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Letter to the Editor

Bariatric surgery in a testicular cancer survivor: Restoring both metabolic and testosterone status

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Dear editor,

After chemotherapy, testicular cancer (TC) survivors develop obesity, metabolic syndrome and hypogonadism earlier and more frequently than the background population [1,2]. Having 5-year survival rates of 70–90%, lowering cardiovascular (CV) risk should be prioritised during TC survivorship.

Since ~30% of TC survivors after chemotherapy is obese, the main goal is losing weight. Obesity and metabolic syndrome are inversely related to hypogonadism, but it is hard to distinguish between cause and effect [3]. Testosterone replacement therapy (TRT) may resolve hypogonadism, but it may not substantially reduce body weight in the obese. For this, bariatric surgery (BS) is likely to be effective, while its effects on hypogonadism after TC treatment are unknown.

Here, we describe a TC survivor who developed severe obesity and illustrate the effects of BS on body weight with the concomitant restoration of the gonadal axis.

A 30-year-old male with stage II, good prognosis, seminoma testis was treated with unilateral orchiectomy followed by four cycles of etoposide-cisplatin chemotherapy. Before chemotherapy, one month after orchiectomy, he had a BMI of 36.0 kg/m^2, a blood pressure of 140/85 mmHg, a borderline abnormal lipid profile, and he smoked 20 cigarettes per day (Fig. 1a, Supplementary table 1). During and after chemotherapy, he gained weight, for which he was counselled by a dietician. After one year, his BMI increased to 39.0 kg/m^2 and he developed metabolic syndrome. Two and a half years after chemotherapy, having a BMI of 43.3 kg/m^2, he developed primary hypogonadism, which was not

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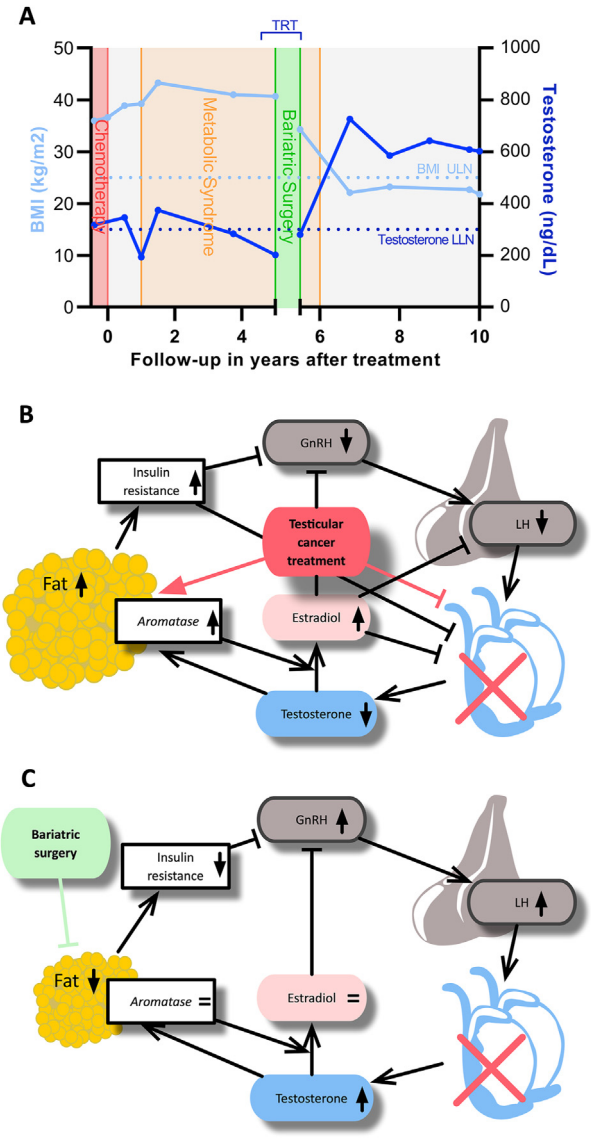

