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CHILDREN/ADOLESCENTS/YOUNG ADULTS AND ATHEROSCLEROSIS (D.P. WILSON, SECTION EDITOR)

Heart Transplant, Kawasaki Disease, and Bone Marrow Transplant: Are There Consequences?

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Abstract

Purpose of Review This article reviews the current landscape of cardiovascular disease (CVD) risk factors, focusing on dyslipidemia, which contribute to atherosclerosis in three unique populations: youth less than 18 years-of-age with a history of Kawasaki disease, and those who have undergone orthotopic heart and bone marrow transplants.

Recent Findings Atherosclerosis, the major cause of CVD, begins in childhood. Acquired and genetic disorders of lipid and lipoprotein metabolism, present at an early age, are major contributors to early precursors of atherosclerosis, which accelerate after age 20. Treatment of the underlying medical condition and optimum management of all risk factors is critical in improving outcomes. Nonetheless, limited data is available to assist clinical decision-making, with the aim of improving outcomes.

Summary Atherosclerosis, beginning in childhood, is multifactorial in origin with complex interplay of inflammation, infection, endothelial dysfunction, and dyslipidemia. Future studies are needed to help elucidate the specific roles of disease mechanisms, with an emphasis on early intervention and prediction of subclinical disease. In addition to a heart healthy lifestyle, there may be a role for use of lipid-lowering medications beginning at an early age.

Keywords Youth · Children · Hyperlipidemia · Atherosclerosis · Kawasaki disease · Bone marrow transplant · Heart transplant

Introduction

Atherosclerosis in Youth

CVD is the leading cause of mortality and premature morbidity in the USA and developed countries throughout the world [1]. Evidence of atherosclerosis, the major cause of CVD, is present from an early age, although clinical manifestations, such as myocardial infarction (MI) and stroke, rarely occur until adulthood. Numerous observational and epidemiologic studies support this association [2, 3]. Dyslipidemia in this age group is caused by genetic variants, acquired causes, or both. Familial hypercholesterolemia (FH) is the prototype of monogenic pathologic variants, which cause hypercholesterolemia, leading to premature CVD during adulthood. The heterozygous form of FH is common affecting 1 in 200–250 people. It is an autosomal co-dominant disorder most often caused by abnormalities in the LDL-C receptor [4, 5]. There is strong causal evidence linking FH with CVD-related events, such as MI and stoke [6]. Compared to individuals with a comparable level of cholesterol, current finding suggests that those with a pathologic variant have a much higher risk of CVD, and may derive a bigger benefit from LLM, especially when initiated at an early age.

Long-term data demonstrating the efficacy and safety of lipid-lowering medications (LLM), such as statins, in youth are limited. Nonetheless, multiple randomized controlled trials have demonstrated minimal adverse effects on brain maturation, pubertal development, and growth in youth as young as 6 years-of-age [7–9].

When present in youth, acquired conditions may also affect CVD risk, and have increasingly been recognized

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as risk enhancers. The most common acquired condition encountered in clinical practice is obesity, often associated with metabolic syndrome, the latter characterized by insulin resistance, hypertension, and dyslipidemia consisting of elevated triglycerides (TG), low levels of high-density lipoprotein cholesterol (HDL-C), and normal to mild elevations in low-density lipoprotein cholesterol (LDL-C). LDL particles tend to be small and dense, enhancing their atherogenicity. Observational studies over 40 years demonstrated that youth with an elevated body mass index (BMI) have higher CVD mortality than their leaner peers [10]. The American Heart Association's (AHA) classification of risk, high, moderate, and at risk, is helpful in clinical practice to aid in risk stratification (Table 1) [1].

This review article will focus on practical considerations in clinical practice, current knowledge, and available evidence in three unique populations — youth less than 18 years-of-age with a history of Kawasaki disease, and those who have undergone orthotopic heart and bone marrow transplants.

Kawasaki Disease

Kawasaki disease (KD), first described in 1967 by Dr. Tomisaku Kawasaki, is the leading cause of acquired heart disease affecting youth in the developed world [11, 12]. The disease is an idiopathic systemic vasculitis affecting small- and medium-sized blood vessels, with a predilection for coronary arteries. Coronary artery abnormalities range from mild coronary ectasia (*Z* score 2–2.5) during the acute phase to large or giant coronary aneurysms (*Z* score > /10 or absolute dimensions of > /8 mm) in youth who are severely affected. Despite timely administration of intravenous (IV) immunoglobulin, approximately 5–7% of youth develop coronary artery aneurysms [13–15]. The majority of those with mild coronary ectasia have resolution of the ectasia within 4–8 weeks. Those with giant coronary aneurysms are at highest risk for coronary artery thromboses, followed by changes in the architecture of the coronary vasculature, leading to coronary artery stenosis. Clinically, these vascular changes predispose an increased risk of myocardial ischemia, infarction, and sudden cardiac death. However, the role of atherosclerosis in youth with coronary artery aneurysms is not clear. The 2017 AHA scientific statement noted that no atherosclerotic features were seen in KD patients, even in those who experienced late deaths and transplants [16]. Youth who have experienced KD-related endothelial damage and dysfunction should be "high risk" or "at risk" for accelerated atherosclerosis, as reflected in the 2006 and 2019 AHA scientific statements [1, 17••] as depicted in Table 1.

