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Abdominal Aortic Calcification in Young Adult Survivors of Childhood Acute Lymphoblastic Leukemia: Results from the St. Jude Lifetime Cohort Study

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Abstract

Abdominal aortic calcification (AAC), metabolic syndrome, and low bone mineral density (BMD) are risk factors for atherosclerotic disease and cardiovascular morbidity. We evaluated AAC in 662 adult survivors of childhood ALL (median age 31 years). AAC was present in 10% of subjects, metabolic syndrome in 36%, and low BMD in 29%. The adjusted odds ratio (OR) for AAC among women with metabolic syndrome was 2.3 (95% CL=1.0, 4.3). The OR for AAC in men with low BMD was 3.1 (95% CL=1.3, 7.3). A substantial proportion of adult survivors of childhood ALL have AAC and/or metabolic syndrome, suggestive of early atherosclerotic disease.

Keywords

adverse late effects; bone mineral density; cancer; cardiovascular disease; epidemiology; metabolic syndrome

INTRODUCTION

Young adult survivors of childhood acute lymphoblastic leukemia (ALL) are at elevated risk for cardiovascular disease, metabolic disorders, and low bone mineral density (BMD),^{1–4} conditions generally associated with older adults. Abdominal aortic calcification (AAC) is a marker of subclinical atherosclerosis and, like metabolic syndrome,⁶ is an established independent risk factor for atherosclerotic-related morbidity and mortality.^{7,8} Evidence also indicates that low BMD is associated with age-related cardiovascular conditions,⁹ including AAC,¹⁰ coronary artery disease,¹¹ and myocardial infarction.¹² The purpose of this study was to evaluate the prevalence of AAC, metabolic syndrome, and low BMD in young adult survivors of childhood ALL, and to evaluate the extent to which metabolic syndrome and low BMD is associated with AAC.

METHODS

St. Jude Lifetime Cohort Study (SJLIFE)

Participants were enrolled in the IRB-approved SJLIFE, as described previously.¹³ Eligibility is restricted to individuals aged 18 years who were treated at St. Jude Children's Research Hospital and were 10 years post-diagnosis at enrollment. Risk-based clinical and laboratory evaluations are performed in SJLIFE consistent with the *Children's Oncology Group Long Term Follow-up Guidelines*.¹⁴ The SJLIFE assessment for ALL survivors includes a quantitative computed tomography (QCT) study of the lumbar spine for evaluation of BMD and AAC, and testing for components of the metabolic syndrome.

Subjects

The recruitment cutoff date was March 31st, 2011. Enrollment was restricted to the first 49 blocks in the stratified random selection process of SJLIFE;¹³ 1159 ALL survivors were eligible for the study. Of these, 726 (63%) were enrolled and 159 (14%) expressed interest but had not completed their evaluation by the cutoff date. Of the 726 participants, 36 completed health surveys but declined the risk-based medical assessment, 21 did not receive a QCT study, and 7 underwent a QCT but images were not sufficient to assess AAC. The final analysis included 662 subjects.

BMD and AAC Assessment

Volumetric BMD was determined by QCT using a GE VCT Lightspeed 64 detector and Mindways QCT calibration phantoms and software, from 28 to 32 three millimeter contiguous slice images of the L1-L2 vertebral bodies. Average BMD was calculated, then standardized to age- and sex-specific normed values and reported as a Z-score. The abdominal aorta is included in the contiguous slices of the QCT and calcification is evident in the images. For those with AAC present, a semi-quantitative rating of calcified aortic wall involvement was scored as 'scattered specks', 'up to of the wall circumference', 'up to of the circumference', or the 'entire wall circumference'.

