Prevalence of the metabolic syndrome and cardiovascular disease risk in chemotherapy-treated testicular germ cell tumour survivors

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Background: Testicular cancer patients have an increased risk for cardiovascular disease (CVD), which might be related to the increased prevalence of the metabolic syndrome (MetS) in this group of patients.

Methods: We assessed the prevalence of MetS and calculated the 10-year CVD risk in a cohort of 255 testicular germ cell tumour survivors (median age, 38.7 years; interquartile range, 31–48) at a mean of 7.8 years after anti-cancer treatment, and compared these with data obtained from 360 healthy men.

Results: Survivors had an age-adjusted increased risk for MetS of 1.9 compared with that of healthy controls. The risk for MetS was highest in survivors treated with combination chemotherapy (CT) 2.3 (Adult Treatment Panel of the National Cholesterol Education Program classification) and 2.2 (International Diabetes Federation classification). The risk of MetS was especially increased in survivors with testosterone levels in the lowest quartile (OR, 2.5). Ten-year cardiovascular risk as assessed by the Framingham Risk Score (3.0%) and Systemic Coronary Risk Evaluation (1.7%) algorithms was low, independent of treatment, and was comparable to controls.

Conclusion: Testicular germ cell tumour survivors have an increased prevalence of MetS, with hypogonadism and CT treatment being clear risk factors for the development of the syndrome. The increased prevalence of MetS was not associated with an increased 10-year cardiovascular risk.

Testicular cancer, the most common cancer in male patients between 25 and 35 years of age, holds an excellent prognosis since the introduction of cisplatin-based chemotherapy (CT) in the treatment regimen (Einhorn, 1997). However, testicular cancer patients treated with CT or radiotherapy are reported to have a 25-year risk of long-term cardiovascular complications of ~16% (van den Belt-Dusebout et al, 2006). An increased incidence of cardiovascular events was indeed recently reported in germ cell tumour (GCT) survivors (Haugnes et al, 2010). Patients who had received CT were found to be more at risk than those patients who had received radiotherapy.
treated with orchidectomy only (Huddart et al, 2003). Over the last two decades, concerns have been raised about the increased risk of cardiovascular morbidity and the increased prevalence of the metabolic syndrome (MetS) with the use of certain treatment modalities in specific cancer types (de Forni and Armand, 1994; Yeh et al, 2004; Carver et al, 2007). Studies in GCT survivors report a wide variation in the prevalence of MetS ranging from 13% to 39% (Nuyer et al, 2005; Haugnes et al, 2007; Wethal et al, 2007) compared with a prevalence of 15% in non-diabetic adult Europeans (Hu et al, 2004).

MetS is a cluster of metabolic and interrelated cardiovascular risk factors, which directly promotes atherosclerotic cardiovascular disease (CVD) (Ingelsson et al, 2006). Various expert panels have developed classifications of MetS to facilitate screening for cardiovascular risk factors, including the Adult Treatment Panel of the National Cholesterol Education Program (NCEP-ATP III), which modified the definition based on similar characteristics used by the WHO (Table 1; Balkau and Charles, 1999; World Health Organization, 1999) and the MetS score developed by the International Diabetes Federation (IDF) (Alberti et al, 2006). A meta-analysis of 21 prospective American and European cohort studies using the NCEP-ATP III or WHO criteria indicated that patients with high MetS prevalence have an increased incidence and mortality for CVD (Galassi et al, 2006). Another meta-analysis, including 37 studies and 172,573 individuals (Gami et al, 2007), showed that MetS carried a relative risk (RR) of cardiovascular events and deaths of 1.78 (95% CI, 1.58–2.0).

