Components of the metabolic syndrome in long-term survivors of testicular cancer

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Received 16 May 2006; revised 3 August 2006; accepted 30 August 2006

Background: A possible explanation of the excess cardiovascular risk in testicular cancer (TC) survivors is development of metabolic syndrome. The association between metabolic syndrome and TC treatment is examined in long-term survivors.

Patients and methods: In a national follow-up study (1998–2002), 1463 TC survivors (diagnosed 1980–1994) participated. Patients >60 years were excluded in the present study, leaving 1135 patients eligible. The patients were divided in four treatment groups: surgery (n = 225); radiotherapy (n = 446) and two chemotherapy groups: cumulative cisplatin dose (Cis) ≤850 mg (n = 376) and Cis >850 mg (n = 88). A control group consisted of 1150 men from the Tromsø Population Study. Metabolic syndrome was defined according to a modified National Cholesterol Education Program definition.

Results: Both chemotherapy groups had increased odds for metabolic syndrome compared with the surgery group, highest for the Cis >850 group (OR 2.8, 95% confidence interval (CI) 1.6–4.7). Also, the Cis >850 group had increased odds (OR 2.1, 95% CI 1.3–3.4) for metabolic syndrome compared with the control group. The association between metabolic syndrome and the Cis >850 group was strengthened after adjusting for testosterone, smoking, physical activity, education and family status.

Conclusion: TC survivors treated with cisplatin-based chemotherapy have an increased risk of developing metabolic syndrome compared with patients treated with other modalities or with controls.

Key words: cisplatin, metabolic syndrome, radiotherapy, testicular cancer

introduction

Testicular cancer (TC) is the most common malignancy among young Norwegian men [1]. Due to better diagnostic tools, the multimodal approach and the introduction of cisplatin-based chemotherapy [2], TC patients are assumed to have a life expectancy almost comparable to healthy age-matched men once they achieve a durable remission. Thus, it is essential to detect and treat any therapy-related long-term morbidity.

Cardiovascular morbidity and mortality has been described as late complications among TC survivors [3–6]. An association between cisplatin treatment and an unfavorable cardiovascular risk profile has been demonstrated by several authors [6–10]. Radiotherapy (RT) may also increase the risk for cardiovascular disease [3]. The suggested mechanisms responsible for the development of cardiovascular morbidity in these long-term survivors, however, need to be further evaluated.

The metabolic syndrome comprises insulin resistance, hypertension, dyslipidemia and abdominal obesity. The World Health Organization (WHO) [11], the National Cholesterol Education Program (NCEP) expert panel [12] and recently the International Diabetes Federation [13] have published definitions of the metabolic syndrome. The syndrome is important because it is associated with cardiovascular morbidity and mortality [14–16].

The increased risk for cardiovascular disease in TC survivors may be mediated via the metabolic syndrome. So far, only one paper has described the prevalence of metabolic syndrome in TC survivors [17]. In this study, Nuver et al. [17] reported a higher prevalence of metabolic syndrome in cisplatin-treated patients as well as in patients with stage I disease when compared with healthy controls.

The aim of our study was to assess the prevalence of metabolic syndrome using a modified NCEP definition in long-term
survivors of TC treated with different modalities (surgery, RT or chemotherapy) through the following research questions: (i) Does the prevalence of metabolic syndrome among TC survivors differ according to previously administered treatment? (ii) And does it differ from controls?

patients and methods

patients and controls

All Norwegian long-term survivors (≥25 years) of unilateral TC aged 18–75 years were invited to participate in a national multicenter follow-up survey. The patients were treated in the period 1980–1994, and the follow-up was conducted during 1998–2002 at five university hospitals. The follow-up survey consisted of (i) a 219-item questionnaire including questions regarding medical history and demographic data and (ii) an outpatient clinical examination including laboratory tests.

