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Review

Standing up to the cardiometabolic consequences of hematological cancers

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ABSTRACT

Hematological cancer survivors are highly vulnerable to cardiometabolic complications impacting long-term health status, quality of life and survival. Elevated risk of diabetes and cardiovascular disease arises not only from the effects of the cancers themselves, but also from the toxic effects of cancer therapies, and deconditioning arising from reduced physical activity levels. Regular physical activity can circumvent or reverse adverse effects on the heart, skeletal muscle, vasculature and blood cells, through a combination of systemic and molecular mechanisms. We review the link between hematological cancers and cardiometabolic risk with a focus on adult survivors, including the contributing mechanisms and discuss the potential for physical activity interventions, which may act to oppose the negative effects of both physical deconditioning and therapies (conventional and targeted) on metabolic and growth signaling (kinase) pathways in the heart and beyond. In this context, we focus particularly on strategies targeting reducing and breaking up sedentary time and provide recommendations for future research.

1. Introduction

Globally, the population of cancer survivors is growing, largely due to significant advances in treatments that have improved prognosis for many cancers. For hematological malignancies, there have been marked improvements in 5-year survival rates [1]. However, survivors of childhood hematological malignancies experience more than twice the number of chronic cardiovascular conditions and almost five times the number of severe cardiovascular disorders compared with controls [2]. While adult survivors have a higher age- and body mass index-adjusted risk of diabetes (3.65 times) and hypertension (2.06 times) compared to siblings [3]. Those undergoing stem cell transplantation (SCT) are particularly vulnerable; they experience significantly elevated rates of cardiovascular death, ischemic heart disease, heart failure, stroke, vascular diseases and heart-rhythm disorders [4]. Such deterioration in cardiometabolic health is due to multiple factors, including direct effects of the cancers themselves, radiation, chemotherapy (including targeted therapies), pre-existing cardiovascular risk factors (e.g. hypertension, dysglycemia, dyslipidemia, obesity) and physical deconditioning. Several reviews have highlighted this complex problem [5–7].

In this context, there is the need for a better understanding of the mechanisms leading to the increased cardiometabolic dysfunction in adult survivors of hematological cancers, in order to identify those most at risk and to develop potential ameliorative approaches. Presently, there are no specific guidelines for the management and prevention of cardiometabolic complications in this group. Rather, recommendations are based on extrapolation from general populations [7] and the National Institute of Health Hematopoietic Cell Transplantation Late Effects Initiative task force has called for urgent studies to develop an evidence base for this patient group [8].

In the general population, habitual moderate-vigorous physical activity has been acknowledged as an effective strategy to prevent and manage type 2 diabetes [9] and cardiovascular disease (CVD) [10]. Moreover, recent large prospective studies have shown detrimental associations of high sitting time with incident type 2 diabetes to be most evident in those who are insufficiently active (not meeting recommended physical activity levels) [11–13]. There is also a growing body of epidemiological and experimental evidence demonstrating the benefit of reducing and breaking up prolonged sedentary (sitting) time on markers of cardiometabolic risk [14–16]. This may be particularly applicable in the context of hematological cancers.

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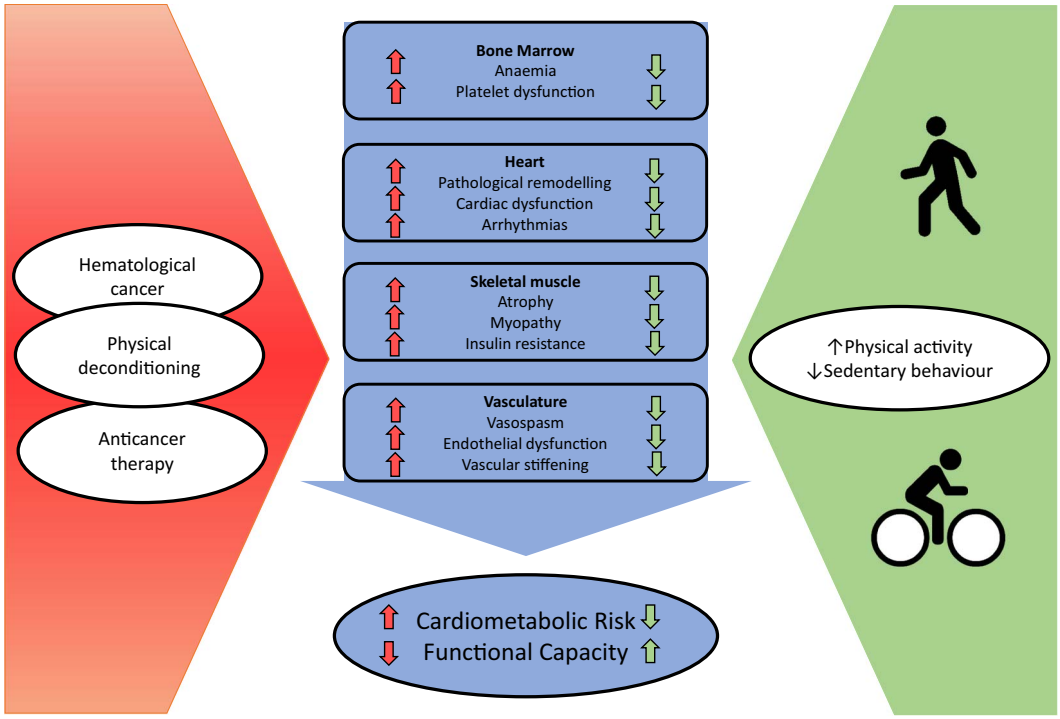