In all classifications used for the MetS, main risk factors for CVD, such as smoking, age, and prothrombotic and proinflammatory state, are excluded to simplify outpatient screening. Of particular interest for GCT patients is that androgen deficiency has been found to be a risk factor for the development of the MetS, and cured survivors are often found to have some degree of CT-induced hypogonadism, which may persist for up to 10 years after treatment (Nord et al, 2003). Hypogonadism can itself promote obesity and insulin resistance, and in turn visceral obesity promotes hypogonadism. Another possible explanation for the observed increased CVD risk in GCT survivors is the fact that patients’ testicular germ cell cancer may be aetiologically linked to other male reproductive abnormalities as a part of the so-called ‘testicular dysgenesis syndrome’ (TDS) (Skakkebaek et al, 2007). This syndrome is present in a proportion of GCT patients before primary GCT originating in the testis, and the Systemic Coronary Risk Evaluation (SCORE) project, which collected and analysed data from 12 European cohort studies, was developed to estimate cardiovascular risk in European clinical practice.

The large differences in MetS and CVD prevalence reported in the literature in GCT patients has prompted us to use both the risk CVD prediction models to calculate 10-year cardiovascular risk in our cohort of long-term GCT survivors compared with healthy male subjects. We assessed MetS prevalence using both NCEP-ATP III and IDF classifications to compare differences in outcome and to facilitate comparison with other studies.

### PATIENTS AND METHODS

**Patients.** In a cross-sectional study design, all patients with a primary GCT originating in the testis, who attended the outpatient clinic of the Clinical Oncology Department of the Leiden University Medical Center between 2008 and 2010 for routine follow-up, were invited to take part in the study and 255 eligible patients were included (Figure 1). Seventy-nine patients had stage-I disease; 58 were treated with orchidectomy alone (‘surgery patients’) and 21 seminoma patients also received one adjuvant dose of carboplatin (AUC7; ‘carboplatin patients’). Patients ($n = 176$) with disseminated disease were treated with orchidectomy and combination CT, primarily bleomycin, etoposide, and cisplatin (‘combination-CT patients’).

Data of 360 healthy men from the general population, living in the same geographical area, obtained from the general practitioners’ health screening records were used as control. These data were obtained in 2009 as part of a programme in which apparently healthy subjects were screened for cardiovascular risk factors.

**Methods.** For all patients and controls, medical history (including smoking behaviour) was taken; body weight, height, body mass index (BMI, kg m$^{-2}$), and waist circumference (WHO standards) were recorded, and blood pressure was measured in duplicate with the participants in a semi-recumbent position after at least 5 min rest. Blood samples were obtained after an overnight fast and measured for cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides using routine assays. The patients’ blood was also analysed for C-reactive protein (CRP) concentrations (standard assay), HbA1c and insulin (LEIA), and gonadal status. The latter was evaluated by measuring serum concentrations of luteinising hormone (LH), follicle-stimulating hormone (FSH) by using electrochemoluminescence immunoassays, total testosterone (TT) and estradiol (E2) by using standard radioimmunoassays, and sex hormone-binding globulin (SHBG) by using a luminescence enzyme immunoassay. Hypogonadism was defined as a

| Table 1. Metabolic syndrome criteria according to two different classification systems |
|---------------------------------------------|
| **NCEP-ATP III** | **IDF** |
| **Hypertension** | BP$_{systolic}$ $\geq$ 135 mm Hg and BP$_{diastolic}$ $\geq$ 85 mm Hg | BP$_{systolic}$ $\geq$ 135 mm Hg or BP$_{diastolic}$ $\geq$ 85 mm Hg |
| **Obesity** | Waist circumference $\geq$ 102 cm | Waist circumference $\geq$ 94 cm or BMI $\geq$ 30 kg m$^{-2}$ |
| **Insulin resistance** | fasting glucose $\geq$ 6.1 mmol l$^{-1}$ (110 mg dl$^{-1}$) | Fasting glucose $\geq$ 5.6 mmol l$^{-1}$ (100 mg dl$^{-1}$) |
| **Dyslipidaemia** | HDL-cholesterol $<$ 0.90 mmol l$^{-1}$ (35 mg dl$^{-1}$) or statin usage HDL-cholesterol $<$ 1.03 mmol l$^{-1}$ (40 mg dl$^{-1}$) or statin usage | HDL-cholesterol $<$ 1.03 mmol l$^{-1}$ (40 mg dl$^{-1}$) or statin usage |
| **Hypertiglyceridaemia** | Triglyceride $\geq$ 1.7 mmol l$^{-1}$ (150 mg dl$^{-1}$) | Triglyceride $\geq$ 1.7 mmol l$^{-1}$ (150 mg dl$^{-1}$) |
| **Metabolic syndrome** | $\geq$ 3 Criteria | Obesity and $\geq$ 2 other criteria |

