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Risk Factors for Cardiovascular Disease in Children and Young Adults with Haemophilia

Jacqueline Limjoco¹ and Courtney D. Thornburg^{1,2}

¹Rady Children's Hospital San Diego, San Diego, CA

²UC San Diego, La Jolla, CA

Abstract

Introduction—The origins of cardiovascular disease (CVD) begin in childhood. The primary objective of this cross-sectional cohort study was to determine the prevalence of cardiovascular risk factors in patients with congenital haemophilia A or B followed at Rady Children's Hospital San Diego Hemophilia and Thrombosis Treatment Center (HTC). We hypothesized that cardiovascular risk factors could be identified as part of a comprehensive clinic visit.

Materials and Methods—Standardized measurement of weight, height, waist circumference and blood pressure plus non-fasting glucose and lipid panel were performed. Participants and/or caregivers completed questionnaires about family history, medical history, and lifestyle. Clinical data were abstracted from the medical record. Descriptive statistics, student's t-test, correlation, Mann-Whitney U test, and chi square test were performed to analyze the data.

Results—Forty-three males (mean 12y, range 5-20y) enrolled. High rates of overweight and obesity, (pre)hypertension, and abnormal lipids were identified. Subjects with normal weight had more days of >60 minutes of physical activity compared to those with overweight or obesity (5.2 ± 2.4 d v. 3.8 ± 2.5 d; $p=0.07$). Higher weight was correlated with higher factor consumption ($cor=0.88$; $p<0.001$). There was no difference in target joints based on weight category (30% in normal weight v. 25% in overweight or obese, $\chi^2=0.11$, $p=0.74$), which may be attributed to high rates of prophylaxis.

Conclusions—Modifiable risk factors for CVD were identified as part of the study during comprehensive clinic visits. The HTC team may develop behavioral interventions to target cardiovascular risk reduction as part of the comprehensive care model.

Keywords

haemophilia; overweight; obesity; hypertension; cardiovascular disease

Corresponding Author: Courtney D. Thornburg MD, MS, Professor of Pediatrics, UC San Diego, 3020 Children's Way, MC 5035, San Diego, CA 92123, Telephone: 858-966-5811, Fax: 858-966-8035, cthornburg@rchsd.org.

DR COURTNEY THORNBURG (Orcid ID : 0000-0002-5665-8958)

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Introduction

An emerging problem in the aging haemophilia population is cardiovascular disease (CVD). [1, 2] Clotting factor deficiency does not appear to prevent CVD,[3–5] and traditional and non-traditional cardiovascular risk factors are associated with CVD in adults with congenital haemophilia.[2, 5, 6] Sun et al. conducted a two-centre prospective cohort study of macro- and microvascular endothelial function endothelial dysfunction, an independent predictor of CVD.[7] Microvascular endothelial function was lower in adults with haemophilia compared to controls. The authors suggest that bleed related inflammation and decreased bioavailability of microvascular vasoactive chemicals may contribute to endothelial dysfunction.

CVD poses more risk to the haemophilia population than the general population since medications used to treat CVD may increase bleeding risk, and patients with haemophilia are at substantial risk for bleeding with surgery.[1, 8] Hypertension, a risk factor for CVD, may be associated with a high risk of intracranial haemorrhage in persons with haemophilia. [9] In addition, obesity, another risk for CVD, is associated with increased joint disease in haemophilia as described by the Centers for Disease Control and Prevention (CDC) and recently reviewed by Kahan et al.[10, 11] Therefore, it is particularly important to prevent CVD and its associated risk factors in this population.

Atherosclerosis, which is the biologic basis for CVD, begins in childhood and is associated with established risk factors including obesity, hypertension, abnormal lipid profile, and family history (FH) of CVD.[12, 13] Overweight and obesity in childhood are prevalent, and there is a high correlation between overweight and obesity as a child and overweight and obesity as an adult.[14–16] Most recent data from NHANES, 2015–2016, identify high rates of overweight and obesity including 41.5% of 16 to 19 year olds with body mass index (BMI) ≥ 85% including 14% with severe obesity (9.5% with class II obesity [body mass index [BMI] ≥ 120% of the 95th percentile] and 4.5% with class III obesity [BMI ≥ 140% of the 95th percentile].[17] Highest rates are in African American and Hispanic children. Overall, between 2006 to 2016, rates of severe obesity increased for children aged 2 to 5 years and for adolescent females aged 16 to 19 years. These findings are of particular concern since severe obesity is related to higher cardiovascular and metabolic risk.[18] High blood pressure (BP) is also increasing in the general pediatric population.[19] The prevalence of prehypertension and hypertension in children 3 to 18 years old are 3.4% and 3.6% respectively. The prevalence is substantially higher in obese children: >30% in obese boys and 23–30% in obese girls. Similarly, abnormal lipid levels are associated with obesity in children.[18] Optimally, strategies to mitigate risk should be initiated in childhood.

