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An Overview about Metabolic Syndrome in Childhood Cancer Survivors

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Abstract

Background: Childhood cancer is defined as cancer that occurs in children under the age of 19 years old. Following the global cancer observatory (, childhood cancer is only 1% of total cancer. Although the low incidence of cancer in children and adolescents, a cancer diagnosis is a life-altering event for them and their families. The incidence of childhood cancer was increasing all over the world except in Sub-Saharan Africa. Metabolic syndrome is a cluster of adiposity, IR/DM, dyslipidemia, and hypertension. It was first described by Reaven in 1988, who found a clustering of symptoms in patients and called this Syndrome. The symptoms of this cluster are related and interacting in various ways.

Keywords: Metabolic syndrome, Childhood Cancer

Introduction

Over the past decades, survival rates of childhood cancer have increased considerably from 5 to 30% in the early seventies to current rates exceeding 80%. This is due to the development of effective chemotherapy, surgery, radiotherapy, and stem cell transplantation (SCT), combined with an optimized stratification of therapy and better supportive care regimens. These improved survival rates currently result in an ongoing increasing number of survivors, which in turn resulted in increased awareness of late side effects of treatment for childhood cancer, and research investigating these late sequelae **(1).**

Several epidemiological studies have reported an increased incidence of cardiovascular disease in survivors of childhood cancer. Standardized mortality risk, e.g. due to stroke and coronary heart disease, ranges from 1.9 to 12.7, with a higher risk for specific subgroups concerning diagnosis, administered treatment, and follow-up time **(2).**

The pathophysiology of the development of cardiovascular disease in childhood cancer survivors is a multifactorial process as in the normal population but with additional

treatment and disease-specific modulators. Frequently reported risk factors for cardiovascular sequelae are adiposity, insulin resistance/diabetes mellitus, dyslipidemia, and hypertension, which cluster as the entity "metabolic syndrome". This narrative review summarizes the existing literature on the frequency and determinants of metabolic syndrome and its components in childhood cancer survivors **(3).**

I. Components of the metabolic syndrome in childhood cancer survivors

1) Overweight, obesity and adiposity

Overweight, obesity, and adiposity are frequently described phenomena in CCS. Overweight is defined as body mass index (BMI) ≥25 and < 30 kg/m2, obesity as BMI ≥ 30 kg/m2. Population-based, the prevalence of overweight has increased enormously over the past decades, especially in developed countries. In 2014, an estimated 1.9 billion adults (i.e. 39% of the adult population worldwide), suffered from overweight, of which a third were obese. Overweight has a negative influence on blood pressure, lipid metabolism, and insulin resistance. A five kg/m2. BMI increase has been described to be associated with a 1.5- or 2-fold risk increase for coronary heart disease, and 4- or 8-fold for diabetes mellitus. Also, overweight enhances the risk of stroke (1.3-fold) and several types of cancer, e.g. postmenopausal breast, colon, thyroid, renal, endometrium, and esophageal, with a relative risk of 1.12–1.59 per 5 points BMI increase **(2).**

Adiposity is a broader term including more accurate measurements of adipose tissue accumulation, such as waist circumference, waist/hip ratio, and sometimes fat percentage or body composition (assessed by Dual-energy X-ray Absorptiometry [DXA]). There is increasing evidence that BMI values reflect underestimations of adiposity, and that the accumulation of visceral fat, as well as body composition as measured by DXA, are more reliable measures for overweight to predict the development of the cardiovascular disease. However, since DXA is a time consuming, financially less attractive diagnostic test which, also, requires low dose radiation in children who have often already been exposed to teratogenic treatments, BMI is the most commonly used tool to study overweight **(4).**

The first reports on overweight risk after childhood cancer were published in the eighties, initiated by the impression that many survivors of childhood leukemia were overweight or obese. A correlation with CRT, often associated with growth hormone deficiency (GHD), was reported, which was confirmed in consecutive studies thereafter. Subsequently, further detailed studies pointed out that the risk of overweight was especially high among female survivors and survivors diagnosed at a younger age and were radiation dose- and site-dependent. On the other hand, a recent meta-analysis in 1742 ALL survivors reported a high prevalence of overweight – 80th BMI percentile –, independent of patient and treatment characteristics. Nine recently published studies performed a multivariable

analysis to describe independent risk factors for overweight, six of which had a cross-sectional design, and three were retrospective studies **(5).**