Of 1814 eligible patients, 1463 (81%) signed the informed consent form and participated in the study [7]. Since the metabolic syndrome is highly prevalent among the elderly [18], patients aged above 60 years were excluded from the present report, leaving 1135 patients eligible (study population, Figure 1). The Ethical Review Board of Region South approved the study.

A control group was recruited from the Tromsø Study [19], a population-based epidemiological study in Tromsø, Northern Norway. The controls have been described in a previous publication [7]. We selected men from the last survey (Tromsø 5, 2001) as controls, since it was conducted during the same time period as our follow-up survey. Control patients aged above 60 years and those treated with testosterone substitution were excluded. Our control group consisted of 1150 males with a median age of 48 years (range 30–60).

treatment groups

Principles for treatment of TC in Norway in the period 1980–1994 are previously described [20]. For this study, the TC survivors were categorized into four treatment groups according to initial and eventual relapse treatment: (i) surgery only; (ii) RT only; (iii) chemotherapy with a cumulative dose of cisplatin ≤850 mg (Cis ≤850); (iv) chemotherapy with a cumulative dose of cisplatin >850 mg (Cis >850).

Patients in the surgery group (n = 225) did not receive treatment with RT or chemotherapy. Of these, 124 had undergone retroperitoneal surgery, while the remaining patients had been included in a surveillance program without subsequent relapse. Patients in the RT group (n = 446) had received either a modified dog-leg (n = 417) or paraaortic (n = 29) field. Two patients had received additional mediastinal irradiation. From early 1980s to mid-1990s the standard applied RT dose was gradually reduced from 40 to 27 Gy.

The cut-off point for the two chemotherapy groups was set at 850 mg Cis to separate patients who received standard four courses or less from those who received more than four courses or ‘higher dose’ chemotherapy regimens due to very advanced disease, poor response, progression or relapse. Overall, 464 patients were treated with chemotherapy, of whom 88 were in the Cis ≤850 group. Most patients (n = 442, 95%) received cisplatin-based chemotherapy, primarily in combination with etoposide and bleomycin or vinblastine and bleomycin. Twenty-two patients (5%) who received carboplatin instead of cisplatin were also included in the Cis ≤850 group, as their risk for the metabolic syndrome did not differ from those who received standard cisplatin-based chemotherapy (data not shown).

Overall 304 (66%) of the patients treated with chemotherapy underwent retroperitoneal surgery, and 47 (10%) received additional RT, primarily infradiaphragmatic.

assessments

Resting blood pressure was measured manually or with an automatic device. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m²). Blood samples were drawn nonfasting by venipuncture at each hospital laboratory between 0800 and 1200 h to assess the levels of serum cholesterol, serum magnesium (Mg) and serum testosterone. Levels of serum total testosterone were determined using a commercial immunoassay, with similar reference ranges at each hospital.

Information regarding the use of antihypertensive, antidiabetic and/or lipid-lowering medication, the prevalence of diabetes and demographic data was obtained from the questionnaire. Respondents with missing questionnaire data on antihypertensive treatment or diabetes were categorized as being without such treatment or nondiabetic, respectively.

Data for family status and educational level were dichotomized according to married/cohabitant versus living alone, and college/university versus lower education. Physical activity was assessed by two questionnaire items, one assessing a low physical activity level (such as walking) and the other a high level (leading to sweating and breathlessness). Based on responses to these items, physical activity was divided into three categories (no, moderate and high activity) as described previously [21]. Cigarette smoking was assessed by pack-years, calculated as number of cigarette packs smoked per day multiplied by the number of years smoked. Accordingly, the patients were categorized into four groups: never smokers, 0.1–9.9 pack-years, 10–19.9 pack-years and ≥20 pack-years.

definition of metabolic syndrome

We applied a modified NCEP definition of the metabolic syndrome (Table 1) [12]. Hypertension was defined as blood pressure ≥140/90 mmHg and/or antihypertensive medication according to the WHO Hypertension Guidelines [22]. As a measure of obesity, we used BMI ≥30 [23].