Abbreviations: BMI = body mass index; IDF = International Diabetes Federation; HDL = high-density lipoprotein; NCEP-ATP III = National Cholesterol Education Program Adult Treatment Panel III 2002.
fasting-morning serum TT concentration of $<10.4 \text{nmol/l}$ (Lackner et al., 2007). Four patients with disseminated disease received testosterone replacement therapy and were excluded for hormonal analysis.

**Metabolic syndrome and 10-year cardiovascular risk evaluation.** We used the NCEP-ATPIII criteria (National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002) and IDF risk score charts (Alberti et al., 2006; Table 1) to establish the prevalence of MetS. The 10-year cardiovascular risk profile was calculated using FRS (Wilson et al., 1987) and SCORE (Conroy et al., 2003).

**Statistical analysis.** SPSS 19 for Windows software package (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The $\chi^2$-test for categorical variables and Student’s $t$-test or Mann–Whitney test (two-sided) for non-normally distributed variables were used as appropriate. Results are expressed as interquartile range (IQR), mean ± s.d., or as median (range). Odds ratios for MetS were calculated using logistic regression analysis and with adjustment for age and kidney function as continuous variables, and smoking and hypogonadism as binary variables. The incidence of MetS was also analysed according to serum testosterone quartiles using $\chi^2$-test for categorical variables. A $P$-value of $<0.05$ (two-tailed) was considered statistically significant. We also investigated whether there was an association between the time elapsed between treatment and the occurrence of MetS by linear regression.

Finally, we used the raw data provided in three reports (Nuver et al., 2005; Haugnes et al., 2007; Wethal et al., 2007) in the literature on MetS in GCT patients to calculate the odds ratios.

**RESULTS**

**Patient characteristics.** The median (range) cumulative carboplatin dose administered to survivors was 1015 (730–1700) mg (Table 2). Seven survivors who were eventually treated with combination CT were first treated with single-dose carboplatin for stage-1 seminoma, and one survivor was treated with three cycles of carboplatin before they developed distant metastasis. The median cumulative cisplatin dose administered to the survivors receiving combination CT was 604 (0–1750) mg; two patients received carboplatin instead of cisplatin as part of their combination CT.

The summary of the patient characteristics (Table 2) showed that at the time of the analysis there were no major differences in age between the different treatment groups of GCT survivors and the controls. Seminoma patients (42.4 years; IQR 35–50) were older than non-seminoma patients (38.0 years; IQR 29–45; $P = 0.003$). The BMI and waist circumference were comparable between the groups.

Smoking behaviour was comparable in all groups of patients and the controls, and amounted to $\sim 40\%$. Moreover, there were no major differences in blood pressure and renal function, assessed as creatinine clearance using the Cockroft formula, between the groups.
Combination-CT patients had significantly higher fasting serum concentrations of cholesterol, LDL-cholesterol, and triglyceride than that in controls, and higher serum cholesterol and triglyceride concentrations compared with that in surgery patients (Table 3). Carboplatin patients had higher fasting serum cholesterol ($P = 0.04$) and LDL-cholesterol ($P = 0.004$) concentrations than that in healthy subjects. Survivors treated with surgery only had higher LDL-cholesterol concentrations than that in healthy subjects. Survivors with combination-CT had significantly lower testosterone and dihydrotestosterone concentrations compared with that in surgery patients (Table 3). Thirty-four (12.9%) GCT survivors had developed diabetes in the follow-up period. The CRP concentrations did not differ between treatment groups. Fasting serum HDL-cholesterol concentrations compared with that in controls, and higher serum cholesterol and triglyceride concentrations compared with that in healthy subjects. Survivors treated with surgery only had a significantly higher prevalence of obesity, dyslipidemia, and hypertriglyceridemia compared with age-matched healthy subjects (Table 4, upper part). In particular, survivors treated with combination CT had the highest prevalence of all NCEP-ATPIII criteria compared with healthy subjects. The prevalence of MetS did not differ between survivors treated with orchidectomy only or survivors treated with an orchidectomy and carboplatin. The prevalence of MetS in all groups was almost twofold higher when classified according to the IDF criteria compared with the NCEP-ATPIII criteria. There was only a minimal influence ($\beta$-coefficient $= 0.02$ cases per year) of the time elapsed between curative treatment and the prevalence of MetS.