The largest is a report from the Childhood Cancer Survivor Study (CCSS), comparing self-reported overweight between 13,000 survivors, after median 24 years' follow-up, and 4000 siblings in 27 participating centers in the United States and Canada. The overweight rate was the same in both study groups (RR 1.0, 95% CI 0.9–1.1). Among survivors, CRT > 18 Gy, total body irradiation (TBI), and abdominal radiotherapy were independent risk factors for overweight. After a follow-up of 24.6 years, the St. Jude Lifetime cohort, consisting of ∼2000 patients that underwent late effect surveillance in the After Completion of Therapy (ACT) Clinic, showed a prevalence of obesity of 36%, with a standardized morbidity ratio of 1.14 when compared to matched controls. CRT (OR 1.66) and previous glucocorticoids treatment (OR 1.37), as well as older age at evaluation, were independent risk factors of becoming obese, whereas previous chest/abdominal/pelvic radiation (OR 0.48) was associated with lower obesity prevalence among survivors **(5).**

In the Swiss Childhood Cancer Survivor Study, the prevalence of self-reported overweight in 2400 CCS was similar to siblings and the general population, and CRT > 20 Gy was an independent risk factor for overweight among survivors. The three other studies with a cross-sectional design comprised between 330 and 900 survivors, and reported the following independent risk factors for overweight or obesity: a brain tumor, CRT, anthracyclines, high BMI at diagnosis, and Hispanic race. In summary, in studies of the highest quality, CRT is the most frequently reported independent risk factor of overweight in CCS. **(2).**

A large cross-sectional study in ∼1000 adult survivors treated with HSCT also revealed TBI as an independent risk factor for DM (OR 3.42). A study in 750 pediatric HSCT treated survivors added asparaginase toxicity, defined as hyperglycemia and/or pancreatitis, as an independent risk factor (Hoffmeister et al., 2004), and a prospective study in 250 CCS reported TBI and hypogonadism as independent risk factors. Chao found no significant increase in DM frequency in 650 survivors compared to 6520 non-cancer controls. In summary, several studies investigated DM in large cohorts of cancer survivors, and radiotherapy – the total body as well as abdominal – seems to be the most frequently reported independent risk factor **(6).**

The link with damage to the pancreas by radiotherapy was closely investigated by De Vathaire. Radiation to the pancreatic tail, where the majority of insulin-secreting Langerhans islets is located, increased the risk of diabetes in a dose-dependent way (RR at 1 Gy 1.61), whereas the radiation dose to the head or body had no significant effect. A similar dose-dependent relation between radiation to the pancreatic tail and the occurrence of DM was found in adult Hodgkin lymphoma survivors **(7).**

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Radiotherapy to the whole pancreas increased the risk of IR, compared to controls and radiation to parts of the pancreas. A study in ALL survivors reported lower pancreatic volume and insulin secretion after TBI, suggesting a reduced beta-cell reserve. Apart from pancreatic radiation damage impairing insulin secretion, it might be that radiotherapy impairs fat cell expansion, which increases liver steatosis and circulation of free fatty acids (FFA), subsequently causing IR and DM. In mice, it has been shown that adipose tissue fibrosis restricts adipocyte enlargement and is associated with local inflammation and systemic IR. Whether these biological mechanisms determine the higher MetS risk in abdominally irradiated cancer survivors as well, needs to be investigated **(8).**

2) Dyslipidemia

Classic parameters of dyslipidemia include elevated fasting levels of total cholesterol and low-density lipoprotein cholesterol and triglycerides, and low levels of high-density lipoprotein cholesterol. These alterations in lipid metabolism are associated with cardiovascular disease. Adipose tissue plays an important causal role in the occurrence of dyslipidemia through the release of FFA, which leads to increased triglyceride and very low-density lipoprotein cholesterol production in the liver. Hence, cancer survivors with an increased risk of overweight carry an increased risk of dyslipidemia as well. Hypogonadism following cancer therapy can cause dyslipidemia directly as well; this was observed in survivors of adult testicular cancer, breast cancer treated with aromatase inhibitors, and prostate cancer treated with LHRH agonists **(8).**

