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REVIEW

Development of Metabolic Syndrome Associated to Cancer Therapy: Review

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Abstract Long-term childhood cancer survivors are at great risk of developing late adverse effects after treatment, such as, reduced growth, obesity, decreased fertility, high blood pressure, cardiovascular diseases, impaired glucose, another form of cancer, among others organ dysfunctions, some of them are part of the metabolic syndrome. Metabolic syndrome and cancer connection is still not entirely understood, but there are some notions about it. Metabolic alterations produced during childhood cancer are more likely determined by treatments like radiotherapy, chemotherapy, glucocorticoids therapy, and surgery. Cancer treatment is associated to vascular alterations, hormone deficiencies, changes in insulin sensitivity, lipid metabolism, and inflammatory mediators. Obesity has been considered a crucial component in metabolic syndrome; obesity risk factors during childhood cancer include cranial radiation, female gender, and exposure to glucocorticoids such as dexamethasone. In addition, local radiotherapy or surgery may cause endocrine deficiencies, depends on the directly damage of endocrine organs. Patients who received some types of cancer treatment should be evaluated periodically to early diagnostic metabolic disorders associated to antineoplastic therapy.

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Introduction

Recently, diagnosis, treatment, and supportive care have increased the survival rates of childhood and adolescent cancer, leading to long-term morbidity and mortality associated with treatment [1–4]. Nowadays, the possibility of successful outcomes in childhood cancer are among 70 % (Table 1) [1–23]. Unfortunately, long-term survivors of childhood cancer are at risk of developing a spectrum of late adverse effects, such as, reduced growth, obesity, decreased fertility, high blood pressure, cardiovascular diseases, impaired glucose, another form of cancer, and organ dysfunction [1, 2, 24]. Cardiac treatment-related death is the most common non-cancer mortality in this population [5].

Epidemiological reports have revealed clinical features of metabolic syndrome (MS) and increased risk factors for cardiovascular disease (CVD) in childhood cancer survivors, mainly acute lymphoblastic leukemia (ALL), central nervous system tumors, lymphomas, disseminated testicular cancer, neuroblastoma, and Wilms' tumors [4]. In addition, numerous studies have reported increased risk for obesity or overweight in children and young adult ALL survivors [23].

MS includes several metabolic abnormalities, such as hyperinsulinemia, glucose intolerance, hypertension, obesity, insulin resistance, and dyslipidemias. The International Diabetes Foundation has established the following diagnosis criteria for MS patients: body mass index (BMI) more than 90th percentile of waist circumference and two factors from the defining criteria. The prevalence of MS in a healthy children population ranges from 3.6 to 4.8 %, increasing radically up to 30 % among overweight and obese children [20].

Low-grade chronic inflammatory status, reflected by increased inflammatory biomarkers, can be one of the common precursors for MS [25]. Visceral adipose tissue plays a central role in the pathophysiology of MS [18].

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Table 1 Long-term childhood cancer survivor percentage