Fig. 1. Cardiometabolic consequences of hematological cancers and potential role of physical activity to ameliorate burden. The combined effects of hematological cancer, physical deconditioning and anticancer therapy have a profound impact on multiple organ systems resulting in decrease in functional capacity and an increase in cardiometabolic risk. In contrast, increasing physical activity and reducing time spent sedentary can potentially counteract such effects preserving functional capacity and cardiometabolic health.

In the following sections we briefly review the link between hematological cancers and cardiometabolic risk (Fig. 1), including the contributing mechanisms in adult survivors. We consider the potential for physical activity interventions that may act to oppose the negative effects of both physical deconditioning and therapies (conventional and targeted) on metabolic and growth signaling (kinase) pathways in the heart and beyond (Fig. 1). In this respect, we focus particularly on the potential of reducing and breaking up sedentary time and provide recommendations for future research.

2. Metabolic dysfunction in hematological cancer

Metabolic disturbances, including obesity, dysglycemia, and dyslipidemia are increasingly common among hematological cancer patients [17] and there is evidence suggesting both cause and effect in these relationships [6]. Epidemiological evidence demonstrates an association between increased body mass index and increased risk of developing several lymphoid and myeloid malignancies [18]. Specifically, it has been estimated that overweight and obesity could account for 14 and 20% of all deaths from solid and hematological cancers in men and women, respectively [19]. That this relationship is at least partly causal is supported by the longitudinal association of insulin resistance and type 2 diabetes with an increase in the incidence of hematological malignancies [20].

Metabolic disorders are also common among survivors who had normal metabolic health prior to receiving treatment. In SCT recipients, the presentation is early in the post-transplant period (within 80 days) [21]. The metabolic syndrome is prevalent among young adult survivors of childhood hematological malignancies [22,23] and adult recipients [3,24] of SCT: prevalence ranges from 5.8% in children [25] to 49% in adults who have received a SCT [21]. Elevation of triglycerides [17,26] and hyperinsulinemia [27] are the most prevalent components of the metabolic syndrome. Several mechanisms could account for the predisposition of SCT recipients to develop the metabolic syndrome. Beyond the effects of prolonged bed rest, the conditioning regimens (chemotherapy and total body irradiation) can cause neurohormonal damage and vascular endothelial dysfunction, while the graft exerts immunological and inflammatory effects which may be further exacerbated by graft versus host disease and its treatment [17].

A cancer diagnosis in adults is often associated with a positive influence on smoking and dietary intake, but a negative influence on overall physical activity levels, with 30% of cancer survivors less physically active than before their diagnosis [28]. This can lead to a vicious cycle of impairments to the musculoskeletal system and cardiopulmonary fitness, increased fatigue and reduced physical functioning which may also promote metabolic dysfunction. In the case of SCT, the necessary confinement of patients to a hospital room, principally to reduce risk of infection, leads to substantial declines in physical (and psychological) functioning [29]. Inactivity and bed-rest contribute to significant under-utilization of skeletal muscle. This “mechanical unloading” stimulates muscle catabolism and depresses contractile function [30]. Deconditioning of skeletal muscle is generally characterized by a loss of muscle mass, decreased cross-sectional area of muscle fibres, increased insulin resistance, reduced force generation and increased fatigability [31]. Skeletal muscle deconditioning is a key aspect of cancer cachexia, and although it can be present in the early stages of disease it is generally associated with advanced or pre-terminal disease [32]. In this setting, skeletal muscle wasting is thought to be promoted by inflammatory mediators (e.g. tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6), tumor-specific factors) and neuroendocrine changes [33]. The combined impact of these insults leads to decreased protein synthesis and increased muscle degradation. Even a healthy individual confined to bed-rest can lose 1–3% of their muscle strength per day for some weeks; so in 3–5 weeks of immobilization (a typical period of time a patient undergoing SCT might spend in hospital), there can be a 50% decrease in muscle strength [34]. There is also a concomitant decrease in whole-body insulin sensitivity [35], which over time, could challenge pancreatic beta cell function and contribute to development of type 2 diabetes. At the same time, one of the consequences of low levels of physical activity is that insulin-independent

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