Approach to metabolic syndrome in childhood cancer survivors

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Abstract

The combined effects of optimized chemotherapy, surgery, radiotherapy, stem cell transplantation regimens, and improved supportive care had drastically increased the survival rate of childhood cancer. Hence, the number of adult survivors of childhood cancer is on the raise and this subset of population is gaining more attention due to the late effects of their cancer therapy. There is growing evidence that pediatric cancer survivors are at a greater risk of developing metabolic syndrome (MS) or the MS component traits than the general population. There is currently no drug therapy to treat MS as a whole disease, as it is a cluster of symptoms that present uniquely among different individuals. Given the recent recognition of MS in adult survivors of childhood cancer, there is a scarcity of long-term follow-up studies of this group. Adherence to a healthy lifestyle with both dietary and physical activity is the only most powerful and most useful armor available now against obesity and its metabolic complications.

Key Words: Adult survivor, childhood cancer, healthy lifestyle, metabolic syndrome

Introduction

Modern, risk-based therapy with a multimodality approach to surgery, chemotherapy, radiotherapy, stem cell transplant and targeted regimens have led to 5 years survival rates of 80% in the childhood cancer survivors.\(^\text{[1,2]}\)

As a result, the numbers of childhood cancer survivors who reach adulthood, and present with treatment-related health problems, have been on the rise. The incidence of cardiac problems, pulmonary complications, second malignancies, impaired fertility, osteoporosis, and obesity have been well documented in survivors of childhood cancer.\(^\text{[3]}\) Gonadal dysfunction, growth hormone (GH) deficiency, and hypothyroidism are the well-known endrocrine complications and of late, the increasingly recognized features are those of metabolic syndrome (MS).\(^\text{[4,5]}\) Survivors of specific pediatric cancer groups such as central nervous system (CNS) tumors, lymphomas, sarcomas, neuroblastomas, acute lymphoblastic leukemia (ALL), Wilms tumors, testicular tumors, and post bone marrow transplant have been found to present with clinical features of MS and therefore are at increased risk of developing the risk factors of cardiovascular disease (CVD).\(^\text{[6-11]}\)

As childhood cancer survivors have increased the risk of dyslipidemia, insulin resistance (IR), obesity and hypertension, American Heart Association and the Council for Cardiovascular Disease in the Young, have declared the post cancer treatment survivors as tier III, implicating that they are at increased risk of manifesting CVD early in adult life.\(^\text{[12,13]}\)

Childhood cancer survivors have been found to have a cumulative incidence of coronary artery disease of 5.3% by the age of 45 years.\(^\text{[14]}\)

Methods

Although several childhood cancer survivor studies have shown the possible relationship between treatment and increased risk of developing risk factors for MS, many of these are limited by small sample sizes, and many studied only one or two features of the MS and focused on only one type of cancer. Hence, a review of literature using the keywords of MS, childhood cancer survivors, obesity, dyslipidemia, hypertension, IR was done in PubMed database.

Definition

MS is a term that encompasses a number of metabolic abnormalities including hyperinsulinemia, glucose intolerance, hypertension, obesity, IR and dyslipidemia.\(^\text{[15]}\)

In 1988, Reaven noted that several risk factors for CVD commonly cluster together and he recognized them as a disease, syndrome X, currently known as MS. IR is considered the primary cause of associated cardiovascular risk factors and the probable mechanism linking all the MS comprising features.\(^\text{[16]}\)

Though clinical criteria for the diagnosis of MS in adults have been well emphasized, there are several difficulties in determining the MS features in the pediatric population. Insulin sensitivity, an important diagnostic condition for MS, is difficult to obtain in pediatric patients as insulin sensitivity changes with age and puberty and it is also negatively correlated with visceral obesity. Rather than body mass index (BMI), waist circumference specific to ethnic origin are being increasingly used in MS definition criteria in pediatric patients. The International Diabetes Federation has also redefined the MS in children and adolescents, recommending the required parameters in absolute values rather than age-related percentile cut-offs.\(^\text{[17]}\) MS should not be diagnosed in children younger than 10 years.

Ever since Reaven identified the syndrome X, there have been many definitions for MS through the years and the 2007 consensus group of the International...
Diabetes Foundation (IDF) uses a simple definition that can be employed in a clinical setting and is the most commonly used. IDF necessitates the BMI more than 90th percentile and two of the five defining criteria-waist circumference >90th percentile, blood pressure systolic >130 mmHg, and diastolic >85 mmHg, triglycerides >150 mg/dl, high-density lipoprotein cholesterol (HDL-C) <40 mg/dl, and fasting glucose >100 mg/dl.[18]

Prevalence

The prevalence of MS in healthy children and adolescents ranges between 3.6% and 4.8%, but it increases dramatically up to 30–50% among overweight and obese children and adolescents.[17,19] Due to the improved survival rates, more of the survivors of childhood cancer are now getting increased attention to identify the late effects of the therapy. A standardized mortality ratio of 9.7 for circulatory diseases has been found in survivors of childhood cancer.[20] Trimi et al. studied the prevalence of MS in 80 survivors of ALL and found a twofold increased prevalence in those treated with chemotherapy alone and a fivefold increase in those treated with chemotherapy and radiotherapy.[21] Hoffman et al. assessed the MS in sarcoma survivors and identified an increased prevalence among those aged 20–39 years. He found that in male survivors, testosterone levels declined as the number of MS traits increased, thereby indicating the relationship between gonadal function and MS.[11] In a group of 466 adult childhood cancer survivors, Van Waas et al. assessed the MS as per modified national cholesterol education program (NCEP) criteria and found a prevalence of 12.6%.[22] Taskinen et al. determined the MS among long-term survivors of bone marrow transplant and identified a prevalence of 38%. MS was found in 60% of patients with GH deficiency in contrast to only 19% of patients with normal GH levels.[10]