Author	Cancer type	Long-term childhood cancer survivors (%)
Armstrong G. et al. [5]	All type of cancer	80 %
Mitry M. and Edwards J. [6]	All type of cancer	70 %
Iughetti L. et al. [7]	Acute lymphoblastic leukemia	5-years event-free survival rate 80 %
Iughetti L. et al. [7]	Acute lymphoblastic leukemia	8-years event-free survival rate 90 %
Nottage K. et al. [8]	Acute lymphoblastic leukemia	90 %
Bhojwani D. et al. [9]	Acute lymphoblastic leukemia	90 %
Quintanilla-Flores D. et al. [10]	Acute lymphoblastic leukemia	80 %
Saha A. et al. [11]	CNS tumors	70 %
Green D. et al. [12]	All type of cancer	5-years event free survival rate 78 %
Ginsberg J. 2011 [13]	All type of cancer	80 %
Çağlar, A. A. et al. [14]	All type of cancer	5-years event-free survival rate 80 %
Latoch E. et al. [3]	All type of cancer	5-years event-free survival rate 80 %
Lee H. J. et al. [15]	All type of cancer	5-years event-free survival rate 80 %
Chow et al. [16]	Acute lymphoblastic leukemia	85 %
Tonorezos E. et al. [17]	Acute lymphoblastic leukemia	85 %
van Waas et al. [18]	All type of cancer	75 %
van Waas et al. [18]	Nephroblastoma	5-years event-free survival rate 92 %
van Waas et al. [18]	Neuroblastoma	5-years event-free survival rate 55 %
Chemaitilly et. al. [19]	Hodgkin's lymphoma	5-years event-free survival rate 90 %
Chemaitilly et. al. [19]	Acute lymphoblastic leukemia	5-years event-free survival rate 80 %
Scott J. et.al. [20]	All type of cancer	5-years event-free survival rate 80 %
Prasad M. et al. [21]	All type of cancer	5-years event-free survival rate 80 %
Esbenshade A. et al. [22]	Acute lymphoblastic leukemia	85 %
Barnea D. et al. [2]	All type of cancer	80 %

Adipose tissue acts as an endocrine organ mediating diverse signals, including insulin and growth hormone, among others. Adipocytes control endothelial function, atherogenesis, and energetic balance, secreting inflammatory mediators and adipokines such as leptin and adiponectin [4]. The link between adipose tissue and insulin resistance can be explained by the increase of fatty acids that are able to trigger insulin resistance through intracellular metabolites that activate protein kinase C; this mechanism can activate serine and threonine kinases that inhibit insulin signaling [26].

Metabolic Syndrome and Cancer

The relation between MS and cancer is still not entirely understood, but there are some notions about it [4]. Studies suggest that metabolic modifications produced during childhood cancer are more likely determined by treatment factors (radiotherapy, chemotherapy, surgery) and less by baseline patient characteristics as we develop further below [18].

Local therapy for the treatment of cancer (surgery and radiotherapy) may cause endocrine deficiencies, damaging organs directly. In the other hand, chemotherapy as systemic treatment may damage endocrine organs and non-hormonal systems [4]. Total body irradiation (TBI) is an independent risk factor for the development of diabetes mellitus (DM) and dyslipidemia or MS in non-obese ALL survivors. TBI as part of the preparation regimen for stem cell transplants has been linked with insulin resistance absent an increase in BMI 1-year post-bone marrow transplant [2]. The Childhood Cancer Survivor Study found an association between TBI and TBI plus chest irradiation with the posterior development of dyslipidemia, arterial hypertension, and diabetes [18].

In general, antineoplastic agents like anthracyclines, taxanes, platinum derivatives, and vinca alkaloids used for cancer treatment are cytotoxic substances. Most of these agents interfere with DNA replication, transcription, protein synthesis, and microtubule function, components necessary for cell regeneration, division, and growth. Therefore, endocrine cells may result to injured and glandular functions deregulated. Moreover, these agents can interact with receptors or second messengers, causing an increase or an inhibition of these hormones. In addition, some of chemotherapeutic agents can compete for binding sites on carrier proteins, perturbing these hormone delivery [27]. Consequently, the aforementioned mechanism may lead to hormone deficiencies, changes in insulin sensitivity, lipid metabolism, inflammatory mediators, and adipokines [20].

Overweight and Obesity

Overweight and obesity are often observed in both ALL and brain tumor survivors [19]. Obesity is associated with a low-grade condition of chronic inflammation in adipose tissue. It is influenced by the activation of the innate immune system, producing a pro-inflammatory status and a consequent oxidative stress. Even though the pathophysiological mechanism of MS is not entirely clear, obesity is considered a crucial component in MS. The secretion of adipokines and cytokines by adipose tissue (composed by adipocytes, fibroblast, endothelial and immune cells) induce the production of reactive oxygen species (ROS) producing oxidative stress (OS) and, consequently, a disorganized production of other adipokines [28].