Vascular Changes

To fully understand the CVD risk imposed by coronary artery aneurysms, it is helpful to understand the formation and progression of these lesions. During the acute phase of KD, infiltration of neutrophils results in necrotizing arteritis of the vessel wall. This leads to degeneration and fragmentation of the elastic tissue of the vessel, resulting in aneurysm formation. In the subacute phase, there is chronic vasculitis characterized by infiltration by plasma cells, lymphocytes, and eosinophils. This eventually leads to myofibroblastic proliferation within the intima, and varying degrees of stenosis. Early clinical diagnosis and timely administration of IV immunoglobulin is often successful of arresting or reversing this process. However, giant or large aneurysms do not typically resolve or regress, and represent the highest risk for thrombus formation [17••]. Aneurysms of lesser severity may diminish or remodel over time, resulting in less risk for thrombus formation.

Endothelial Dysfunction

Variable damage to the coronary vasculature, leading to endothelial dysfunction, serves as the primary mechanism,

Table 1 Disease stratification by risk

High risk	Homozygous FH, T2DM, end-stage renal disease, T1DM, Kawasaki disease with persistent aneurysms, solid-organ transplant vasculopathy, childhood cancer survivor (stem cell recipient)
Moderate risk	Severe obesity, heterozygous FH, confirmed hypertension, coarctation, Lp(a), predialysis CKD, AS, childhood cancer survivor (chest radiation)
At risk	Obesity, insulin resistance with comorbidities (dyslipidemia, NAFLD, PCOS), white-coat hypertension, HCM, and other cardiomyopathies, pulmonary hypertension, chronic inflammatory conditions (JIA, SLE, IBD, HIV), s/p coronary artery translocation for anomalous coronary arteries or transposition of the great arteries, childhood cancer (cardiotoxic chemotherapy only), Kawasaki disease with regressed aneurysms (zMax ≥ 5)

AS, aortic stenosis; *CKD*, chronic kidney disease; *FH*, familial hypercholesterolemia; *HCM*, hypertrophic cardiomyopathy; *IBD*, inflammatory bowel disease; *JIA*, juvenile rheumatoid arthritis; *Lp(a)*, lipoprotein (a); *NAFLD*, nonalcoholic fatty liver disease; *PCOS*, polycystic ovarian syndrome; *SLE*, systemic lupus erythematosus; *s/p*, status post; *T1DM*, type 1 diabetes mellitus; *T2DM*, type 2 diabetes mellitus; and *zMax*, maximum *z* score at any time during the course of illness. (Adapted from: de Ferranti SD, et al. Circulation. 2019 Mar 26;139(13):e603-e634. https://doi.org/10.1161/CIR.0000000000000618, with permission from Wolters Kluwer Health, Inc.) [17••]

which accelerates development of atherosclerosis in the most severely affected youth. Measurement of carotid intimal medial thickness (cIMT), a surrogate marker for atherosclerosis, has primarily been used as a research tool, but may be helpful in clinical practice [18]. There are numerous studies documenting higher mean cIMT in youth with vs those without KD [19–21], changes which may persist for up to 7 years after the acute episode [22]. Endothelial dysfunction can also be measured using flow mediated dilation (FMD) [23]. FMD is reduced following KD, especially in youth with coronary artery aneurysms [20, 24, 25], when compared to those with minimal involvement of coronary arteries.

Inflammation

The role of inflammation and contribution of persistent subclinical vasculitis in this disease is well recognized. Levels of high sensitivity CRP and homocysteine have been studied in KD with mixed results [26, 27].

Derangements in Lipid and Lipoprotein Metabolism

The majority of studies have found no differences in the lipid and lipoprotein levels in youth with KD compared to the normal population. However, using nuclear magnetic resonance spectroscopy to estimate the lipoprotein levels in KD patients, Lin et al. reported lower concentrations of TC, LDL-C, and TG concentrations [28].

