

These findings reveal a mechanism for the elevated levels of high-molecular-weight VWF observed in diabetic patients and possibly also for the increased risk of thrombotic events. Further work will be required to assess whether miR-24 and VWF levels can be manipulated in humans (eg, with miR-24 mimics) and whether such interventions have potential as antithrombotic therapies in patients with diabetes mellitus. Targeting the polyol pathway seems conceptually attractive because of the coincident activities on platelets^{3,4} and VWF¹ (see figure), although it is not the only source of oxidant stress in diabetes. Indeed, several aldose reductase inhibitors have been developed and undergone clinical testing primarily for diabetic neuropathy, but there remains uncertainty regarding their efficacy and safety. One of the problems in diabetic neuropathy is the imprecision of biomarkers and measures of efficacy. However, the impact of aldose reductase inhibitors on VWF concentrations and platelet function may be more quantitatively assessable.

These novel results on the molecular mechanisms contributing to thrombosis in diabetic patients may lead to new opportunities for therapeutic intervention.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Ness et al, page 3411

Fitness deficits in long-term ALL survivors

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In this issue of *Blood*, Ness et al report that, despite the omission of prophylactic cranial radiotherapy (CRT) in the treatment of acute lymphoblastic leukemia (ALL), adult survivors of childhood ALL remain at risk for impaired fitness, body composition, and energy balance.¹

Survival rates for most childhood cancers have increased dramatically over the last 40 years, with >80% of pediatric patients diagnosed with ALL becoming 5-year survivors.² Unfortunately, healthspan is not keeping pace, and the challenge now is to reduce treatment-related chronic health problems that occur in ~70% of long-term survivors.³ Childhood cancer survivors are twice as likely to be obese compared with their siblings,⁴ and adult survivors of childhood ALL are at an increased risk of adiposity, dyslipidemia, diabetes, and cardiovascular disease.⁵⁻⁷ Furthermore, many studies have reported additive long-term detrimental effects of receiving prophylactic CRT during primary cancer treatment.⁵⁻⁷ Once a standard treatment of ALL, CRT has all but been replaced with intrathecal and systemic chemotherapy to reduce radiation-associated late complications such as cancer recurrence, cognitive decline, and metabolic risk.² However, for the sake of future childhood ALL survivors, it is important to know if omitting CRT has alleviated long-term health problems associated with excess adiposity and poor cardiorespiratory fitness.

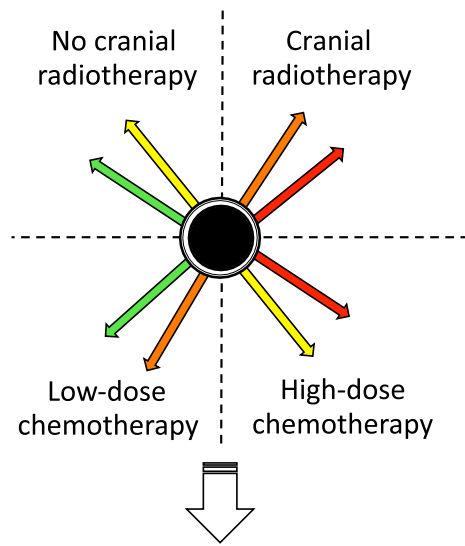
Ness et al determined the impact of CRT on the well-characterized decrements in body composition, energy balance, and physical fitness in adult survivors of childhood ALL. All participants (n = 365) were >18 years of age, at least 10 years from diagnosis, had a mean survival time of 21.9 years, and were previously treated for ALL at St. Jude Children's Research Hospital (SJCRRH) when <18 years of age. A noncancer comparison group that was age, sex, and race matched to the study participants was recruited from SJCRRH visitors. The study recruited 87.7% of all eligible patients, and the "gold standard" techniques of indirect calorimetry, dual x-ray

absorptiometry, and doubly labeled water were used to assess physical fitness, body composition, and energy expenditure, respectively.

Survivors exposed to CRT had higher body mass index and percentage of body fat scores than survivors not exposed to CRT, but only male non-CRT survivors had less favorable body composition scores than the comparative group. Body-mass-adjusted total daily energy expenditure and activity energy expenditure were also lower in CRT compared with non-CRT survivors. Moreover, cardiorespiratory fitness (peak oxygen uptake) and muscular strength (handgrip and quadriceps) and endurance (quadriceps) were lower in CRT-exposed survivors compared with non-CRT survivors. Measures of cardiorespiratory fitness, peripheral sensory integrity, proximal muscle strength, and flexibility were markedly lower in ALL survivors than in the comparative group. Although CRT exposed survivors had the lowest mean values for most physical fitness measures, non-CRT-exposed survivors still had large fitness deficits relative to the comparison group, particularly for proximal muscle strength and aerobic exercise capacity. Ness et al also reported for the first time that cumulative exposure to asparaginase and glucocorticoids was associated with impaired flexibility and weak hand strength, respectively. They also confirmed previously reported associations between vincristine dose and peripheral neuropathy and between intrathecal methotrexate dose and balance problems.