The rate of dyslipidemia in CCS varied greatly and different outcome measures are reported. Only one study reported independent risk factors for dyslipidemia in CCS. In 330 survivors, after 16.1 years of follow-up, older age at diagnosis (HR 1.1), TBI (2.7), GHD (2.3) and autologous SCT (3.2) were independent risk factors for hypercholesterolemia, and TBI (6.5) and GHD (7.2) were also independent risk factors for hypertriglyceridemia. Chao studied dyslipidemia in 650 survivors and reported a higher risk (incidence rate ratio 1.9) compared to controls, but no specific prognostic variables were identified in multivariable analysis. In the CCSS the incidence of dyslipidemia was 8.9%, compared to 6.0% in siblings; this increased to a significant difference at age 50 (23.0 vs 13.6%), whereas the obesity rate at an older age in this cohort was significantly higher among siblings. In a large Finnish cohort of ∼2500 survivors, the rate of dyslipidemia, defined as the purchase of lipid-lowering drugs, was 4.3 times higher than in siblings **(9).**

1) Hypertension

Arterial hypertension is a condition in which blood pressure is persistently raised, defined as ≥140mmHg systolic or ≥90 diastolic. Globally, the overall prevalence of hypertension in the general population aged 25 and over has been reported to be around 40%. The availability of low-cost medication has significantly decreased the occurrence of hypertension to e.g. 18% in the USA. Hypertension is a major risk factor for coronary heart disease and ischemic as well as hemorrhagic stroke, being responsible for ∼50% of deaths due to these diseases. Also, blood pressure level as a continuous variable is related to the risk of stroke, coronary heart disease, heart failure, peripheral vascular disease, renal impairment, and retinal hemorrhage **(10).**

Already in 1989, Kantor described hypertension in 20% of long-term survivors of childhood renal cancer. According to a Cochrane review by Knijnenburg, the prevalence of hypertension in childhood cancer survivors ranges from 0% to 18.2%. Three reports thereafter showed even higher prevalence, and one of these observed a sharp increase with age, exceeding 70% by age 50. In most case-control studies, survivors reveal relatively high hypertension rates. A study in ∼650 survivors found no significant difference between survivors and controls, but this was a study with a rather short follow-up time of 6 years. In the CCSS, the presence of hypertension significantly increased the risk of major cardiac events and cardiac-specific mortality. The aforementioned Cochrane review included 24 studies with ∼4000 survivors in total, and a high BMI was the only consistent independent risk factor for hypertension reported in multiple studies. Other reported independent risk factors are the use of the total body or abdominal irradiation, nephrectomy, acute kidney injury, SCT, growth hormone therapy, older age at screening, and male sex **(11).**

II. The metabolic syndrome in childhood cancer survivors

1) Definition

Metabolic syndrome is a cluster of adiposity, IR/DM, dyslipidemia, and hypertension. It was first described by Reaven in 1988, who found a clustering of symptoms in patients and called this Syndrome. The symptoms of this cluster are related and interacting in various ways. In general, imbalance in energy intake and consumption results in increased (visceral) adiposity. Secondary effects of adiposity include increased circulating FFA and reduced adiponectin – thus, an increase in IR factors – and increased pro-inflammatory and prothrombotic mediators such as IL-6, TNF-alpha, and PAI-1. Increased lipid flux into the liver can result in steatosis, which also mediates IR. The liver also produces fibrinogen, enhancing the pro-thrombotic state. IR in the liver and muscle leads to hyperinsulinemia, with result in adipose tissue growth and tissue resistance to insulin **(6).**

Hyperinsulinemia also contributes to hypertension through enhanced sodium resorption and sympathetic nervous system activation. It is estimated that 20–25% of the world's adult

population suffers from MetS and, consequently, are three times more likely to have a heart attack or stroke and twice as likely to die from cardio- and cerebrovascular disease, Insulin resistance and diabetes mellitus in childhood cancer survivors. people without MetS. Also, patients with MetS are five times more likely to develop DM2 and people with diabetes are three times more likely to develop cardiovascular disease. Metabolic syndrome is also associated with fatty liver disease, gallstones, hepatocellular carcinoma, chronic kidney disease, and polycystic ovary syndrome **(8).**