Risk Enhancement

Other high-risk conditions (see Table 1) or health behaviors, like smoking, alcohol use, physical inactivity, and unhealthy eating habits, can further contribute to premature atherosclerosis in youth with a history of KD.

The Role of Lipid-Lowering Therapy

Statins are the cornerstone of therapy for primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD)-related events in adults [29]. There is ample evidence demonstrating that statins have favorable effects on vascular endothelium, inflammation, platelet aggregation, and oxidative stress. Empiric use of statins has been given a class IIb recommendation for KD patients who presently have one or more aneurysms or a previous history of aneurysms [16]. Statins have been shown to cause autophagy and mitophagy, thus interrupting the NLRP3 inflammasome pathway, which inhibits activation of the inflammatory cascade of IL-1beta, speculated to be involved in KD pathogenesis [30•]. They have also been shown to inhibit myofibroblast formation via matrix metalloproteinase 9 (MMP-9) dependent and independent mechanisms [31]. Tremoulet et al. reported the results of a phase 1/IIA, two center, first dose-escalation pharmacokinetic study of atorvastatin in children with acute KD and coronary artery aneurysms, which showed safety and tolerability in a group of 34 children greater than 2 years-of-age [32••]. The rationale for using statins as adjunctive therapy for acute KD was based on their ability to inhibit MMP-9 secretion and myofibroblast transformation, both of which have been implicated in the formation of CAA in this disease [33, 34]. A smaller study of youth with KD and coronary artery aneurysms ≥ 1 year following the acute phase of the disease reported improvement in high sensitivity CRP levels and improved brachial artery FMD after 6 months of pravastatin therapy [35].

Orthotopic Heart Transplants

Heart transplantation is the final recourse for individuals with end-stage heart disease. Kantrowitz and colleagues performed the first heart transplant involving a child in 1968 [36]. Since then, approximately 500–550 children undergo heart transplantation annually, about 10% of the total heart transplantations. Information from the 2017 International Society of Heart and Lung Transplant (ISHLT) registry notes that children less than 1 year-of-age at the time of transplantation have the longest survival, with a median of 22.3 years. Survival decreases with age, adolescents (11–17 years) having the lowest survival time at 13.1 years-of-age; 18.4 years for those ages, 1 to 5 years, and 14.4 years for those 6 to 10 years [37]. Death is more common in the first year post-transplant, the major cause being acute rejection for all age groups. Survival beyond the first year of transplant conferred a survival advantage for all age groups.

Cardiac Allograft Vasculopathy

Cardiac allograft vasculopathy (CAV) is the leading cause of mortality in heart transplant recipients beyond 3 years post-transplantation [37]. CAV is characterized by diffuse epicardial and microvascular coronary artery dysfunction. Varying degrees of intimal proliferation and medial wall thickening eventually lead to progressive luminal stenosis. The incidence of CAV in heart transplant recipients in the pediatric population is 5%, 15%, and 28% at 2, 5, and 10 years-of-age, respectively, and results in a 50% graft survival at 5 years [38]. There are many factors associated with CAV, including older age of the recipient, older age of the donor, need of re-transplantation, recipients who are black, rejection in the first year post-transplant, and two or more episodes of rejection in the first year post-transplant [37, 39, 40].

Diagnosis of CAV is usually made by coronary angiography, which includes hemodynamic measurements. Intravascular ultrasound is a promising tool to help identify CAV,

although utilization is limited by costs, expertise in preforming and interpreting the study, and the need for larger catheters, which essentially confines its use to older children [41].

The 2010 ISHLT consensus statement graded CAV into 4 categories (CAV 0–3) depending on the severity of the coronary artery narrowing and the presence or absence of allograft dysfunction [38, 42]. Severe CAV involves allograft dysfunction (left ventricular ejection fraction < 45%, regional wall motion abnormalities, restrictive physiology).

The etiology of CAV is poorly understood, but likely multifactorial in origin. Dyslipidemia appears to play a role, in part due to the effects of immunosuppressive medications [43]. CAV is best characterized as a chronic low-grade inflammatory state, aggravated by the number of rejections in first year post-transplant and a susceptibility to viral infections, like cytomegalovirus and Epstein-Barr virus. Well-described CVD risk factors, like diabetes mellitus, systemic hypertension, and metabolic syndrome, are also prevalent in transplant recipients.