In lack of serum triglycerides and high-density lipoprotein (HDL) cholesterol assessments, we used serum total cholesterol. Hypercholesterolemia was defined as total cholesterol ≥5.2 mmol/l [12] and/or the use of lipid-lowering drugs. Since blood glucose was measured nonfasting and only in a subgroup of patients, we instead applied patient-reported prevalence of diabetes and/or use of antidiabetic medication.

According to our definition, metabolic syndrome was present if two or more of the following four components were present: hypertension, obesity, hypercholesterolemia or diabetes (Table 1). Additionally, we carried out analyses using a more restrictive definition of metabolic syndrome, defined as three or more components present.
Table 1. Definitions of the metabolic syndrome

<table>
<thead>
<tr>
<th>NCEP definition</th>
<th>Our modified definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least three of the following:</td>
<td>At least two of the following:</td>
</tr>
<tr>
<td>Blood pressure ≥130/85 mmHg or</td>
<td>Blood pressure ≥140/90 mmHg or</td>
</tr>
<tr>
<td>medication</td>
<td>medication</td>
</tr>
<tr>
<td>Waist circumference &gt;102 cm</td>
<td>BMI ≥30</td>
</tr>
<tr>
<td>Fasting plasma glucose ≥5.6 mmol/l</td>
<td>Self-reported prevalence</td>
</tr>
<tr>
<td>Serum triglycerides ≥1.7 mmol/l</td>
<td>Serum total cholesterol</td>
</tr>
<tr>
<td>Serum HDL cholesterol &lt;1.0 mmol/l</td>
<td>≥5.2 mmol/l or medication</td>
</tr>
</tbody>
</table>

NCEP, National Cholesterol Education Program; BMI, body mass index; HDL, high-density lipoprotein.

**Statistical analysis**

The matching of cases and controls were carried out at a group level, not at an individual level, due to an inadequate number of young controls. Mean chemotherapy values in the two chemotherapy groups were compared using Student’s t-test. Multiple logistic regression with metabolic syndrome as the dependent variable was used to evaluate possible differences between treatment groups, between cases and controls and to evaluate the influence of possible predictors for metabolic syndrome. Metabolic syndrome was also analyzed using ordinal logit regression, with the variable divided into quintiles (0, 1, 2, 3 or all 4 components). The model calculated the probability for having a larger number of metabolic syndrome components. A test of parallel lines confirmed that the proportional odds assumption was met.

Differences between treatment groups with respect to continuous variables, such as age, total cholesterol, total testosterone and Mg, were analyzed using multiple linear regression. The surgery group was used as reference when comparing the impact of different treatment modalities. Persons with missing values were excluded from the analyses where the missing variable was the dependent or explanatory variable. All regression analyses were adjusted for age. All P values are two-tailed, with statistical significance set at P < 0.05. The data were analyzed using the SPSS 11.0 statistical package (SPSS Inc., Chicago, IL).

**Results**

**Patient characteristics**

Median age at follow-up was 43 years for both responders and nonresponders (P = 0.62). Stage, histology and treatment were similar in both groups (data not shown).

Characteristics of study patients and controls are listed in Table 2. The median observation time was 11.1 years. Compared with the surgery group, the RT group was older at diagnosis and at follow-up (P < 0.001, both), while the Cis >850 group was younger at diagnosis (P = 0.016) and at follow-up (P < 0.001), and had a shorter observation time (P = 0.001). Patients in the Cis >850 group were less educated [odds ratio (OR) 0.58, 95% confidence interval (CI) 0.34–0.99] and had a lower smoking prevalence (OR 0.58, 95% CI 0.35–0.97) than the surgery group. Otherwise, there were no differences across the treatment groups with regard to demographic variables.