Currently, three definitions of metabolic syndrome are commonly used: those created by the World Health Organization (WHO), National Cholesterol Education Program – Third Adult Treatment Panel (NCEP/ATP III), and the International Diabetes Foundation (IDF). Although the definition of MetS is based on the principle of clustered components, these components themselves are also independent risk factors for the development of the cardiovascular disease. The prevalence of MetS can vary, depending on which definition is used. In young adults, who less frequently meet al.,l MetS criteria, partial clustering of risk factors should be examined. The Mets definitions provide useful guidelines to identify those individuals at risk for the development of DM2, atherosclerotic cardiovascular disease, and cardiovascular death. Mets is a "disguised" syndrome; without measurement of blood pressure and lipids, metabolic sequelae can develop for years. This underlines the need for active surveillance **(3).**

2) Risk and determinants

Several studies have focused on the development of MetS in CCS. Comparison of these studies is hampered by the fact that often small patient groups are analyzed, the heterogeneity of malignancies as well as therapies, and the different definitions of MetS that are used. An overview of existing literature on the frequency of MetS and prognostic factors in CCS. The first study on this subject was by Talvensaari, reporting a prevalence of 16% in 50 survivors, compared to none of the controls. Since then, reported frequencies of MetS in CCS to vary between zero and 39 percent **(6).**

Authors' literature search retrieved twenty-two studies, six of which performed multivariable analyses in search of risk factors for developing MetS. Only three out of six had a prospective study design. These were all reports from the French LEA program, a cohort of acute leukemia survivors. Mets occurred in 6.9–17.1% of the survivors. In the first study, HSCT with TBI as a conditioning regimen was the only risk factor for metabolic syndrome (OR 3.9). In the second study, TBI was not a risk factor for MetS, nor were gender, total post-transplant steroid dose, and follow-up duration. The only risk factor was a higher BMI at the time of transplantation (OR 1.57). In the third study, male sex (OR 2.64), older age at evaluation, and higher BMI at diagnosis were risk factors for MetS, whereas CNS irradiation was not. The three other studies with multivariable analyses had

a cross-sectional or retrospective study design. The largest study investigated MetS in 784 ALL survivors in the St. Jude Lifetime Cohort, compared to 777 healthy controls. Metabolic syndrome was present in 33.6 percent of survivors (RR 1.43). Risk factors in multivariable analyses were CRT, especially with craniospinal radiation (RR 1.88), and older age at evaluation. Steroid dose was not a risk factor. A smaller study in 74 ALL survivors also revealed HSCT (OR 22.99) as a risk factor for MetS. In a large, retrospective study in 648 Indian childhood cancer survivors, no patient fully met the criteria for Mets. Only when overweight patients were included (next to obese patients), the prevalence was 2.4% for underage (< 18 years old) survivors and 9.6% for survivors aged 18 years and older. It should be mentioned that follow-up in this study was short (6 and 11.5years median for survivors below and over 18 years, respectively). **(6).**

Of the remaining sixteen studies that our search yielded, three had a prospective design. The largest described MetS in a single-center cohort of 103 nephro- and neuroblastoma survivors. Survivors had more components of MetS than healthy controls (OR 5.2 in nephroblastoma, 6.5 in neuroblastoma) and frequency was three times higher in patients who received abdominal irradiation (28% vs 9%). A small study in 21 AML survivors reported SCT as a risk factor for having more MetS components than healthy controls (OR 24.1), whereas chemotherapy only was not a risk factor. In the third study, none of the 45 survivors of a hematological malignancy treated with HSCT had MetS, but this was also a study with a short follow-up time. Risk factors described in the other studies include cranial and abdominal radiation, while the other studies found no significant prognostic variables or did not perform this analysis **(1).**

Summarizing the studies with the highest quality of data, the following prognostic variables were risk factors for developing the MetS inCCS: the treatment components HSCT, CRT, TBI (although not all studies support this finding) and abdominal radiation, and the patient characteristics male sex (not in all studies), higher BMI at diagnosis or time of transplantation, and older age at evaluation **(2).**