Dyslipidemia

Compared to the general population, youth who undergo heart transplant have higher levels of TG (> 75th centile) and lower HDL-C (< 25th centile). In the Pediatric Heart Transplant Society study of 1610 recipients from 21 institutions, no differences were found in the median values of TC and LDL-C [43]; TC levels being > 200 mg/dl in 14% and > 170 mg/dl in 33%. LDL-C was > 130 mg/dl in 12%, > 110 mg/dl in 27%, and > 100 mg/dl in 39% 1 year post-transplant [43]. Older age and use of a calcineurin inhibitor were significant predictors of higher LDL-C. Recipients using tacrolimus had a lower LDL-C level compared to treat with cyclosporine. Steroid use was a significant predictor for high TG levels. The authors noted that despite statistically non-significant values for TC and LDL-C, several recipients met standard criteria for statin use.

Role of Statins

Despite a lack of proven causality, there is anatomic evidence of lipid vacuoles in coronary vessel walls in recipients with CAV [44]. This finding supports the role of non-immunologic factors, like lipids, as being as contributing to CAV. The 2019 AHA scientific statement recommends use of statins in youth who have undergone a heart transplant, especially in those with lipid abnormalities, and categorizes the presence of vasculopathy following solid organ transplant as being "high risk lesions" (17).

Nonetheless, the optimal age for initiation of LLM and the thresholds to help guide clinical decision-making is not clear. Significant practice variation exists between centers in the use of statin. In a retrospective multicenter PHTS registry review of 964 pediatric heart transplant recipients, only 30–35% above 10 years-of-age were prescribed a statin within a year of heart transplantation [45•]. In the 5–9 years age group, 20% were receiving a statin by 1 year and 30% by 2 years post-transplant. Statin use was similar in youth 10–14 and 15–18 years-of-age. Use became more common with increasing time post-transplant; however, at least one-third of recipients > 10 years-of-age were not prescribed a statin. Of note, the study concluded that statin therapy did not confer a survival benefit and was not associated with delayed onset of post-transplant lymphoproliferative disease (PTLD) or CAV. In fact, the use of statins (< 1 year post-transplant) was associated with an increased frequency of rejection. These findings are in contrast to previous, albeit smaller pediatric studies, which showed lower incidence of CAV in recipients treated with a statin. Mahle et al., using multivariate analysis, demonstrated that the use of pravastatin was associated with a lower incidence of CAV ($p = 0.03$), whereas an increased frequency of late rejection ($p = 0.003$) and earlier year of transplantation ($p = 0.04$) were associated with increased risk of CAV [46].

A single-center study evaluated the use of atorvastatin early in the post-transplant phase, reported 1, 3, and 5 years freedom from CAV higher in the early treatment group (97%, 93%, and 93%) compared to the control group (72%, 65%, and 60%; $p < 0.005$) [47]. Similarly, in adult heart transplant recipients, use of statins has shown beneficial effects on cardiac rejection with hemodynamic compromise, development of CAV, and improved survival [48]. In a separate multicenter observational study of 1186 adults, statin-treated recipients had a lower frequency of death and rejection [49]. It is notable that these effects were independent of lipid values, which appeared early on and persisted 2.5 years post-transplant. Support for use of statins in heart transplant recipients, in part, relates to their pleotropic effects on immunomodulation, inflammation, and lipid lowering.

Bone Marrow Transplant

Introduction

Bone marrow transplantation (BMT), also referred to as hematopoietic stem cell transplantation (HSCT), has been successfully used to treat a variety of malignant, non-malignant, and immunologic disorders [50]. The procedure is performed using the recipient's own cells (autologous) or those of a living-related donor (allogenic) [51–53]. High-dose chemotherapy or total body irradiation (TBI) is administered prior to HSCT, depending on the underlying condition. Following HSCT, immunosuppression is used to prevent rejection and graft versus host disease (GVHD). First successfully accomplished in the 1970s, approximately 50,000 HSCTs are performed annually worldwide. Despite

its success, a high incidence of long-term CVD-related mortality and morbidity has been reported in HSCT recipients [54]. Exceeded only by malignancies and GVHD, CVD has become the third leading cause of mortality [55, 56]. In addition to the inheriting transplant-associated risks of TBI and GVHD, HSCT patients have higher susceptibility to develop systemic hypertension and dyslipidemia [57, 58].

There is evidence of early development of a subclinical cardiometabolic phenotype in long-term survivors of HSCT. A cross-sectional study of 64 pediatric HSCT recipients under 18 years-of-age showed a high prevalence of traditional risk factors such as adiposity, systemic hypertension, microalbuminuria, microinflammation, dyslipidemia, and low levels of physical activity. Aortic stiffening with elevated pulse wave velocity (PWV) (6%), atherosclerosis with increased IMT values (48%), left ventricular hypertrophy (11%), and decreased left ventricular ejection fraction (7%) were significant findings [59••]. This is in contrast to other studies where IMT and PWV values were no different in survivors of HSCT [60, 61]. Increased IMT is independently associated with increased inflammatory markers in autologous HSCT recipients [62].