Prevalences of the metabolic syndrome, its components, serum testosterone and serum Mg are presented in Table 3.
were then included in multiple regression models (Table 5). When analyzing testicular survivors only, treatment group (Cis >850 mg), total serum testosterone and smoking history (‡20 pack-years) were independent predictive factors. Table 5 also presents the results of these analyses in patients and controls, using the controls as reference. Here, treatment group (Cis >850 mg) and total serum testosterone appeared as independent predictors.

**impact of chemotherapy**

Median chemotherapy doses for the agents cisplatin, bleomycin, etoposide and vinblastine are listed in Table 2. Patients in the Cis >850 group received more cisplatin ($P < 0.001$) and etoposide ($P < 0.001$) than patients in Cis ≤850 group. Mean vinblastine ($P = 0.74$) and bleomycin dose ($P = 0.06$) did not differ significantly between the two groups.

**Metabolic syndrome** was positively associated with cumulative cisplatin ($P = 0.001$), bleomycin ($P = 0.001$) and etoposide doses ($P = 0.002$) in age-adjusted analyses. Cumulative vinblastine dose was not associated with metabolic syndrome ($P = 0.27$). Logistic regression using a backward stepwise model with all four chemotherapy agents and age included, left only age and cumulative cisplatin dose as significant variables.

**discussion**

In this study, previously cisplatin-treated TC survivors show an increased age-adjusted risk of developing metabolic syndrome in comparison to those treated with surgery, while patients treated with RT did not differ from the surgery group. The risk was most pronounced after cumulative cisplatin doses above...
This heavily treated group also had an increased risk compared with the control group. Treatment with surgery or RT alone did not increase the risk for metabolic syndrome in comparison to the control group.

The major strengths of this study are the large patient population permitting subgroup analyses between the different treatment groups and the case–control design allowing comparisons between TC survivors and healthy controls. Another strength is the concurrent assessments of metabolic syndrome-related factors in patients and controls.

A limitation of the study is the age difference between TC survivors and controls (median 43 versus 48 years). Age-adjusted analyses may not completely equalize the impact of age on the metabolic syndrome, but any age bias will underestimate rather than overestimate the association between cisplatin treatment and metabolic syndrome. Another limitation is the inability to evaluate the TC survivors’ complete metabolic syndrome status at diagnosis. However, in our recently published longitudinal study in this group [7], there were no differences in BMI and blood pressure between treatment groups at diagnosis.

As the present study was planned and partially conducted before the publication of the WHO and NCEP definitions, we lack necessary data for the correct definition of metabolic syndrome. Surrogate markers were used for fasting blood glucose, triglycerides and HDL cholesterol. The prevalence of diabetes may be underestimated, since those not clearly reporting a diagnosis of diabetes were classified as being nondiabetic. Using a modified definition of metabolic syndrome may complicate comparisons of our results with others. Nevertheless, the major aim of this study was to compare

Table 3. Prevalences of the metabolic syndrome and its components, serum testosterone and Mg levels at follow-up according to treatment group and controls