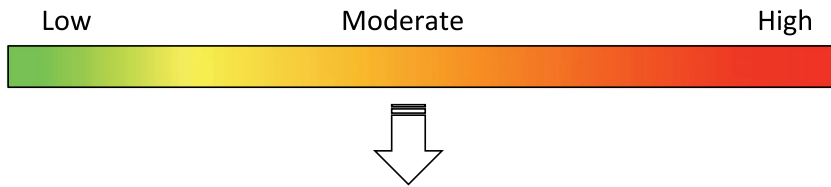
It is intuitive to speculate that the detrimental effects of CRT exposure on body composition and fitness are due to treatment-related deficiencies in hypothalamic pituitary hormones. Another recent study

Treatment for childhood acute lymphoblastic leukemia



Hypothalamic pituitary hormone deficiency

- ↓ Growth hormone
- ↓ Luteinizing hormone
- ↓ Thyroid-stimulating hormone
- ↓ Adrenocorticotrophic hormone
- ↓ Follicle-stimulating hormone



Fitness and body composition outcomes as adults

- | | | |
|-----------------------------|------------------------------|---------------------------|
| • Healthy BMI | • Overweight/obese | • Obesity |
| • Low body fat | • Impaired strength | • Negative energy balance |
| • Normal strength | • Impaired exercise capacity | • Muscle weakness |
| • Average exercise capacity | • Low aerobic fitness | • Poor exercise tolerance |
| • Average aerobic fitness | • Average energy expenditure | • Balance problems |
| • Good energy expenditure | | • Low physical activity |

Long-term health outcomes

- | | | |
|-----------------------------|-------------------|--------------------|
| • Progression-free survival | • Morbidity | • Severe morbidity |
| • Good QoL | • Low/average QoL | • Mortality |
| | | • Poor QoL |

whereas both untreated GH and LH/FSH deficiency were independently associated with abdominal obesity, low energy expenditure, and muscle weakness.⁸ It has also been suggested that CRT may damage appetite-regulatory sensors in the brain that may lead to leptin resistance and overeating.⁷ Indeed, leptin per kilogram of fat mass is elevated in adult survivors of childhood ALL and is further elevated in those exposed to CRT.^{5,6}

The findings by Ness et al and others indicate that the omission of prophylactic CRT for the treatment of childhood ALL has certainly lowered the risk of physical fitness and body composition impairments in adult survivors.^{6,7,9} The magnitude of this risk reduction appears to be greater for body composition than for fitness, as non-CRT survivors may have the same likelihood of being overweight or obese as the general population.⁷ Indeed, Ness et al found this to be the case for females, who had body composition scores comparable to their peers. Thus, the notion that childhood ALL results in long-term impairments in body composition independently of prior CRT exposure remains contentious. However, Ness et al do provide strong evidence that the elimination of CRT does not completely prevent fitness deficits in long-term survivors of childhood ALL and that health problems associated with impaired fitness are still likely to exist in future survivors. The extent of exposure to chemotherapy may be 1 factor, as anthracycline dose is inversely correlated with impaired exercise capacity and left ventricular cardiac function in adult survivors of childhood ALL.¹⁰ One limitation is that Ness et al compared fitness and body-composition scores between childhood ALL survivors and a comparative group of individuals who were generally overweight and less fit than the general population. It is likely, therefore, that the magnitude of energy balance and fitness impairment in the ALL survivors has been unduly masked, particularly for peak oxygen uptake in which the group differences were in the order of only 1 to 1.5 metabolic equivalents.