Detection of early, subclinical target organ damage and development of CVD risk prediction models integrating subclinical markers and traditional risk factors specific to this vulnerable population should be a priority for scientific organizations and research communities to help improve outcomes.

Dyslipidemias

Dyslipidemia is frequently reported in HSCT survivors. Kagoya and associates described a cohort of 194 adult HSCT recipients followed for a median of 77 months, 42.8% of whom developed hypercholesterolemia and 50.8% who developed hypertriglyceridemia [63]. Survivors experienced rapid onset with a median interval to occurrence of hypercholesterolemia and hypertriglyceridemia of 11 and 8 months post-allogeneic HSCT. In a larger retrospective study of 761 adult patients, 73.4% and 72.5% developed hypercholesterolemia and hypertriglyceridemia, respectively [64]. A large proportion of these subjects were receiving tacrolimus, sirolimus, and glucocorticoids, all of which are known to cause disturbances in lipid and lipoprotein levels.

Other post-transplant complications can also affect lipid homeostasis. Chronic GVHD can result in liver failure, impeding bile acid, and cholesterol clearance, the latter increasing levels of non-apo B containing lipoprotein X [65]. Hypogonadism and hypothyroidism have been noted following TBI, which can also contribute to dyslipidemia [66, 67]. In a large pediatric multicenter study of 661 HSCT survivors (median duration of follow up of 97 months) (24–230), low HDL-C, high TG, and mild elevation in LDL-C were present in 18% [68]. Pre-transplant anthracycline, chest irradiation, and chronic GVHD are additional risk factors for dyslipidemia; 4.2% of survivors experiencing at least one of the primary outcomes. In a study by Bis et al., 198 HSCT recipients aged 0.5–20 years were followed over a period of 3.8 + /1.8 years following HSCT [69]. The most common findings were increased TG, TC, and low HDL-C levels, which were most pronounced in the first 6 months to 1 year following HSCT. Levels of LDL-C were not affected. During HSCT, TG levels rose higher in patients with low HDL-C levels [69]. In a study of 340 childhood cancer survivors (CCS) followed over 16 years, hypercholesterolemia and hypertriglyceridemia were found in 20% and 6% patients, respectively [70]; TBI and growth hormone deficiency increasing the risk of both conditions. The risk of hypercholesterolemia was higher in those with auto-HSCT and platinum-based chemotherapy. From these studies, it appears that in the short term, survivors of HSCT frequently experience dyslipidemia, which improves with time.

Role of Statins

The role of statin therapy is not well established in HSCT survivors. In part, this may be related to the concern for drug-drug interactions, which may aggravate GVHD, and lack of evidence supporting the use of statins [71, 72]. The reported rate of statin use in adult HSCT survivors ranges from 5 to 29% [64, 73–75]. A retrospective study by Blaser et al. found that efficacy of statin use did not appear to be inferior to general population and was well-tolerated [64]. One randomized, placebo-controlled clinical trial in 27 CCS did not find an improvement in endothelial function or arterial stiffness following 6 months of treatment with atorvastatin [76]. The results of this study, however, should be interpreted with caution due to lack of sufficient power.

Despite the lack of evidence, the current Children's Oncology Group's "Long-term follow up Guidelines for Survivors of Childhood, Adolescent and Young adult cancer" guidelines recommend lipid screening of HSCT recipients and CCS [77, 78]. According to the 2006 and 2019 AHA scientific statements, HSCT is recognized as a high risk and CCS a moderate risk condition [1, 17••]. Hence, risk stratification and management algorithms provided in these statements [1, 17••] should guide the clinical management of these individuals.

Conclusions

Youth with a history of Kawasaki disease, and orthotopic heart and bone marrow transplant recipients, represent unique populations that are medically and socially fragile. Based upon our current understanding, there is little

doubt that youth with these conditions are at increased risk of accelerated atherosclerosis. The main stay of management is adoption of a healthy lifestyle, with an emphasis on heart healthy dietary choices and exercise, if tolerated. While incomplete, a better understanding of the exact role of inflammation, infection, endothelial dysfunction, and dyslipidemias in the pathophysiology of atherosclerosis is critically needed to help guideline clinical management. Such knowledge will improve prediction of CVD risk and encourage early intervention during the subclinical phase of the disease process. While promising, the role of LLM, such as statins, remains unclear. Sufficiently powered, robust randomized controlled clinical trials and long-term observational studies are needed to evaluate outcomes.

Declarations

Conflict of Interest The author declares that he does not have any conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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