Statistics

The objectives were to estimate the prevalence odds ratio (OR) of AAC in relation to metabolic syndrome and low BMD Z-score. Logistic regression was used for multivariable modeling, with AAC categorized as present or absent and, consistent with standard criteria,¹¹ BMD Z-score categorized as low (-1 standard deviation score (SDS)) or normal (> -1 SDS). As previously defined,^{1,6} metabolic syndrome was dichotomized by the presence or absence of at least 3 of 5 components: elevated waist circumference, elevated triglycerides, low HDL-cholesterol, elevated blood pressure, elevated fasting glucose. To evaluate potential confounding, we encoded *a priori* dependency assumptions in a directed acyclic graph to identify a minimal sufficient set of covariates for adjustment.¹⁵ Body mass index, race, and cranial radiation exposure were considered, but the final models included stratification by sex and adjustment for age (continuous), smoking history (ever *vs.* never), and physical activity (fulfilling or not fulfilling current guidelines for physical activity in adults of at least 150 minutes of moderate physical activity/week)¹⁶.

RESULTS

Participants vs. non-participants

Table 1 provides characteristics of the 662 evaluable subjects. The median age of participants was 31 years (interquartile range 26–37). A comparison of the 497 eligible non-participants (including the 159 who expressed interest but had not been seen yet) to the

participants revealed a higher frequency of males (55% vs. 49%; $p=0.035$) and fewer White individuals (89% vs. 93%; $p=0.024$) among the non-participants. Age at diagnosis, current age, and years since diagnosis were nearly identical between the groups.

Metabolic syndrome and AAC

AAC was present in 67 (10%) participants. The majority of these (79%) had only scattered specks observable on the QCT images, indicating early stage aortic calcification (Table I). Mean age (SD) among those with AAC was 39 years (6.9) vs. 31 years (6.8) in those without AAC. The prevalence of metabolic syndrome was 36%. The adjusted OR for AAC among those with metabolic syndrome, compared to those without, was 1.5 (95%CL=0.85, 2.6) (Table II). The AAC-metabolic syndrome association was apparent in women (adjusted OR=2.3), but not in men (adjusted OR=1.0). The AAC-metabolic syndrome association did not differ statistically by cranial radiation exposure ($p=0.52$).

BMD and AAC

The prevalence of low BMD was 29% overall; 38% in men and 20% in women. If one assumes an age-specific normal distribution for BMD, then 16% would be expected to be at < -1 SDS. Clearly, the prevalence of low BMD in the male ALL survivors, if not females, is far higher than expected. In men, the adjusted odds ratio for AAC in those with low BMD compared with normal BMD was 3.1 (95%CL=1.3, 7.3).

DISCUSSION

Our results suggest that a substantial proportion of young adult survivors of childhood ALL have early signs of atherosclerotic disease, as indicated by presence of AAC in 10% and metabolic syndrome in 36%. We also found a high prevalence of low BMD, particularly in men (38%). Children treated for ALL are exposed to high doses of cytotoxic agents such as glucocorticoids, methotrexate, and in select cases, cranial irradiation, all of which can adversely affect bone mass and turnover.³ Anthracycline drugs, frequently used in the treatment of childhood ALL, are cardiotoxic agents and heart failure is a relatively unusual but well-described potential effect of high dose exposure.^{4,17} Our results show that atherosclerotic cardiovascular diseases, which may be directly promoted by the interrelated risk factors in the metabolic syndrome,⁶ might also be of significant concern in long-term childhood ALL survivors.

Limitations of the study include the possibility that AAC prevalence and severity may be underestimated because the low dose QCT technique is accurate for determining BMD but less sensitive for measuring AAC, although superior to abdominal X-ray.¹⁸ Because our study was cross-sectional in nature, the temporal sequence of metabolic syndrome progression and AAC formation cannot be determined, nor can we project differential adverse outcomes from these conditions. Nevertheless, both AAC and metabolic syndrome are established risk factors for atherosclerotic disease, so our findings are consistent with the empirical evidence that childhood ALL survivors are at premature risk of mortality and morbidity from cardiac and vascular outcomes.⁴ In the general U.S. population, the prevalence of metabolic syndrome in 20–39 year old men is 20%, and in 20–39 year old women it is 16%,¹⁹ considerably lower than observed in our ALL survivors at median age 31 years (34% men, 38% women); we found no similar prevalence comparisons for AAC in young adults.