Adipokines (leptin and adiponectin) are peptide hormones, involved in a large system of communication between hypothalamus, adipocytes, and the gut. These hormones regulate hunger, satiety, energy usage, and energy storage. Cancer and its treatment cause systemic inflammation producing damage of adipose tissue, which may result in adipocyte dysfunction and declined adiponectin secretion [20]. Tonorenzos et al. describe an imbalance in adipokines in ALL childhood survivors, which could explain the body change composition. In addition, they found insulin resistance and serum leptin changes in non-obese and non-overweight ALL survivors [17].

Obesity risk factors include cranial radiation, female gender, and exposure to glucocorticoids such as dexamethasone [19]. Retrospective studies have shown that weight gain in ALL children occurs during the first month of therapy, returns to their initial weight, before gaining excessive weight again for the period of maintenance, progressing to obesity during the survivorship phase. This could be caused by pulses of corticosteroids exposure during the maintenance chemotherapy [22]. Glucocorticoids and insulin activate lipoprotein lipase, which produces the relocation of fat deposits from arms and legs to abdominal [29]. Obesity is also associated with adipocytes hypertrophy and an increased adipogenesis, reflecting the differentiation of precursor cells into adipocytes [30]. Glucocorticoids also regulate the maturation process of pre-adipose cells, to be differentiated in adipose cells [29]. Adipocyte differentiation is controlled by several transcription factors, which regulate adipocyte gene expression. An early reaction to hormonal signals of adipogenesis is the activation of the C/EBPβ and C/EBPδ, expression inductors of C/EBPα and peroxisome proliferator-activated receptor γ (the two principal adipogenic transcription factors). Even though adipogenic transcription factors are well known, it is poorly understood how hormones and glucocorticoids induce this process [30]. Elevated central glucocorticoid levels are related to a concomitant increase in hypothalamic neuropeptide Y (an appetite regulator, which increase food intake and decrease physical activity) and decreased corticotropin release hormone levels. In consequence with the presence of hypocorticosteronemia, secondary to the feedback inhibition of the hypothalamus-pituitary-adrenal (HPA) axis [31], another explanation for obesity in childhood cancer patients may be the increase of the sedentary lifestyles and unhealthy eating habits during and after of treatment. Intervention in this sedentary lifestyle is seen in the Exercise and Nutrition Routine Improving Cancer Health (ENRICH) program, this modifications improve physical activity, weight, body mass index, and vegetable consumption [22, 32].

Glucose Homeostasis Impairment

Chemotherapy combined with radiotherapy reduce osteoblast and estrogenic precursors, producing decreased plasma osteocalcin (a regulatory hormone of glucose metabolism, bone and cartilage mineralization) levels, causing impaired glucose tolerance [20, 33]. Osteocalcin has been found to be part of the type 2 diabetes process, leading β cell proliferation and insulin expression and secretion; additionally, this hormone interferes in peripheral tissue sensitivity to insulin [33].

Long-term cancer survivors may have impaired hormone production due to gonadal failure, which is a frequent adverse effect of alkylating agents and platinum derivatives [20]. Cisplatin-treated testicular cancer survivors show an increased age-adjusted risk of developing MS in comparison to those patients treated with surgery or radiotherapy. Gonadal dysfunction is a possible long-term complication after high cumulative doses of cisplatin treatment. Haugnes et al. found a strong negative association between total testosterone and the prevalence of metabolic syndrome [34]. This effect is closely related to lower testosterone levels in men and seems to be an independent cardiovascular risk factor closely associated with the metabolic syndrome [35].

Asparaginase is a chemotherapeutic agent administered in combination with daunorubicin, vincristine, and prednisone; they are used during remission, induction, and intensification phases in ALL therapy [10]. L-asparaginase side effects are abdominal pain, liver dysfunction, thrombosis, acute pancreatitis, hyperglycemia, and diabetic ketoacidosis. Hyperglycemia is induced by L-asparaginase through the depletion of L-asparagine and its consequent decrement of insulin synthesis, depleted insulin and other protein stores, causing a relative insulin insufficiency which potentially injures B cells, impairs insulin receptor function, and causes hyperglucagonemia. Nevertheless, association between insulin resistance among off-therapy survivors, hyperglycemia during therapy, or asparaginase dose is still uncertain [10, 36].