GCT survivors had an increased age-adjusted NCEP-ATPIII risk of 1.9 (95% CI, 1.1–3.2) and an IDF risk of 1.8 (95% CI, 1.2–2.7; Table 4). Compared with healthy subjects, combination-CT survivors had the highest age-adjusted risk to develop MetS, that is, 2.3 (95% CI, 1.3–4.0, NCEP-ATPIII classification) and 2.2 (95% CI, 1.4–3.3, IDF classification; Table 4). In surgery-alone survivors, age-adjusted risk to develop MetS was, respectively, 1.5 (95% CI, 0.6–3.9, NCEP-ATPIII) and 1.7 (95% CI, 0.8–3.6, IDF) compared with healthy subjects. Irrespective of the use of the IDF or NCEP-ATPIII criteria, survivors with the lowest quartile testosterone levels (<12.0 nmol l$^{-1}$) had a MetS prevalence higher than the other three quartiles (OR, 2.5 and 95% CI, 1.3–4.7; and OR, 1.7 and 95% CI, 0.8–3.6, respectively). The prevalence of MetS was not associated with other gonadal hormone concentrations or with alcohol use (data not shown).

According to the NCEP-ATPIII criteria, GCT survivors who were smokers had a twofold increased risk (95% CI, 1.0–4.0) for MetS compared with non-smokers. In healthy subjects, smokers and non-smokers had a 1.6-fold increased risk (95% CI, 0.7–3.4) for MetS compared with non-smokers. Smoking-adjusted risk of MetS for all survivors and for combination-CT survivors alone compared with healthy subjects was, respectively, 1.8 (95% CI, 1.1–3.1) and 1.5 (95% CI, 1.1–2.0).
There was no treatment-related difference in age-adjusted 10-year cardiovascular risk in GTC survivors.

**DISCUSSION**

We observed that the prevalence of the MetS is 2.2- to 2.3-fold higher at a mean duration of 7.8 years after cure in testicular GCT survivors treated with combination CT compared with age-matched healthy subjects. In particular, abdominal obesity, hypertension, hypertriglyceridemia, and other dyslipidemias were more frequently observed in CT-treated cancer survivors. Notably, also fasting LDL-cholesterol, which is not included in any MetS classification was consistently higher in all GCT survivors. It is remarkable that in our cohort all GCT survivors, but in particular combination-CT survivors, had higher BMI and were significantly more overweight than controls. In the survivor population, low testosterone concentrations correlated with MetS and the patients treated with combination CT had an average 2.7 nmol l$^{-1}$ lower testosterone than those treated with surgery alone. After adjusting for testosterone, there still was a significant difference in MetS prevalence between the two groups, also after adjusting for age and smoking. In GCT survivors, MetS may be related to a possible pre-existing underlying TDS (Skakkebaek et al, 2007) as well as to partial hypogonadism induced by CT, or both. The 10-year cardiovascular risk estimated with either FRS or SCORE was low (3.0% and 1.6%, respectively) and did not differ between treatment groups or between treatment groups and controls.

