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Cancer treatment induced metabolic syndrome: Improving outcome with lifestyle

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ABSTRACT

Increasing numbers of long-term cancer survivors face important treatment related adverse effects. Cancer treatment induced metabolic syndrome (CTIMetS) is an especially prevalent and harmful condition. The aetiology of CTIMetS likely differs from metabolic syndrome in the general population, but effective treatment and prevention methods are probably similar. In this review, we summarize the potential mechanisms leading to the development of CTIMetS after various types of cancer treatment. Furthermore, we propose a safe and accessible method to treat or prevent CTIMetS through lifestyle change. In particular, we suggest that a lifestyle intervention and optimization of energy balance can prevent or mitigate the development of CTIMetS, which may contribute to optimal survivorship care.

1. Introduction

The number of long-term cancer survivors is growing. According to recent data, the age-adjusted 5-year survival in Europe was about 50% for all cancer types (Baili et al., 2015). Factors like bet-

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Table 1
Criteria of the metabolic syndrome according to the NCEP ATP III.

Three or more of the following:		
	Male	Female
Waist circumference (cm)	≥102	≥88
High density lipoprotein cholesterol (HDL-C) (mmol/L)*	<1.03	<1.29
Triglycerides (mmol/L)*	≥1.7	
Blood pressure (mmHg)*	systolic ≥ 130/diastolic ≥ 85	
Fasting plasma glucose (mmol/L)*	≥5.6	

*Or drug treatment for respectively low HDL, elevated triglycerides, elevated blood pressure or elevated plasma glucose.

ter cancer-care organization (e.g. screening, prevention programs, access to medical facilities), more effective treatment options, evidence based tumour-specific protocols and a more multidisciplinary approach have contributed to this (Baili et al., 2015; Haward, 2006 Haward, 2006). The encouraging increase in overall survival is accompanied by increasing numbers of cancer survivors whose prognosis and quality of life are hampered by the potentially harmful long-term and late side effects of their treatments. Long-term survivors of childhood, breast, colorectal and testicular cancer and of several haematological malignancies face an increased risk of treatment-induced cardiovascular disease (Lenihan and Cardinale, 2012) and metabolic syndrome (MetS) (de Haas et al., 2010). MetS is a clustering of central obesity, insulin resistance, dyslipidaemia and hypertension (de Haas et al., 2010, 2013). This syndrome is associated with inflammatory and prothrombotic features and might be an important link between cancer treatment, cardiovascular toxicity and accelerated atherosclerosis in cancer survivors (Van Gaal et al., 2006). The high prevalence of weight gain and sedentary lifestyle in this population (Irwin, 2009; Kroenke et al., 2005), is a contributing factor to the higher occurrence of MetS and cardiovascular morbidity in cancer survivors. Besides the fact that obesity is rapidly taking over smoking as the most preventable cause of cancer in the United States (Arnold et al., 2015; US Cancer Statistics, 2012), it is plausible that obesity is part of a vicious circle of cancer treatment-related fatigue (Minton et al., 2013), impaired physical function, discomfort, physical inactivity and continued weight gain (Lucia et al., 2003). One of the possible ways to safely and effectively treat MetS in the general population is a lifestyle intervention with the goal to optimize energy balance by increasing physical activity and reducing caloric intake. Although the aetiology of MetS in non-cancer patients probably differs from the aetiology in cancer patients (de Haas et al., 2010), it is reasonable to assume that the same treatment strategies may have similar positive effects on the prevention and treatment of the different components of MetS.

In this review, we focus on the aetiology of the different components of CTIMetS and corresponding measures to prevent or mitigate this syndrome. We summarize different types of cancer and cancer treatments and their relation to CTIMetS. Furthermore, we review if interventions regarding exercise level or diet can influence CTIMetS. Finally, we discuss the influence of timing of these interventions.

2. The metabolic syndrome

According to Grundy (2008), at least 25% of the population in the Americas, Europe and India has MetS. The commonly used criteria for MetS are those defined by the National Cholesterol Education Program's Adult Treatment Panel (NCEP ATP) III (Evaluation and Treatment of High Blood Cholesterol in Adult, 2001; Grundy et al., 2005) (Table 1). Patients with MetS are at increased risk of developing a cardiovascular event or type 2 diabetes mellitus (Sattar et al., 2008; Eckel et al., 2010). Early detection of insulin resistance, dyslipidaemia and/or hypertension or their aetiological factors makes treatment or prevention possible with the aim to reduce cardiovascular morbidity (Eckel et al., 2010). Obesity can be considered as a major driving force in the development of MetS, leading to both cardiometabolic risk and insulin resistance (Giugliano et al., 2008; Kahn, 2007) and is the first component that should be dealt with (Fig. 1). A key aspect of this process is thought to be the release of free fatty acids (FFAs) (Boden, 2008). Adipose tissue stores and releases adipokines and FFAs, which have been linked to insulin-resistance (Boden et al., 1994). More adipose tissue mass releases more FFAs. Moreover, the antilipolytic action of insulin is inhibited by elevated levels of plasma FFAs, which further increases FFA release (Jensen et al., 1989). Obesity and insulin resistance are associated with increased production of very low density lipoprotein triglycerides by the liver. The increase in FFAs and hyperinsulinaemia are believed to be responsible for this (Bamba and Rader, 2007). Insulin resistance reduces endothelial production of nitric oxide, which results in decreased vasodilatation and increased blood pressure, with hypertension occurring more frequently (Boden, 2008).

3. Cancer treatment induced metabolic syndrome

The aetiology of CTIMetS is multifactorial and differs between treatment type, cancer diagnosis and patients characteristics. Surgery, radiotherapy, chemotherapy and hormonal therapy have been shown to induce MetS, probably due to different and sometimes overlapping mechanisms (Table 2). In Table 3, an overview of the odds ratios or relative risk of MetS in different patient groups is given.

3.1. The role of surgery

Pituitary or hypothalamic damage can result in hormonal disturbances, for example after surgical treatment for brain tumours (Pietila et al., 2009). Pietilä et al. reported that 8% of brain tumour patients, mean age 14.4 years, had MetS, and this was associated with pituitary or hypothalamic damage ($P = 0.003$). Additional cranial radiotherapy made these patients even more prone to hormonal disturbances and, as a consequence, to CTIMetS in 20% of the patients (Pietila et al., 2009).

Orchiectomy in testicular cancer survivors may result in gonadal endocrine dysfunction, i.e. low testosterone and/or high luteinizing hormone (LH) levels (primary hypogonadism). After the removal of one testicle, LH may increase, which is probably the result of fewer Leydig cells. The remaining Leydig cells have to be more active to produce sufficient amounts of testosterone. Low testosterone levels are related to CTIMetS (Nuver et al., 2005).

Risk-reducing salpingo-oophorectomy (RRSO) is also strongly associated with CTIMetS. Michelsen et al. (2009) found an association with CTIMetS with an odds ratio (OR) of 2.46 (95% confidence interval (CI) 1.63–3.73) in women who had undergone RRSO (mean follow-up 6.5 years) (Table 3) compared to the general population. Especially waist circumference and central obesity were determinative criteria in the scoring of CTIMetS. Probably, loss of oestrogen causes alterations in body fat distribution with increased waist circumference and central obesity (Michelsen et al., 2009). Careful follow-up for these women is clearly advisable.

3.2. The role of radiotherapy

Cranial radiotherapy in particular is strongly associated with disturbances in the hypothalamus-pituitary axis, which has mostly been studied in childhood cancer survivors. For example, deficiency of growth hormone is the most common endocrine dysfunction in patients treated with cranial radiotherapy and is associated with