Radiotherapy on pancreatic tissue may induce apoptosis of β cells, consequently decrease insulin production, which in turn may cause hyperglycemia, elevated free fatty acids levels, hypertriglyceridemia, and insulin resistance. Van Waas et al. show that TBI is the main determinant of MS in long-term survivors of nephroblastoma and neuroblastoma.

Additionally, they show that radiotherapy involving the head and tail of the pancreas influenced the occurrence of dyslipidemia and insulin resistance [18].

Cortisol contributes to the gluconeogenesis process, fat, protein, and carbohydrate metabolism and suppresses the immune system. Basal cortisol levels have seen associated with insulin resistance, dyslipidemia, and atherosclerosis. In the non-cancer population, cortisol levels are known to be highly dependent on stress activities. Up-regulated levels of cortisol have been observed in childhood cancer survivors after cranial radiation and adrenalectomy. In addition, cortisol levels elevation may be produced by the direct damage to the hypothalamus or pituitary or been induced by the physical and psychological stress [18, 37].

High levels of glucocorticoids increase glucose production in the liver, induced by increased transcription of glucose-6-phosphatase among other enzymes involved in the gluconeogenesis process, increasing the action of different insulin-antagonist hormones, mainly glucagon. Glucocorticoid therapy interferes with the post-receptor signaling pathway of the insulin receptor; consequently, it produces an excess on glucose uptake and glycogen synthesis in the skeletal muscle [38].

Current pediatric ALL protocols include a 2–3 years long maintenance phase; through this period, patients are exposed to pulses of high-dose corticosteroids leading to significant weight gain [22, 36]. Low dose glucocorticoids therapy exposure can induce a reduction of insulin sensitivity and damage of β cell function in genetically predispose patients, even if the dose is minimal. ALL patients at high-dose glucocorticoid therapy have shown hyperglycemia and obesity, even patients without known risk factors for diabetes [36]. In a retrospective analysis, Chow et al. found a dose-response association between cumulative glucocorticoid dose and the risk of obesity, some of the patients remaining overweight or obese 5 years after diagnosis [16].

Cross-sectional studies have shown that female ALL survivors with a history of cranial radiotherapy have higher levels of fasting insulin and glucose and two or more cardiovascular risk factors than control subjects. Moreover, those ALL survivors had lower lean body mass with more abdominal and visceral fat mass, lower levels of high-density lipoprotein (HDL), higher triglycerides, and higher body mass index (BMI) [2].

In a retrospective study with adult survivors of childhood cancer, exposed to cranial radiotherapy, Chemaitilly et al. 2015 found that individuals with luteinizing hormone/follicle stimulating hormone deficiency were independently associated with abdominal obesity, hypertension, dyslipidemia, low bone mineral density, low energy expenditure, and slow walking [39].

Endothelial Dysfunction, Arterial Hypertension, and Cardiovascular Damage

Chemotherapy and radiation cause endothelial dysfunction, damage to endocrine organs, magnesium metabolism and adipose tissue, increasing cardiovascular risk [20]. Chemotherapy is associated with higher systolic blood pressure and dyslipidemia; the exact mechanism is unclear, but it may be due to damage of the vascular endothelium, resulting in vascular alterations [18]. For example, vascular endothelial injury is accelerated by cardiovascular risk factors, like a sedentary lifestyle and high levels of arterial tension. This vascular endothelial damage is the cornerstone of atherosclerotic cardiovascular disease pathogenesis and may be a result of radiation or chemotherapy such as cisplatin and anthracyclines [40]. Moreover, abnormal aortic calcification is an early indicator of atherosclerotic disease and MS. It has been found in adult survivors of childhood ALL [20].