Different definitions are used for MetS worldwide, and we show here that depending on the classification that is used, the prevalence of MetS may vary greatly. There was an almost twofold increased RR for MetS in a smaller GCT survivor cohort with a worldwide cohorts (Rathmann et al, 2005) observed a higher MetS prevalence and an increased RR for MetS in a smaller GCT survivor cohort with a similarity of NCEP-ATPIII has been repeatedly demonstrated in worldwide cohorts (Rathmann et al, 2006). The use of different or adapted scoring systems may also explain why the prevalence of MetS in our cohort varied with those previously reported. Three other cross-sectional studies reported different MetS prevalences in GCT survivors, possibly because of the different methodologies used in the evaluation of the MetS (Table 5). In keeping with our data, Nuver et al (2005) observed a higher MetS prevalence and an increased RR for MetS in a smaller GCT survivor cohort with a similar incidence of MetS in their controls (Table 5). A large multicentre cross-sectional study conducted in five university hospitals in Norway (Haugnes et al, 2007) reported an unusually high prevalence of MetS...
high MetS prevalence of 52% in healthy subjects, and 45% and 33%, respectively, in GCT survivors treated with CT or orchiectomy alone. Discrepancies may be explained by non-adherence to the 2002 NCEP-ATPIII classification, the use of non-fasting blood samples, using (at least two) modified criteria to assess the MetS and of only serum total cholesterol. In another report from a single institution (Wethal et al, 2007), which participated in the multicentre study (Haugnes et al, 2008), the authors also did not adhere to above mentioned classification methodology, which may have led to an overestimation of MetS.

As in other studies the high prevalence of MetS does not necessarily translate into increased cardiovascular risk. In keeping with the 2.2% cumulative incidence reported by Haugnes et al (2008) in their patients, our GCT survivors have a low 10-year risk reported for another Dutch cohort of 408 healthy males of the same age (de Visser et al, 2009). Whatever the explanation is, low testosterone and SHBG levels are considered risk factors for MetS in otherwise healthy men (Muller et al, 2005; Kupelian et al, 2006; Miner and Sadovsky, 2007). We indeed found an association between low MetS and most of the GCT survivors have long-term partial or complete hypogonadism (Berger et al, 1996). As a proportion of GCT patients already have TDS, it is unknown whether the infertility results from this condition, the CT, or from both (Williams et al, 2009). Whatever the explanation is, low testosterone and SHBG levels are considered risk factors for MetS in otherwise healthy men (Muller et al, 2005; Kupelian et al, 2006; Miner and Sadovsky, 2007). We indeed found an association between low serum concentrations of testosterone and MetS in all patients and, in particular, CT patients, but there was no association between SHBG, LH, or FSH levels and MetS. We argue that because hypogonadism is associated with increased cardiovascular risk GCT survivors should be treated with testosterone supplementation. Although testosterone supplementation has not (yet) been shown to prevent CVD, clinical trials with testosterone supplementation have resulted in a significant reduction of cholesterol levels (Fernandez-Balsells et al, 2010; Monroe and Dobs, 2013). Apart from these favourable effects on lipid metabolism, testosterone supplementation also results in increased BMD, muscle mass, and fat-free body mass (Snyder et al, 2000; Aversa et al, 2010). In particular, use of daily transdermal testosterone gel may be attractive, as this is reported to be without side effects. As the risk to develop prostate cancer after long-term use of

**Table 4. Prevalence of metabolic syndrome according to NCEP-ATPIII (upper part) and IDF criteria (lower part) in survivors and in healthy subjects**

| Parameters (%) | Healthy subjects (N = 360) | Surgery (N = 57*) | Carboplatin (N = 20*) | Combination CT (N = 174*) | Survivors (N = 251*) | Combination CT, OR (95% CI)² | Survivors OR (95% CI)² |
|----------------|---------------------------|------------------|----------------------|--------------------------|----------------------|-----------------------------|------------------------|
| **According to NCEP-ATP III** | | | | | | | |
| Hypertension | 81 (22.5) | 8 (14.0) | 4 (20.0) | 53 (31.0) | 66 (26.3) | 1.6 (1.0–2.3) | 1.2 (0.8–1.8) |
| Obesity | 70 (19.4) | 10 (17.5) | 6 (30.0) | 51 (29.3) | 67 (26.7) | 1.7 (1.1–2.6) | 1.5 (1.0–2.2) |
| Insulin resistance | 16 (4.4) | 2 (3.5) | 1 (5.0) | 11 (6.3) | 14 (5.6) | 1.5 (0.7–3.2) | 1.3 (0.6–2.7) |
| Dyslipidemia⁴ | 36 (10.0) | 7 (12.3) | 4 (20.0) | 35 (20.1) | 46 (18.3) | 2.3 (1.4–3.8) | 2.0 (1.3–3.2) |
| Hypertriglyceridemia⁴ | 84 (23.3) | 13 (22.8) | 6 (30.0) | 61 (35.1) | 80 (31.9) | 1.8 (1.2–2.6) | 1.5 (1.1–2.2) |
| Metabolic syndrome | 29 (8.1) | 5 (8.8) | 2 (10.0) | 29 (16.7) | 36 (14.3) | 2.3 (1.3–4.0) | 1.9 (1.1–3.2) |