Fig. 1. **A. Changes in BMI, testosterone levels and metabolic syndrome (NCEP ATPIII) over time. B. Primary and secondary hypogonadism before bariatric surgery. C. Compensated primary hypogonadism after bariatric surgery.** Abbreviations: BMI, body mass index; GnRH, Gonadotropin-Releasing Hormone; LH, Luteinising Hormone; LLN, lower limit of normal; TRT, testosterone replacement therapy; ULN, upper limit of normal. SI units conversion factor: To convert testosterone to nmol/L, multiply by 0.0347.

treated at that time. Furthermore, he developed obstructive sleep apnea syndrome (OSAS) a year later, for which Continuous Positive Airway Pressure (CPAP) overnight was needed.

He started a lifestyle program consisting of a diet and supervised physical activity 3–5 times per week, but without any clear effect on his weight. Because of developing complaints of hypogonadism (erectile dysfunction, loss of body hair, less energy) in combination with low testosterone levels, he started TRT with Tostran gel 40 mg daily four and a half years after chemotherapy. Using this, he felt more energetic, and his libido increased. Unfortunately, these interventions did not result in the amount of weight loss he needed. He underwent a mini gastric bypass when his BMI was 40.7 kg/m^2. TRT was simultaneously discontinued.

Within two months after BS, five years after chemotherapy, he lost over 20 kg of weight. Two years after BS, his BMI was reduced to 23.2 kg/m^2, and other CV risk factors (lipids, HbA1c, metabolic syndrome) improved significantly. Interestingly, his testosterone level had also completely normalised. Ten years after chemotherapy, his CV risk profile is optimal, and he is doing well. Two additional TC patients in follow-up at our clinic were treated with BS and showed the same pattern of metabolic recovery (Supplementary table 2a and b).

Weight gain post-chemotherapy and being obese are common features in TC survivors. Patients who already have a higher BMI before chemotherapy are at higher risk of gaining weight and developing metabolic syndrome [4]. Adjusting to a healthier lifestyle during and after an intensive treatment is difficult because of physical (taste changes, fatigue, neuropathy), mental (anxiety, depression), or social (changes in employment, finances and family role) barriers. On top of that, orchiectomy and chemotherapy may cause a fall in testosterone levels. This can be the start of a vicious circle, maintained by obesity and hypogonadism [3].

The interplay between obesity and hypogonadism is complex, and various factors interact. In brief, fat accumulation can cause low levels of testosterone through two different pathways: higher levels of estradiol and insulin resistance (Fig. 1b). A direct effect of fat accumulation is the conversion of testosterone into estradiol by aromatase, leading to higher amounts of estradiol and lower amounts of testosterone. High levels of estradiol impair Leydig cell function by luteinising hormone (LH)-receptor inhibition and suppress the production of gonadotropin-releasing hormone (GnRH) and LH by the negative feedback of the hypothalamic-pituitary-gonadal axis, resulting in lower testosterone levels [3]. Insulin resistance affects the testis by reducing Leydig cell function, and therefore, testosterone production. Insulin resistance also inhibits testosterone production indirectly by suppressing GnRH through kisspeptin [3].

The only way to break the vicious circle is by losing fat, for which dieting and supervised physical activity should be advised first. Furthermore, TRT may have beneficial effects on fat mass and CV risk profile in patients with obesity and/or diabetes type 2 (DM2) who have hypogonadism [5]. However, in patients with BMI >30 kg/m^2, the effect size of TRT on fat mass is small [6]. TRT in young male cancer survivors may improve their body composition, but this is only reported in a

single trial that also included patients with a normal BMI [7].

Hypogonadism in obese TC survivors can have a primary and secondary origin, which is not easy to distinguish. Our case was defined as primary hypogonadism before BS. By the firm increase in LH after BS in combination with a normal testosterone level, this case shows that the remaining testis actually was capable of producing normal amounts of testosterone. In retrospect, our patient had primary and secondary hypogonadism before BS and fully compensated primary hypogonadism afterwards (Fig. 1c). Whether TRT should be considered in obese TC survivors to promote weight loss remains questionable.