The first step for prevention in the haemophilia population is to determine the prevalence of cardiovascular risk factors. Some cardiovascular risk factors including overweight, obesity, and hypertension are more prevalent in adults with haemophilia than in the general population.[5, 6, 9, 20–23]

Majumdar et al. identified 21% of their pediatric patients with haemophilia in Mississippi as obese and 16% as overweight with increasing prevalence with age.[24] Data from the CDC

Universal Data Collection Program demonstrate highest rates of obesity in Hispanics.[25] Alperstein et al. compared the prevalence of obesity, hypertension, abnormal lipids, and diabetes mellitus, defined by ICD-9 codes and adjusted for sex, in hospitalized children using the 2012 National Health Cost and Utilization Project database.[26] In this study, 2.64% of males with haemophilia were obese compared to 1.32% of males in the non haemophilic population, $p<0.0001$, and 1.52% with haemophilia had hypertension, compared to 1.22% in the non haemophilic population, $p=0.26$. Overall, there were low rates of abnormal lipids and diabetes mellitus. Further data are needed for non-hospitalized patients and from primary data rather than ICD-9 codes.

The primary objective of this cross-sectional cohort study was to determine the prevalence of cardiovascular risk factors in patients with congenital haemophilia followed at Rady Children's Hospital San Diego (RCHSD) Hemophilia and Thrombosis Treatment Center (HTC). We hypothesized that cardiovascular risk factors could be identified as part of a comprehensive clinic visit.

Materials and Methods

Eligible subjects included children and young adults, age 5-20.99 years with congenital haemophilia A or B. Between March 2016 to June 2017 the research team approached eligible individuals during comprehensive care visits at RCHSD HTC. The UC San Diego Institutional Review Board approved the study and consent/assent was obtained for study participation prior to study activities.

Data were abstracted from the electronic health record (EHR). Data elements included demographics including self-reported race/ethnicity; type and severity of haemophilia, type of haemophilia treatment, co-morbidities, and assessment and plan of the HTC dietician.

At RCHSD HTC, each provider has a role in evaluating and mitigating risk factors for CVD (Table 1). Education regarding healthy lifestyle is provided to all patients. For the purpose of the study, the research coordinator collected information about FH, medical history, and lifestyle using questionnaires.

Study procedures included standardized measurement of weight, height, waist circumference and BP, in duplicate, and non-fasting laboratory measurement of glucose (<200 mg/dL is normal) and lipid panel (to calculate non-high-density lipoprotein [non-HDL-C]; the non-HDL-C results were categorized as normal, borderline high, or high per age-based norms). [27] BMI percentile was determined for children <18 years, and BMI was calculated for adults. Weight category of underweight, normal weight, overweight or obese was assigned based on established norms for BMI percentile and BMI. Waist-to-height ratio (WHtR) was calculated; >0.5 is considered a cardiometabolic risk factor. For children, systolic BP (SBP) and diastolic BP (DBP) percentiles were determined based on age, gender, and percentile of height.[28] Hypertension was defined as SBP and/or DBP 95th percentile.[28] Prehypertension was defined as SBP and/or DBP 90th percentile but less than 95th percentile. For adults, hypertension was defined as SBP and/or DBP 140/90 and prehypertension was defined as SBP and/or DBP 120/80.[29] For analysis, subjects

meeting criteria for hypertension or prehypertension are grouped together as (pre)hypertension.

Participants who had (pre)hypertension and/or abnormal non-HDL-C were referred back to their primary care physician (PCP) and this recommendation was documented in the EHR.

Study data were collected and managed using REDCap electronic data capture tools hosted at UC San Diego.[30] Descriptive statistics were calculated to describe the demographics and clinical characteristics of the study cohort. Student's t-test, correlation, Mann-Whitney U test, and chi square test were performed to analyze the data.

Results

During the study period, 69 eligible individuals had comprehensive clinic visits. Twenty-six were not enrolled for reasons including lack of interest, did not want study blood draw, did not have extra time, and enrolled in other studies. Forty-three males (mean age 12y, range 5-20y, including 6 young adults) were enrolled. The majority were White race (88%) and Hispanic ethnicity (65%). Twenty-one (49%) had state insurance, 14 (33%) had commercial insurance, 7 (16%) had military insurance and 1 (2%) had other insurance. Twenty-three (53.5%) had severe haemophilia A including two with high titer inhibitors. Thirty-three (77%) are on continuous prophylaxis, including two with high titer inhibitors.