| **According to IDF** | | | | | | | |
| Hypertension | 170 (47.2) | 21 (36.8) | 8 (40.0) | 83 (47.7) | 112 (44.6) | 1.0 (0.7–1.5) | 0.9 (0.7–1.2) |
| Obesity | 165 (45.8) | 24 (41.2) | 13 (65.0) | 107 (61.5) | 144 (57.4) | 1.9 (1.3–2.7) | 1.6 (1.1–2.2) |
| Insulin resistance | 57 (15.8) | 6 (10.5) | 3 (15.0) | 34 (19.5) | 43 (17.1) | 1.3 (0.8–2.1) | 1.1 (0.7–1.7) |
| Dyslipidemia⁴ | 36 (10.0) | 7 (12.3) | 4 (20.0) | 35 (20.1) | 46 (18.3) | 2.3 (1.4–3.8) | 2.0 (1.3–3.2) |
| Hypertriglyceridemia⁴ | 84 (23.3) | 13 (22.8) | 6 (30.0) | 61 (35.1) | 80 (31.9) | 1.8 (1.2–2.6) | 1.5 (1.1–2.2) |
| Metabolic syndrome | 59 (16.4) | 9 (15.8) | 5 (25.0) | 52 (29.9) | 66 (26.3) | 2.2 (1.4–3.3) | 1.8 (1.2–2.7) |

Abbreviations: CT = chemotherapy; CI = confidence interval; GCT = germ cell tumour; IDF = International Diabetes Federation; OR = odds ratio; NCEP-ATP III = National Cholesterol Education Program Adult Treatment Panel III 2001.

*Four survivors diagnosed with diabetes mellitus before orchidectomy (N = 1), single-dose carboplatin (N = 1), or combination CT (N = 2) are excluded in this table.

²OR for risk stratification between healthy subjects and combination CT survivors.

³OR for risk stratification between healthy subjects and all GCT survivors.

⁴Prevalence of dyslipidemia and hypertriglyceridemia are similar according to NCEP-ATPIII and IDF criteria.
transdermal androgens is currently unknown, it may be prudent to consider monitoring of PSA when initiating treatment (Lakshman and Basaria, 2009).

Our data confirm that according to the NCEP-ATPIII and IDF criteria, the subgroup of hypogonadal GCT survivors who received combination CT is the main group at increased risk for developing a MetS compared with the general population. We observed no clear increase in the calculated 10-year CVD risk in long-term GCT survivors, although the follow-up period was perhaps too short. Long-term CT-related cardiovascular toxicity may result from acute direct endothelial damage or from indirect long-term CT-induced hormonal and metabolic changes, including liver and gut damage, thereby affecting lipid uptake, transport, and metabolism over a period of many years.

In conclusion, our findings suggest an increased prevalence of MetS in GTC survivors who received CT. Of these CT patients, we further identify patients with low androgen levels as a subgroup that is particularly at risk of developing MetS. On the basis of this important clinical finding we advocate that guidelines to monitor gonadal hormone status should be introduced in international urology/oncology guidelines rather than monitoring potential complications of treatment. This is particularly important, as the current standard of follow-up is focused on the detection of cardiac and pulmonary late effects.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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