III. athophysiology of the metabolic syndrome in childhood cancer survivors

1) Growth hormone deficiency

Disease as well as treatment, i.e., respectively, brain tumors, CRT, and brain surgery, but also TBI and chemotherapy can damage the hypothalamus and pituitary gland, which leads to several endocrine disorders, the most common being GHD. GHD induces the components of the metabolic syndrome, as shown in several studies: adiposity, insulin resistance, dyslipidemia, and hypertension. A recent study in CCS associated GHD with the development of clusters of three or more cardiovascular risk factors. GHD has also been linked to endothelial dysfunction and atherosclerosis and decreased left ventricular

ejection fraction, further increasing the risk of cardiovascular complications. Schneider et al. reported an increased ten-year risk of cardiovascular events in ~350 GHD patients compared to healthy controls (4.6% vs. 3.7%). **(12).**

The hypothalamus, rather than the pituitary gland, is regarded as the primary site of radiation damage. The somatotropic axis is affected first, followed by the gonadal axis, and, least sensitive, the thyroid and adrenal axis. After radiotherapy growth hormone secretion may gradually and irreversibly decrease over years in a dose-dependent manner; at 16 Gy the risk of developing GHD five years off treatment is 50%. The most relevant radiotherapy threshold is not clear: other reported thresholds are 18 Gy and 30 Gy. In a meta-analysis by Mulder, the pooled prevalence of GHD after cranial radiation was 35.6% **(1).**

In non-cancer survivors with GHD, it has been shown that growth hormone replacement has positive effects on cardiac function, cardiovascular risk factors such as body composition, lipid levels, and blood pressure, and on the occurrence of cardiovascular events. On the other hand, a large study in ~2500 growth hormone deficient adults found no decrease in the prevalence of MetS after three years of replacement, and Claessen even reported a substantial increase in MetS after ten years of treatment in 98 patients, from 32.7% to 57.1%. Unfortunately, there is only scarce literature on growth hormone replacement in CCS. Furthermore, clinical interpretation of these studies is commonly complicated by methodologic shortcomings such as lack of a control group and the use of surrogate markers instead of cardiovascular morbidity and mortality. A small study in eighteen ALL survivors with GHD on two years' replacement therapy reported improved cardiac systolic function and reduced incidence of metabolic syndrome **(13).**

Another small study with eleven ALL survivors on twelve months growth hormone replacement reported positive effects on fat mass and fat-free mass, but hyperleptinemia and insulin resistance remained unaffected. Van den Heijkant found a higher lean mass and lower percentage fat after two years of therapy in 14 ALL survivors and Murray reported beneficial effects on waist-hip ratio, cholesterol, and triglycerides in 27 ALL and brain tumor survivors after twelve months' therapy **(11).**

2) Gonadal impairment, thyroid morbidity, and adrenal insufficiency

The production of other pituitary hormones and damage to other endocrine end organs seems to be less frequently affected after childhood cancer and therapies. CRT > 30 Gy caused long-term central hypogonadism in 20–30% of survivors, and regimens harming the gonads can be causative factors as well. Mainly tested in men, hypogonadism is reported to contribute to MetS and vice versa. A few studies associated gonadal impairment with MetS traits in CCS. A recent meta-analysis reported that testosterone supplementation in men with testosterone deficiency syndrome had positive effects on body weight and

composition and glucose and lipid metabolism. There are no studies available that investigated the effect of sex hormone therapy on metabolic syndrome in CCS, so far **(6).**
Cranial radiation doses of 30 Gy and higher caused central hypothyroidism in 3–9% of survivors. Thyroid malignancies (although rare in children) or neck and mantle radiation for other cancer types damage the thyroid and lead to primary hypothyroidism. Metabolic manifestations of hypothyroidism include adiposity, hypertension (due to an increase in peripheral vascular resistance), and dyslipidemia. As in the normal population, hypothyroidism after childhood cancer is treated with levothyroxine. Although it is anticipated that levothyroxine treatment has positive effects on the metabolic profile of CCS, no studies have investigated this yet **(14).**
Adrenal insufficiency occurred in 3–6% of patients receiving > 30 Gy CRT and can also temporally be caused by high-dose steroid treatment. Hypocortisolism in itself is not associated with MetS features, but treatment with corticosteroids – especially dexamethasone – is notorious for causing short term adiposity, IR, and diabetes. It is conceivable that the use of glucocorticoids in childhood cancer treatment can have these consequences in long term as well. Van Beek showed that treatment with prednisone or dexamethasone is associated with long-term increases in BMI and body fat in ALL and Hodgkin lymphoma survivors **(6).**