Cardiovascular fitness is inversely and strongly related to metabolic syndrome.²⁰ Since components of the metabolic syndrome and other cardiovascular disease risk factors are modifiable, not only with medication, but also through increased physical activity and

nutritional improvements, clinicians could facilitate prevention by referring patients to appropriate persons or programs that can help potentiate important lifestyle changes.

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References

1. Gurney JG, Ness KK, Sibley SD, et al. Metabolic syndrome and growth hormone deficiency in adult survivors of childhood acute lymphoblastic leukemia. *Cancer*. 2006; 107(6):1303–1312. [PubMed: 16894525]
2. Oeffinger KC. Are survivors of acute lymphoblastic leukemia (ALL) at increased risk of cardiovascular disease? *Pediatr Blood Cancer*. 2008; 50(2 Suppl):462–467. [PubMed: 18064658]
3. Wasilewski-Masker K, Kaste SC, Hudson MM, Esiashvili N, Mattano LA, Meacham LR. Bone mineral density deficits in survivors of childhood cancer: Long-term follow-up guidelines and review of the literature. *Pediatrics*. 2008; 121(3):e705–e713. [PubMed: 18310191]
4. Ness KK, Armenian SH, Kadan-Lottick N, Gurney JG. Adverse effects of treatment in childhood acute lymphoblastic leukemia: General overview and implications for long-term cardiac health. *Exp Review Hematol*. 2011; 4(2):185–197.
5. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *Br Med J*. 2009; 339:b4606. [PubMed: 19996459]
6. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation*. 2005; 112(17):2735–2752. [PubMed: 16157765]
7. Rennenberg RJ, Kessels AG, Schurgers LJ, van Engelshoven JM, de Leeuw PW, Kroon AA. Vascular calcifications as a marker of increased cardiovascular risk: a meta-analysis. *Vasc Health Risk Manag*. 2009; 5(1):185–197. [PubMed: 19436645]
8. Wilson PW, Kauppila LI, O'Donnell CJ, et al. Abdominal aortic calcific deposits are an important predictor of vascular morbidity and mortality. *Circulation*. 2001; 103(11):1529–1534. [PubMed: 11257080]
9. Colón-Emeric C, O'Connell MB, Haney E. Osteoporosis piece of multi-morbidity puzzle in geriatric care. *Mount Sinai Journal of Medicine: A Journal of Translational and Personalized Medicine*. 2011; 78(4):515–526.
10. Hyder JA, Allison MA, Barrett-Connor E, et al. Bone mineral density and atherosclerosis: The Multi-Ethnic Study of Atherosclerosis, Abdominal Aortic Calcium Study. *Atherosclerosis*. 2010; 209(1):283–289. [PubMed: 19819456]
11. Marcovitz PA, Tran HH, Franklin BA, et al. Usefulness of bone mineral density to predict significant coronary artery disease. *Am J Cardiol*. 2005; 96(8):1059–1063. [PubMed: 16214438]
12. Wiklund P, Nordstrom A, Jansson JH, Weinehall L, Nordstrom P. Low bone mineral density is associated with increased risk for myocardial infarction in men and women. *Osteoporos Int*. 2012; 23(3):963–940. [PubMed: 21505909]
13. Hudson MM, Ness KK, Nolan VG, et al. Prospective medical assessment of adults surviving childhood cancer: Study design, cohort characteristics, and feasibility of the St. Jude Lifetime Cohort study. *Pediatr Blood Cancer*. 2011; 56(5):825–836. [PubMed: 21370418]
14. Landier W, Bhatia S, Eshelman DA, et al. Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. *J Clin Oncol*. 2004; 22(24):4979–4990. [PubMed: 15576413]
15. Pearl, J. *Causality: Models, Reasoning, and Inference*. Cambridge UK: Cambridge University Press; 2009.

16. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007; 116(9):1081–1093. [PubMed: 17671237]
17. Barry E, Alvarez JA, Scully RE, Miller TL, Lipshultz SE. Anthracycline-induced cardiotoxicity: course, pathophysiology, prevention and management. *Expert Opin Pharmacother*. 2007; 8(8): 1039–1058. [PubMed: 17516870]
18. Bellasi A, Raggi P. Techniques and technologies to assess vascular calcification. *Semin Dial*. 2007; 20(2):129–133. [PubMed: 17374086]
19. Ervin RB. Prevalence of Metabolic Syndrome Among Adults 20 Years of Age and Over, by Sex, Race and Ethnicity, and Body Mass Index: United States, 2003–2006. *National Health Statistics Reports*. May 5.2009 (13):1–8. [PubMed: 19634296]
20. Grundy, SM.; Barlow, CE.; Farrell, SW.; Vega, GL.; Haskell, WL. Cardiorespiratory Fitness and Metabolic Risk. *Am J Cardiol*. Jan 3. 2012 in press[Epub ahead of print]. <http://dx.doi.org/10.1016/j.amjcard.2011.11.031>

Table I

Characteristics of the 662 participating adult survivors of childhood ALL

Characteristic	Frequency	Percent
Sex		
Female	337	50.9
Male	325	49.1
Race		
White	614	92.7
Black	45	6.5
Other	5	0.8
Age at assessment		
18–24	102	15.4
25–34	310	46.8
35–44	216	32.6
45–59	34	5.1
Age at diagnosis		
<5	331	50.0
5–9	193	29.2
10–14	104	15.7
15–21	34	5.1
Years from diagnosis		
10–19	122	18.4
20–29	346	52.3
30–49	194	29.3
Cranial radiation dose		
None	222	33.5
<24 Gy	203	30.7
24 Gy	237	35.8
Smoking Status		
Current	143	21.6
Former	57	8.6
Never	462	69.8
Physical Activity Guidelines met		
Yes	342	51.7
No	320	48.3
Abdominal Aortic Calcification		
Yes	67	10.1
No	595	89.9
Abdominal Aortic Calcification		
None	595	89.9
Scattered specks	53	8.0
½ wall	8	1.2

Characteristic	Frequency	Percent
¾ wall	3	0.5
Entire wall	3	0.5
BMD Z-score (age- and sex-specific)		
> 1 SDS	77	11.6
> 0 to 1 SDS	167	25.2
> -1 to 0 SDS	227	34.3
> -2 to -1 SDS	157	23.7
-2 SDS	34	5.1
Low BMD (-1 SDS)		
Yes	191	28.9
No	471	71.1
Metabolic Syndrome Components		
Elevated waist circumference	254	38.4
High fasting glucose	223	33.7
Low HDL-cholesterol	317	47.9
Elevated triglycerides	206	31.1
Elevated blood pressure	314	47.4
Metabolic Syndrome (3 components)		
Yes	238	36.0
No	424	64.0

Table II

Metabolic syndrome and bone mineral density in association with presence of abdominal aortic calcification (AAC) in 662 adult survivors of childhood ALL

	Any AAC (n)	No AAC (n)	Odds ratio ^a (95% CL)
<i>Overall</i>			
Metabolic syndrome	38	200	1.5 (0.85, 2.6)
No metabolic syndrome	29	395	1.0 (Reference)
<i>Males</i>			
Metabolic syndrome	15	96	1.0 (0.44, 2.4)
No metabolic syndrome	15	199	1.0 (Reference)
<i>Females</i>			
Metabolic syndrome	23	104	2.3 (1.03, 5.1)
No metabolic syndrome	14	196	1.0 (Reference)
<i>Overall^b</i>			
BMD -1 SDS	22	169	1.6 (0.9, 2.8)
BMD > -1 SDS	45	426	1.0 (Reference)
<i>Males</i>			
BMD -1 SDS	15	110	3.1 (1.3, 7.3)
BMD > -1 SDS	15	185	1.0 (Reference)
<i>Females</i>			
BMD -1 SDS	7	59	0.8 (0.3, 2.0)
BMD > -1 SDS	30	241	1.0 (Reference)

^aOR and 95%CL: odds ratios and 95% confidence limits, adjusted for smoking history, physical activity, and, except for the BMD-SDS ORs and 95%CLs, age.

^bBMD: bone mineral density; SDS: standard deviation score (Z-score)