Patients exposed to chest radiotherapy and anthracycline therapy show a 12 % of cumulative incidence of congestive heart failure by 30 years from diagnosis [5]. One of the most representative anthracycline is doxorubicin, which acts at different levels by diverse molecular mechanisms, such as iron interaction, upsetting calcium homeostasis, modifying the activity of mitochondrial oxidant enzymes and this agent bind to topoisomerases producing dysfunction of this enzyme. Doxorubicin interacts with topoisomerase and DNA to form a DNA cleavage complex. It has been hypothesized that oxidative stress affects the nuclear topoisomerase function to stabilize the topoisomerase/DNA complex during the inhibition of the relegation process, increasing DNA strand breakage [6]. Cardio-toxicity induced by anthracycline may be related to ROS formation and site-specific DNA damage. Oxidative stress can induce sarcomere vacuolar degeneration; swelling, disruption, and dysfunction of the mitochondria; myofilament degeneration and loss of pro-survival signaling [41, 42]. The molecular myocyte injury is a multifactorial process; a frequently referred pathway is anthracycline-induced generation of ROS. Anthracyclines can catalyze the formation of intracellular oxygen radicals through the non-enzymatic pathway (reacting with ferric iron, leading to free radicals and alcohol adducts) and the enzymatic pathway (interacting with cardiolipin in the mitochondrial respiratory chain and with other cytochrome-containing enzymes, producing ROS) [42].

In vitro studies have shown that radiation therapy causes in endothelial colony forming cells (ECFCs) changes associated to vascular damage and subsequent atherosclerosis. In vivo, Pradhan K. et al. confirm the sensitivity of ECFCs to radiation levels above 10 GY [40]. Atherosclerotic changes in the vascular wall have been related with an increased risk for development of strokes in Hodgkin's lymphoma, brain tumor, and ALL patient [20].

Cisplatin-based therapy has been associated with cardiovascular damage such as cardiac ischemia, diastolic disturbances, hypertension, and microalbuminuria [43]. Microalbuminuria, which is an indicator of endothelial dysfunction and a predictor of cardiovascular diseases, appears to be prevalent in testicular cancer survivors treated with

cisplatin, in vitro studies evidenced cisplatin-induced endothelial damage [34].

Chemotherapy also produces direct injury in the endothelium and disrupts nitric oxide pathway [20]. Cisplatin and bleomycin induce endothelial cell damage and indirectly impact endothelial cell function thru inflammatory and fibrinolysis factors [44]. Nuver et al. found that patients in cisplatin therapy had higher plasma levels of endothelial, as well as inflammatory marker proteins like fibrinogen, C-reactive protein (hsCRP), von Willebrand factor (vWF), plasminogen activator inhibitor, and tissue-type plasminogen activator. The influence of these proteins may produce more severe endothelial dysfunction and consequently atherosclerosis [45]. Altena R. et al. have shown that plasma Growth Differentiation Factor 15 (GDF-15) protein levels in testicular cancer patients after BEP-chemotherapy (Bleomycin, Etoposide and Cisplatin) are related to endothelial damage biomarkers such as vWF and hsCRP [44].

GDF-15 is a cytokine associated to the transforming growth factor-β superfamily; this cytokine is released to plasma under pathological conditions, induced by several factors (cytokines, chemotherapy, and radiotherapy), may produce different anti-inflammatory, anti-apoptotic, and anti-proliferative effects. In addition, GDF-15 studies have associated cytokines to metabolic disorders, such as insulin resistance and obesity, as well as well growth factor precedes and predicts the development of macro- and microalbuminuria [44]. Even though, the pathophysiological role of GDF-15 is not completely understood, it may indicate early tissue damage. In inflammatory states such as rheumatoid arthritis and some type of cancers, GDF-15 has been identified as a predictor of cardiovascular diseases [46]. Besides diabetes, hypertension and some stress factors (oxidative stress, inflammation, dyslipidemia) could be part of accelerated vascular aging [47]. Recent studies suggest a direct role for GDF-15 in energy homeostasis regulation in cachectic situations. Making GDF-15 a potential candidate molecule to modulate food intake or body adiposity plays an important role in the development and progress of inflammatory and atherosclerotic processes. Increased plasma levels of GDF-15 are stimulated by hydrogen peroxide (H_2O_2), showing a possible involvement of oxidative stress in the stimulation of GDF-15 synthesis by several stimuli such as p53 pathway activation. This pathway could be involved in the pathophysiology of obesity [46].