If lifestyle interventions do not result in relevant weight loss, BS should definitely be considered in cancer survivors. We know that BS in non-cancer patients with DM2 has better outcomes than intensive lifestyle and medical treatment regarding weight loss, LDL-cholesterol, blood pressure and HbA1c; hence, the also common name 'metabolic surgery'. [8]. Additionally, BS improves testosterone levels [9]. On the other hand, BS may be complicated by dumping syndrome, reflux and vitamin deficiencies, and large lifestyle changes remain necessary afterwards. Reports in the literature on BS for cancer survivors are scarce. Two studies report that a history of cancer is not a predictor for weight loss after BS, and there is no difference in weight loss one and seven years post-surgery compared to subjects without a history of cancer [10,11]. We found no evidence in the literature that both groups respond differently as regards to metabolic improvements.

In TC survivors, CV risk management should not only include a healthy diet and physical activity as lifestyle interventions but also consist of considering BS in case of severe obesity (BMI > 40 kg/m^2) or obesity (BMI 30–40 kg/m^2) with comorbidities like DM2 and perhaps hypogonadism. BS in these patients may not only tackle metabolic disorders and decrease CV risk but may also restore testosterone levels.

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Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.09.002.

References

[1] de Haas EC, Altena R, Boezen HM, et al. Early development of the metabolic syndrome after chemotherapy for testicular cancer. Ann Oncol 2013;24(3):749–55. https://doi.org/10.1093/annonc/mds527.

[2] Bandak M, Jørgensen N, Juul A, et al. Testosterone deficiency in testicular cancer survivors - a systematic review and meta-analysis. Andrology 2016;4(3):382–8. https://doi.org/10.1111/andr.12177.

[3] Fernandez CJ, Chacko EC, Pappachan JM. Male obesity-related secondary hypogonadism - pathophysiology, clinical implications and management. Eur Endocrinol 2019;15(2):83–90. https://doi.org/10.17925/EE.2019.15.2.83.

[4] Nuver J, Smit AJ, Wolffenbuttel BH, et al. The metabolic syndrome and disturbances in hormone levels in long-term survivors of disseminated testicular cancer. J Clin Oncol 2005;23(16):3718–25. https://doi.org/10.1200/JCO.2005.02.176.

[5] Corona G, Giagulli VA, Maseroli E, et al. Therapy of endocrine disease: testosterone supplementation and body composition: results from a meta-analysis study. Eur J Endocrinol 2016;174(3):R99–116. https://doi.org/10.1530/EJE-15-0262.

[6] Dimitriadis GK, Randeva HS, Aftab S, et al. Metabolic phenotype of male obesity-related secondary hypogonadism pre-replacement and post-replacement therapy with intra-muscular testosterone undecanoate therapy. Endocrine 2018;60(1):175–84. https://doi.org/10.1007/s12020-017-1516-x.

[7] Walsh JS, Marshall H, Smith IL, et al. Testosterone replacement in young male cancer survivors: a 6-month double-blind randomised placebo-controlled trial. PLoS Med 2019;16(11):e1002960. https://doi.org/10.1371/journal.pmed.1002960. Published 2019 Nov 12.

[8] Ikramuddin S, Korner J, Lee WJ, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. J Am Med Assoc 2013;309(21):2240–9. https://doi.org/10.1001/jama.2013.5835.

[9] Lee Y, Dang JT, Switzer N, et al. Impact of bariatric surgery on male sex hormones and sperm quality: a systematic review and meta-analysis. Obes Surg 2019;29(1):334–46. https://doi.org/10.1007/s11695-018-3557-5.

[10] Philip EJ, Torghabeh MH, Strain GW. Bariatric surgery in cancer survivorship: does a history of cancer affect weight loss outcomes? Surg Obes Relat Dis 2015;11(5):1105–8. https://doi.org/10.1016/j.soard.2014.12.028.

[11] Strain GW, Cooley V, Ebel F, Christos P. Weight loss after bariatric surgery in cancer survivors. Surg Obes Relat Dis 2020;16(5):670–3. https://doi.org/10.1016/j.soard.2020.02.007.