancers in seven European countries between 1970 and 2005. *Int J Public Health* 2014;59:341–50.
12. European Association of Urology (EAU). Male hypogonadism (http://uroweb.org/guideline/male-hypogonadism; accessed 28 November 2019).
13. British Society of Sexual Medicine (BSSM). *Guidelines on the management of sexual problems in men: the role of androgens*. Fisherwick: BSSM, 2010.
14. Traish AM, Haider A, Doros G, *et al*. Long-term testosterone therapy in hypogonadal men ameliorates elements of the metabolic syndrome: an observational, long-term registry study. *Int J Clin Pract* 2014;68(3):314–29.
15. Araujo AB, Dixon JM, Suarez EA, *et al*. Endogenous testosterone and mortality in men: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011;96:3007–19.
16. Ruige JB, Mahmoud AM, De Bacquer D, *et al*. Endogenous testosterone and cardiovascular disease in healthy men: a meta-analysis. *Heart* 2011;97:870–5.
17. Haring R, Volzke HV, Steveling A, *et al*. Low serum testosterone levels are associated with increased risk of mortality in a population-based cohort of men aged 20–79. *Eur Heart J* 2010;31:1494–501.
18. Muraleedharan V, Marsh H, Kapoor D, *et al*. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *Eur J Endocrinol* 2013;169:725–33.
19. Daka P, Langer RD, Larsson CA. Low concentrations of serum testosterone predicts acute myocardial infarction in men with type 2 diabetes mellitus. *BMC Endocr Disord* 2015;15:35.
20. Steggink LC, van Beek AP, Boer H, *et al*. Insulin-like factor 3, luteinizing hormone and testosterone in testicular cancer patients: effects of β-hCG and cancer treatment. *Andrology* 2019;7:441–8.
21. Abu Zaid MI, Menendez AG, El Charif O, *et al*. Adverse health outcomes in relationship to hypogonadism (HG) after platinum-based chemotherapy: A multicentre study of North American testicular cancer survivors. Abstract

presented at ASCO, 3 June 2017 (https://meetinglibrary.asco.org/record/147393/abstract; accessed 28 November 2019).
22. Wiechno PJ, Kowalska M, Kucharz J, *et al*. Dynamics of hormonal disorders following unilateral orchiectomy for a testicular tumour. *Med Oncol* 2017;34:84.
23. Nakazumi H, Sasano H, Maehara I, *et al*. Estrogen metabolism and impaired spermatogenesis in germ cell tumours of the testis. *J Clin Endocrinol Metab* 1996;81:1289–95.
24. Kiserud CE, Megelssen H, Fedorcsak P, *et al*. Gonadal function after cancer treatment in adult men. *Tidsskr Nor Laegeforen* 2008;128(4):461–5.
25. Choi JC, Chung MI, Lee YD. Modulation of pain sensation by stress-related testosterone and cortisol. *Anaesthesia* 2012;67(10):1146–51.
26. Bhongade MB, Prasad S, Jiloha RC, *et al*. Effect of psychological stress on fertility hormones and seminal quality in male partners of infertile couples. *Andrologia* 2015;47(3):336–42.
27. Oldenburg J. Hypogonadism and fertility issues following primary treatment for testicular cancer. *Urol Oncol* 2015;33(9):407–12.
28. Alberti KG, Eckel RH, Grundy SM, *et al*. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;20;120(16):1640–5.
29. Abu Zaid M, Gathirua-Mwangi WG, Fung C, *et al*. Clinical and genetic risk factors for adverse metabolic outcomes in North American testicular cancer survivors. *J Natl Compr Canc Netw* 2018;16(3):257–65.
30. Santosa S, Jensen MD. Effects of male hypogonadism on regional adipose tissue fatty acid storage and lipogenic proteins. *PLoS One* 2012;7:e31473.
31. Bagatell CJ, Knopp RH, Vale WW, *et al*. Physiologic testosterone levels in normal men suppress high-density lipoprotein cholesterol levels. *Ann Intern Med* 1992;116(12Pt 1):967–73.
32. Ijpma I, Renken RJ, Gietema JA, *et al*. Taste and smell function in testicular cancer survivors treated with cisplatin-based chemotherapy in relation to dietary intake, food preference and body composition. *Appetite* 2016;105:392–9.
33. Westerink NL, Nuver J, Lefrandt JD, *et al*. Cancer treatment induced metabolic syndrome: improving outcome with lifestyle. *Crit Rev Oncol Hematol* 2016;108:128–36.
34. Yeap BB, Chubb SAP, Hyde Z, *et al*. Lower serum testosterone is independently associated with insulin resistance in no-diabetic older men: the Health in Men Study. *Eur J Endocrinol* 2009;161:591–8.
35. Gietema JA, Meinardi MT, Messerschmidt J, *et al*. Circulating plasma platinum more than 10 years after cisplatin treatment for testicular cancer. *Lancet* 2000;355:1075–6.
36. Brouwers EEM, Huitema ADR, Beijnen JH, *et al*. Long-term platinum retention after treatment with cisplatin and oxaliplatin. *BMC Clin Pharmacol* 2008;8:7.