Pathogenesis

Insulin resistance and dyslipidemia

In childhood cancer survivors, the cancer therapies have been found to activate certain pathways that lead to hormone deficiencies, changes in insulin sensitivity, lipid metabolism, inflammatory mediators, and adipokines. Chemotherapy causes damage to endocrine organs, magnesium metabolism and adipose tissue and endothelial dysfunction thereby leading to increased cardiovascular risk.[13,23] Combination of chemotherapy and radiation depletes osteoblast and estrogenic precursors, leading to a significant decrease in plasma osteocalcin levels, thereby contributing to impaired glucose tolerance. Chemotherapy and glucocorticoids impair skeletal muscle glucose uptake and transport, predisposing to inflammation and atherogenic dyslipidemia by producing reactive oxygen species and stimulating hepatic de novo lipogenesis. Chemotherapy causes a direct damage to the functional integrity of the endothelium and disrupts nitric oxide pathway.[24–28]

It is the viscerally distributed adipose tissue rather than subcutaneous fat that plays a significant role in MS. Adipose tissue, considered as an endocrine organ secretes inflammatory mediators and adipokines that regulate endothelial function, atherogenesis, and energetic balance. Systemic inflammation related to cancer itself and amplified by treatment creates the primary damage of adipose tissue resulting in adipocyte dysfunction and decreased adiponectin secretion. Adipokines also activate intracellular pathways regulating the subacute inflammatory state associated with obesity and development of IR and Type 2 diabetes mellitus. The more the components of MS that are evident, higher is the cardiovascular mortality rate.[29,30] A substantial proportion of adult survivors of childhood ALL has been found to have abdominal aortic calcification, which is a marker of early atherosclerotic disease and MS.[31,32]

Endocrinal Dysfunction

GH deficiency in childhood cancer survivors may be due to the CNS tumor location itself or as an adverse effect of cranial radiotherapy and chemotherapy. GH deficiency frequently induces MS like disorders, such as hypertriglyceridemia, low HDL-C, coagulopathy, and hypertension. The two important conditions related to GH deficiency are IR and endothelial dysfunction.[23]

Estrogens and testosterone are known to influence body composition, lipid metabolism, vascular tone, and blood pressure. Gonadal failure is a frequent adverse effect in long-term cancer survivors, which may result in impaired hormonal production and the risk of developing MS. Chemotherapy comprising alkylant agents and platinum compounds may cause gonadal failure. Magnesium plays a role in insulin sensitivity and vascular tone. Hypomagnesemia has been implicated in the development of IR, hypertension, increasing the risk of atherosclerosis and CVD. Cisplatin-containing cytotoxic agents are the common drugs causing hypomagnesemia.[23]

Tumors of CNS requiring craniospinal radiotherapy, lymphomas, neck tumors, conditioning total body irradiation are the causes of thyroid dysfunction. The hypothyroid state affects the cardiovascular system through both an influence on the heart and adverse effects on serum lipids, increasing the risk of development of CVD.[33] Hypothyroidism causes modest weight gain, due to fluid retention and decreased metabolism. Decreased thyroid hormone can increase levels of total cholesterol and a change in HDL-C due to alteration in metabolic clearance. Hypothyroidism also causes fatigue, loss of energy, contributing to weight gain.

Obesity

Excessive weight gain during ALL treatment is usually related to steroids effects, CNS treatment on appetite regulation and as well as less energy expenditure. The association of obesity and cranial radiotherapy is well established and the cancer survivors who received >20 Gy cranial RT were at increased risk of overweight and obesity especially females who were treated at a young age (<5 years).[34] Variation of long-term toxicity in equally treated subjects, suggests that genetic and environmental factors influence the incidence and severity of late effects. The development of a secondary leptin resistance plays
Hypothalamic obesity often results in devastating metabolic and psychosocial complications, requiring the provision of dietary and behavioral modifications, encouragement of regular physical activity and psychological counseling.

The primary approach to the prevention and treatment of MS is lifestyle modification. While a substantial component of MS is attributed to unhealthy diet and sedentary lifestyle, following a healthy diet and maintaining a normal physical activity would be of utmost significance in preventing them.

Adherence to a heart healthy lifestyle which involved both dietary and physical activity guidelines has been found to lower the risk of MS among childhood cancer survivors. Slater et al. state that higher levels of physical activity can address the serious long-term consequences of MS in childhood cancer survivors and is an important strategy to maintain good health in these vulnerable population.

Regular monitoring of blood pressure and hypertension control are important measures to prevent cardiovascular disease, as is smoking cessation. Replacement therapy for GH is also a part of the management of MS.

**Conclusion**

With the better care committed to children with cancer, the survival rates are greatly improving, and MS is becoming the major target for intervention in the follow-up of cancer survivors. Hence, it is pertinent that physicians providing primary care to these adult survivors should be aware of the adverse effects of the long-term hormonal deficiencies and cardiovascular and diabetes risk profiles, following cancer treatment. As dyslipidemia and hypertension are often asymptomatic, screening is important in the follow-up. As MS cannot be treated by a single drug therapy, the individual risk factors should be treated separately.

One of the effective and practical solutions to address MS in clinical practice is to have a regular discussion about health-promoting behaviors between the health care providers and childhood cancer survivors.

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**References**