<table>
<thead>
<tr>
<th></th>
<th>Surgery, n = 225</th>
<th>Radiotherapy, n = 446</th>
<th>Cis ≤850 mg, n = 376</th>
<th>Cis &gt;850 mg, n = 88</th>
<th>Controls, n = 1150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>77 (34)</td>
<td>201 (46)</td>
<td>166 (45)</td>
<td>42 (48)</td>
<td>568 (50)</td>
</tr>
<tr>
<td>Obesity (BMI ≥30)</td>
<td>28 (13)</td>
<td>55 (12)</td>
<td>60 (16)</td>
<td>23 (26)</td>
<td>237 (21)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>151 (67)</td>
<td>311 (70)</td>
<td>246 (67)</td>
<td>63 (73)</td>
<td>963 (84)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>4 (1.8)</td>
<td>13 (2.9)</td>
<td>11 (2.9)</td>
<td>2 (2.3)</td>
<td>33 (2.9)</td>
</tr>
<tr>
<td>Metabolic syndrome, ≥2 factors included</td>
<td>72 (33)</td>
<td>184 (42)</td>
<td>149 (40)</td>
<td>42 (48)</td>
<td>584 (51)</td>
</tr>
<tr>
<td>Metabolic syndrome, ≥3 factors included</td>
<td>15 (6.7)</td>
<td>37 (8.3)</td>
<td>29 (7.8)</td>
<td>11 (12.6)</td>
<td>170 (15)</td>
</tr>
<tr>
<td>Serum total testosterone, nmol/l, mean (SD)</td>
<td>16.2 (4.9)</td>
<td>15.5 (5.3)</td>
<td>15.6 (5.8)</td>
<td>14.8 (5.8)</td>
<td>14.4 (5.5)</td>
</tr>
<tr>
<td>Serum Mg, mmol/l, mean (SD)</td>
<td>0.83 (0.07)</td>
<td>0.81 (0.06)</td>
<td>0.81 (0.07)</td>
<td>0.83 (0.07)</td>
<td>0.82 (0.05)</td>
</tr>
</tbody>
</table>

Metabolic syndrome defined as either ≥2 or ≥3 of the following four factors: hypertension, obesity, hypercholesterolemia and diabetes. Data are number (%) unless otherwise specified. There are missing data for some of the variables.

*Hypertension is defined as systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 and/or the use of antihypertensive medication.

Hypercholesterolemia is defined as serum total cholesterol ≥5.2 mmol/l and/or the use of lipid-lowering drugs.

BMI, body mass index; SD, standard deviation.

850 mg. This heavily treated group also had an increased risk compared with the control group. Treatment with surgery or RT alone did not increase the risk for metabolic syndrome in comparison to the control group.

Figure 2. Age-adjusted odds ratios (OR) for the different components of the metabolic syndrome and for the syndrome itself (≥2 components present) in different treatment groups, using surgery group as reference. Bars indicate 95% confidence interval for OR. Bars indicate 95% confidence interval for OR.

Figure 3. Age-adjusted odds ratios (OR) for metabolic syndrome (≥3 components present) in different treatment groups using the surgery group as reference. Bars indicate 95% confidence interval for OR.
and report possible differences between treatment groups and between these groups and controls, with the same definition applied.

Hypertension, obesity and hypercholesterolemia all seem to be involved in the increased risk for metabolic syndrome in our heavily cisplatin-treated patients. Hypertension and obesity have been discussed in more detail in our previous publication [7]. Our hypercholesterolemia rates of 67% and 73% after standard and high cumulative cisplatin doses, respectively, are in line with previous studies reporting rates at 67% to 84% [6, 8–10].

The first study examining the association between metabolic syndrome and treatment of TC in 86 cisplatin-treated patients, 44 stage I patients treated with orchiectomy and 47 healthy controls was recently published [17]. These investigators reported higher prevalence of metabolic syndrome in both cisplatin-treated (26%) and stage I patients (36%) compared with healthy controls (9%). Surprisingly, they found the highest prevalence of metabolic syndrome in stage I patients. These results are inconsistent with our data since the Cis >850 group alone had a significantly higher prevalence of metabolic syndrome when compared with controls. A possible explanation for the discrepancy between our results and those presented by Nuver et al. [17] may in part be the different criteria applied in the definition of metabolic syndrome. Besides the larger number of cases and controls in our study, our control group may be more representative for the general population. The median follow-up time of 11 years in our study, compared with 7 years in the Dutch study, may also influence the results.