3) General fitness

Another potential mechanism for the development of MetS in CCS is physical inactivity, as this promotes obesity and IR. In the St. Jude Lifetime cohort, 28% of survivors were found not to adhere to lifestyle guidelines. Males and females who did not follow these guidelines were approximately twice more likely to have MetS. Similarly, Warner reported total energy expenditure and physical activity to be lower in 34 ALL survivors compared to 21 survivors of other childhood malignancies, and healthy controls. This was negatively associated with percentage body fat, but it remains the question whether this is either a cause or a consequence **(6).**
Additionally, the authors showed that especially male neuroblastoma survivors might be at risk for reduced physical activity. Visual impairment after certain brain tumors may enhance MetS risk, due to the reduced ability to perform physical activity. For example, in a study in 178 childhood- and adult-onset craniopharyngioma survivors, visual impairment was a borderline significant independent risk factor for MetS. To date, it is not entirely clear yet whether reduced physical activity and sedentary lifestyle play a causative role in the development of MetS. However, as it is one of the few modifiable factors that might decrease MetS, it is of great value to initiate intervention studies concerning physical activity in CCS **(1).**

4) Genetic susceptibility

The role of genetic susceptibility in the development of Mets and cardiovascular disease in childhood cancer survivors has not been extensively studied yet. In our cohort of 532 survivors, we used a candidate gene approach, containing genes previously associated with components of the metabolic syndrome, i.e. JAZF1, THADA, IRS1, TFAP2B, MSRA, and ATP2B1. None of the allelic variants was associated with metabolic syndrome, indicating that treatment factors were more dominant than genetic variation. England et al. performed whole-exome sequencing in 209 ALL survivors and reported that variants in BAD and FCRL3 genes were associated with a phenotype of three or more cardiometabolic risk factors. In the St. Jude Lifetime cohort, a genome-wide association study (GWAS) identified single nucleotide polymorphisms associated with obesity in the following genes: FAM155 A, which is expressed in the hypothalamus and pituitary, and GLRA3, SOX11, and CDH18, which are involved in neural growth, repair and connectivity. To date, these findings have not been validated, nor has GWAS been performed to identify genetic variants associated with diabetes, dyslipidemia, hypertension, and MetS in CCS **(15).**

IV. ummary and Future perspective

After almost 25 years of research on childhood cancer survivors, we have gained knowledge on potential late effects, of which the metabolic syndrome so far has been rather disguised. Many CCS are already at risk for cardiovascular disease, for example, due to anthracycline- or radiation-induced cardiotoxicity. Additionally, they face an additive risk after CRT, causing GHD and MetS. The role between MetS and other risk factors, such as abdominal radiation, specific chemotherapeutic agents, steroids, gonadal impairment, thyroid morbidity, and genetics, warrants further investigation. It is however clear that specific groups of CCS are at higher risk of developing components of the MetS , which underlines the need for close monitoring. These survivors might benefit from early interventions targeting overweight, hypertension, and dyslipidemia, for instance, lifestyle and diet advice and medication. Since MetS is a cluster of symptoms with heterogeneous presentation among individuals, medical treatment requires a personalized approach **(6).**

Future research may focus on the following three topics:

1) Unraveling the pathophysiologic mechanism of the development of the MetS in specific CCS subgroups,
2) Determining which subgroups of CCS are at risk to develop (components of) MetS by using prediction models, and
3) Determining which preventive and therapeutic interventions are successful in targeting the MetS in CCS – favorably multiple components with the same intervention. As childhood cancer is relatively rare, research will benefit from

collaborations between (inter)national cohorts, to enhance effect size and for replication purposes **(6).**

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