This formative study by Ness et al provides the most detailed and comprehensive assessment of body composition and physical fitness in adult survivors of childhood ALL to date. The finding that adult survivors of ALL remain at risk for proximal muscle weakness and poor exercise tolerance, despite

Hypothetical framework showing the impact of primary childhood ALL treatment on fitness, body composition, and health outcomes in adult survivors. Deficits in fitness and body composition may be directly related to the level of hypothalamic pituitary hormone deficiency as a result of primary cancer treatment. More severe decrements in body composition and fitness result in less favorable health outcomes, survival, and quality of life. BMI, body mass index; QoL, quality of life.

on the same cohort revealed significant associations between cumulative CRT doses and deficiencies in growth hormone (GH), luteinizing hormone/follicle-stimulating

hormone (LH/FSH), thyroid-stimulating hormone, and adrenocorticotrophic hormone.⁸ Survivors with untreated GH deficiency had decreased muscle mass and exercise tolerance,

the omission of CRT, is of great importance given the well-established relationships among physical fitness, energy balance, adiposity, and morbidity and mortality in the general population. These findings highlight the need to implement randomized controlled trials to determine the effectiveness of lifestyle interventions on health outcomes and quality of life across the entire cancer care continuum.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● LYMPHOID NEOPLASIA

Comment on Jitschin et al, page 3432

Chronic lymphocytic leukemia and the Warburg effect

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In this issue of *Blood*, Jitschin et al demonstrate a microenvironmental glycolytic shift in chronic lymphocytic leukemia (CLL) cells mediated by Notch-c-Myc signaling. Interfering in the Notch-c-Myc pathway and reprogramming glycolytic metabolism could contribute to overcoming drug resistance in CLL.¹

CLL is the prototypical tumor in which the microenvironment plays a key role in the physiopathology of the disease. CLL cells cultivated in vitro die quickly unless they are grown in a microenvironment-mimicking milieu. The CLL microenvironment (an admixture of stromal cells, monocyte-derived nursing cells, T cells, and macrophages) promotes cell growth, traffic of cells between tissues and blood, and cells homing in protected niches. Importantly, the microenvironment also protects CLL cells from both spontaneous- and cytotoxic-mediated apoptosis. Unraveling the mechanisms accounting for these effects

is therefore crucial to understanding CLL physiopathology and identifying potential treatment targets.

The microenvironment activates and protects CLL cells through several mechanisms. CLL surface molecules (eg, B-cell receptor, CD38, CXC chemokine receptor 4 [CXCR4]), chemokines (eg, CXC chemokine ligands 12, 13 [CXCL12, CXCL13]), adhesion molecules (eg, fibroblast growth factor, platelet-derived growth factor, very late antigen-4, stromal-derived factor), and tumor necrosis factor (TNF) receptor members (eg, CD40, B-cell maturation antigen, B cell-activating factor receptor,

transmembrane activator and calcium modulator and cyclopholin ligand interactor) engage in crosstalk with their respective tissue ligands. This results in survival and expansion of the CLL clone, and protects CLL cells from apoptosis.²

On the other hand, a main feature of cancer cells is their ability to avidly take up glucose and convert it to lactate, even in the presence of sufficient oxygen (“Warburg effect”). This altered glycolytic dependency leads to a less efficient generation of adenosine triphosphate compared with the oxidative phosphorylation process which occurs in normal cells.³ It has been shown that CLL cells exert increased oxidative phosphorylation in mitochondria,⁴ but whether stromal cells may induce metabolic changes in CLL cells is largely unknown. In this context, it is worth mentioning that oncogenes and tumor suppressor genes are strongly linked to metabolic pathways through transcriptional or posttranscriptional regulation of metabolic enzymes.³

To shed light on these issues, Jitschin et al studied the glycolytic metabolism in 49 peripheral blood samples coculturing CLL cells with the HS-5 human bone marrow stromal cell line, primary bone marrow-derived mesenchymal stromal cells, or lymph node-derived fibroblasts. They found that CLL cells showed increased glycolysis accompanied by higher lactic acid production, glucose uptake, and glucose transportation, as well as expression of key enzymes (eg, hexokinase-2, lactate dehydrogenase A, enolase-1) involved in this process. Furthermore, they demonstrated that Notch-c-Myc signaling participates in these events. In line with recent evidence linking Notch signaling with stromal cell-mediated effects,⁵ cocultivated CLL cells upregulated the expression of the Notch-1 receptor and the downstream target gene *Hes-1*, reflecting a canonical Notch activation. Interestingly, a correlation between Notch-1 mutated CLL cells and an increased glycolytic metabolism was also found. To close the loop, CLL cells cocultured in a microenvironment-mimicking milieu displayed a significant upregulation of the *c-Myc* gene and its protein expression. In fact, the inhibition of the Notch signaling pathway by a γ -secretase inhibitor (GSI) resulted not only in decreased stromal-mediated upregulation