It has been demonstrated that a low serum total testosterone level is an independent predictor for the development of metabolic syndrome [24]. Gonadal dysfunction is a possible long-term complication after treatment of TC, particularly after high cumulative doses of cisplatin [25]. In line with this, both

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Study patients only</th>
<th>Study patients and controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>–</td>
<td>1.00 Reference</td>
</tr>
<tr>
<td>Surgery</td>
<td>1.00</td>
<td>0.67</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>1.11</td>
<td>0.76</td>
</tr>
<tr>
<td>Cis ≤ 850 mg</td>
<td>1.45</td>
<td>0.99</td>
</tr>
<tr>
<td>Cis &gt;850 mg</td>
<td>3.13</td>
<td>2.16</td>
</tr>
</tbody>
</table>

OR indicates the probability for having a larger number of metabolic syndrome components (0, 1, 2, 3 or all 4 components).

### Table 5. Logistic regression, with metabolic syndrome (≥2 components present) as the dependent variable

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
<td>1.00</td>
<td>Reference</td>
<td></td>
<td>1.00</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>1.00</td>
<td>Reference</td>
<td>0.75</td>
<td>0.43–1.10</td>
<td>0.54–1.03</td>
<td>0.002</td>
<td>1.00</td>
<td>Reference</td>
<td>0.80</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>1.44</td>
<td>0.98–2.12</td>
<td>0.89</td>
<td>0.71–1.12</td>
<td>0.51–0.89</td>
<td></td>
<td>0.96</td>
<td>0.75–1.24</td>
<td>0.004</td>
</tr>
<tr>
<td>Cis ≤ 850 mg</td>
<td>3.05</td>
<td>1.72–5.40</td>
<td>2.10</td>
<td>1.31–3.66</td>
<td>1.06–2.18</td>
<td></td>
<td>2.43</td>
<td>1.46–4.04</td>
<td>0.001</td>
</tr>
<tr>
<td>Total testosterone</td>
<td>0.96</td>
<td>0.93–0.98</td>
<td>0.001</td>
<td>0.95</td>
<td>0.93–0.96</td>
<td>&lt;0.001</td>
<td>0.95</td>
<td>0.93–0.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pack-years</td>
<td>2.73</td>
<td>0.40</td>
<td>0.40</td>
<td>0.27</td>
<td>0.40</td>
<td>0.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (never smoker)</td>
<td>1.00</td>
<td>Reference</td>
<td>1.00</td>
<td>Reference</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1–9.9</td>
<td>1.05</td>
<td>0.73–1.50</td>
<td>1.09</td>
<td>0.86–1.38</td>
<td>1.16</td>
<td>0.90–1.49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–19.9</td>
<td>1.10</td>
<td>0.75–1.60</td>
<td>1.02</td>
<td>0.80–1.31</td>
<td>1.04</td>
<td>0.80–1.35</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥20</td>
<td>1.48</td>
<td>1.00–2.01</td>
<td>1.23</td>
<td>0.96–1.58</td>
<td>1.29</td>
<td>0.98–1.69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>0.200</td>
<td>0.041</td>
<td>0.041</td>
<td>0.12</td>
<td>0.041</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No activity</td>
<td>1.00</td>
<td>Reference</td>
<td>1.00</td>
<td>Reference</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate activity</td>
<td>0.96</td>
<td>0.64–1.44</td>
<td>1.08</td>
<td>0.83–1.41</td>
<td>1.19</td>
<td>0.90–1.58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hard activity</td>
<td>0.75</td>
<td>0.50–1.15</td>
<td>0.85</td>
<td>0.65–1.11</td>
<td>0.97</td>
<td>0.73–1.30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td>0.61</td>
<td>0.018</td>
<td>0.018</td>
<td>0.12</td>
<td>0.018</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.00</td>
<td>Reference</td>
<td>1.00</td>
<td>Reference</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (college/university)</td>
<td>0.93</td>
<td>0.70–1.23</td>
<td>0.81</td>
<td>0.67–0.96</td>
<td>0.83</td>
<td>0.68–1.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family status</td>
<td>0.57</td>
<td>0.99</td>
<td>0.99</td>
<td>0.12</td>
<td>0.91</td>
<td>0.91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living alone</td>
<td>1.00</td>
<td>Reference</td>
<td>1.00</td>
<td>Reference</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/cohabitant</td>
<td>0.91</td>
<td>0.66–1.26</td>
<td>1.00</td>
<td>0.80–1.25</td>
<td>1.01</td>
<td>0.80–1.29</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Odds ratio (OR) and 95% confidence interval (CI) for different predictors of the metabolic syndrome.