Cisplatin-based therapy commonly causes hypomagnesaemia, which increases the risk for atherosclerosis, hypertension, and cardiovascular diseases [20]. Magnesium (Mg^{+2}) has an anti-inflammatory and vasodilatory effect. In addition, Mg^{+2} deficiency promotes oxidative stress in endothelial cells, producing increased ROS, a permanent state of inflammation is produced at the endothelium, marked by increased nuclear factor-kB (NFkB) activity. NFkB regulates the transcription of cytokines and pro-inflammatory genes, resulting in local inflammation in the vessel wall, which will recruit monocytes and activate the proliferation and migration of vascular smooth muscle cells. This progression, assisted by increased expression of matrix metalloproteases 2 and 9, in low-Mg^{+2} concentrations, may result in atherosclerosis, vascular calcifications, and thrombosis [48].

Dyslipidemia

Dyslipidemia is a common metabolic syndrome component in immunosuppressed patients, such as kidney and bone marrow transplanted patients, and patients with breast cancer, prostate cancer, or ALL [49]. Chemotherapy and glucocorticoids modify skeletal muscle glucose uptake and transport, predisposing to inflammation and atherogenic dyslipidemia by producing ROS and stimulating hepatic de novo lipogenesis [20].

Asymptomatic hypertriglyceridemia has been reported as adverse effect of L-asparaginase. Its effect may be related to decreased lipoprotein lipase activity, which may increase exogenous chylomicrons, and elevate endogenous very low density lipoproteins (VLDL) synthesis [50]. Combinations of asparaginase and corticosteroids used for ALL treatment produce rapidly forming triglyceride-rich lipoproteins, but it may be inadequately cleared, showing severe hypertriglyceridemia; this might be explained by the corticosteroids effects on lipoprotein, which induce an increase of triglycerides synthesis and the activity of lipoprotein lipase (enzyme needed for the hydrolysis of triglycerides) [9].

Glucocorticoid treatment promotes increased fat mass and induces impaired insulin signaling, producing an increase of free fatty acids and triglyceride synthesis in visceral fat [22]. Free fatty acids are the main substrate for VLDL cholesterol synthesis. In addition, free fatty acid synthetase and acetyl-CoA carboxylase are augmented by steroids and increase the activity of HMG-CoA, which is the rate-determining step in the cholesterol synthesis. Moreover, glucocorticoids and insulin activate lipoprotein lipase, which reduces triglyceride clearance [51].

Cranial radiotherapy and chemotherapy of the central nervous system (CNS) tumor location may produce gonadotropin hormone (GH) deficiency, which induces hypertriglyceridemia, low HDL-C, coagulopathy, and hypertension [20, 36]. Moreover, this GH deficiency after cranial radiation is well known as a factor for reduced child growth, even when the dose is as low as 12 Gy [3].

Conclusion

Cancer survivors can develop several side effects associated to the treatment; most chemotherapy side effects are temporal and disappear once the treatment is over, but there are

treatments associated with long side effects in specific body organs. Cancer treatment may lead to hormone deficiencies, changes in insulin sensitivity, lipid metabolism, endothelial damage, and obesity, and all of these metabolic dysfunctions could be related to the development of MS.

Patients who received chemotherapy should be followed up during their life, to recognize the development of MS and second malignancies associated with the therapy and the metabolic modifications. Physicians may be aware of the late adverse effects in this susceptible population, screening for dyslipidemia and hypertension; diabetes and cardiovascular risk profiles are important in order to promote better health care for childhood cancer survivors.

Compliance with Ethical Standards

Conflict of Interests The authors declare that they have no conflict of interest.

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