- For testicular cancer survivors only.
- Adjusted for age and all listed variables
- For control population and testicular cancer survivors.
- There are missing data for 18 patients and nine controls in age-adjusted analyses. There are missing data for 125 patients and 117 controls in the multiple-adjusted analyses.
- Number of cigarette packs per day multiplied by number of smoking years.
our study and the Nuver study [17] found a strong negative association between total testosterone and the prevalence of metabolic syndrome. Thus, a more liberal policy regarding testosterone substitution in TC survivors to prevent metabolic syndrome may be justified. Yet, our analyses show an unaltered OR for metabolic syndrome in the Cis >850 group after adjusting for total testosterone. This indicates the importance of other causative mechanisms beyond gonadal dysfunction.

Several demographic factors are known to influence the development of the metabolic syndrome. Physical activity may reduce the risk of the metabolic syndrome [26], while smoking is associated with an increased risk [27]. The metabolic syndrome is less prevalent in persons with a university education [28], and marriage seems to protect against cardiovascular death [29]. Although patients in the Cis >850 group had a lower smoking prevalence compared with the surgery group, the association between the metabolic syndrome and the Cis >850 group was actually strengthened after adjusting for demographic factors.

The increased risk for metabolic syndrome reported in this article may be related to other agents than cisplatin. However, since cumulative cisplatin dose alone was associated with the metabolic syndrome in our backward stepwise model, this agent appears to be an important causative factor.

Nephrotoxicity is a well-known side-effect after high cumulative cisplatin doses or when cisplatin and RT are combined [30]. Persistent hypomagnesemia, a potential consequence of cisplatin-induced damage of proximal renal tubules, has been associated with insulin resistance [31], and may be a possible link between cisplatin treatment and the metabolic syndrome. Mean serum Mg levels in our study were similar in the Cis >850 and the surgery group, and serum Mg was not associated with metabolic syndrome. Possibly, the intracellular level of Mg might be more important with regard to insulin resistance than the serum level [31].

There is increasing evidence for an association between metabolic syndrome and endothelial dysfunction [32]. Microalbuminuria, an important indicator of generalized endothelial dysfunction [33], appears to be prevalent in TC survivors treated with cisplatin-based chemotherapy [6, 34]. In vitro studies have yielded evidence for cisplatin-induced endothelial damage [35]. Recently, it was demonstrated that the level of von Willebrand factor increased during chemotherapy, indicating endothelial activation [36]. Thus, the increased risk of metabolic syndrome following cisplatin-based treatment may be due to endothelial dysfunction, although further studies are needed to evaluate a possible causal mechanism.

Patients treated with surgery or irradiation alone actually had lower ORs for the metabolic syndrome than the controls. A possible explanation could be that these survivors may change their lifestyle after having experienced a TC diagnosis, thereby reducing their risk for metabolic syndrome. Alternatively, TC itself may be associated with a reduced risk for metabolic syndrome.

In summary, TC survivors previously treated with high cumulative cisplatin doses have an increased risk of developing metabolic syndrome years after treatment, when compared with patients without previous chemotherapy or to controls. Therefore, cisplatin-treated TC survivors should be followed regularly with respect to the development of metabolic syndrome.

**Acknowledgements**

Supported in part by grants from Erna and Olav Aakres Legacy, the Odd Fellow Medical-Scientific Research Fund and the Norwegian Foundation for Health and Rehabilitation (grant no. 1998/27). Thanks to project secretary Vigidis Opperud for assistance with the database. The study is a national clinical study as part of the Norwegian Urological Cancer Group III project.

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