No subjects reported congenital heart disease, kidney disease, diabetes mellitus, glucose intolerance, hypercholesterolemia, (pre)hypertension, or cardiovascular events. Two subjects reported a prior diagnosis of overweight or obesity, and both had been referred to a weight and wellness program. Seven (16%) participants reported a FH of CVD (myocardial infarction or stroke) in a male relative <55y and/or a female relative <65y. In addition, participants reported the following FH: 23 (53%) diabetes mellitus, 30 (70%) hypertension and 25 (58%) hypercholesterolemia. Six (14%) reported at least one household member who smokes tobacco products.

A summary of measured cardiovascular risk factors is shown in Table 2. Prevalence of overweight or obesity was not different between Hispanic (11/28, 39%) versus non-Hispanic (5/15, 33%) subjects; χ^2 0.15, $p=0.70$. There was no difference in mean age for participants who were normal weight, overweight, or obese (12.1 ± 4.5 , 12.9 ± 4.3 , and $10.6 \pm 3.8y$ respectively; $p=0.57$). There was no difference in type of insurance (commercial versus state) between subjects who were normal weight versus overweight or obese ($p=0.16$). There was a trend to higher rate of overweight or obesity in participants with a FH of CVD ($p=0.08$). Figure 1 shows a representative example of a growth chart for a subject with class II obesity. Twenty-eight percent (10/28) with BP measured in duplicate had (pre)hypertension. When comparing variables between subjects with normal BP versus (pre)hypertension there was no difference in mean age (12.7 ± 4.2 and $11.0 \pm 4.4y$ respectively; $p=0.32$), type of insurance ($p=0.99$), or positive versus negative FH of hypertension ($p=0.99$). Thirty-seven percent (16/43) had abnormal WHtR ratio. When comparing subjects with normal versus abnormal WHtR there was no difference in mean age (11.9 ± 4.4 and $12.3 \pm 4.4y$ respectively; $p=0.76$), type of insurance ($p=0.99$) or FH of CVD

($p=0.99$). Twenty percent (8/43) had borderline high or high non-HDL-C; these participants were younger than those with normal non-HDL-C (10.0 ± 1.8 and 12.5 ± 4.6 years respectively; $p=0.02$). Abnormal non-HDL-C was not associated with insurance type ($p=0.99$) or FH of hypercholesterolemia ($p=0.43$).

Subjects or their adult caregiver rated the subject's diet from poor to excellent. Twenty-seven (63%) reported their diet as very "good" or "excellent" and 16 (37%) reported their diet as "poor" or "fair". The HTC dietician evaluated each participant as part of standard clinical care, and based on these assessments the dietician recommended limiting sugary drinks for 14 (33%), increasing fruit and vegetable intake for 20 (47%), increasing dairy intake for 5 (12%), and increasing iron rich foods for 1 (2%). The dietician typically reviews "My Plate" as an educational tool for a healthy diet.[31] Thirty-one (72%) reported having heard of "My Plate" with 18/31 (58%) having looked up information about "My Plate", and 16/18 (89%) having tried to follow the recommendations. Most (41/43, 95%) monitor what their child eats but no one reported using a food log.

More than half (24/43, 55%) report an average of 2 or more hours spent watching TV or videos per day in addition to time spent playing computer or portable video games. Participants reported participating in a variety of types of physical activities. Forty subjects (93%) reported participation in physical activities in the past 7 days, most commonly aerobics/weight training, basketball, bike riding, football, jumping rope, playground activities, running, soccer, swimming, walking and active video games. Thirty of 32 (93%) who have physical education at school participate in PE, and 22 of 24 (92%) who have recess participate in recess. One reported using a FitBit®. Subjects with normal weight had more days of >60 minutes of physical activity compared to those with overweight or obesity (5.2 ± 2.4 v. 3.8 ± 2.5 ; $p=0.07$).

Prophylaxis regimen was evaluated for subjects with severe haemophilia A without inhibitor. All 21 subjects with severe haemophilia A were prescribed standard half-life clotting factor at the time of the study. In these 21 subjects, there was no difference between subjects with normal weight (6300 units/week, range 2250-14,000) and subjects with overweight or obesity (6500 units/week, range 2250 - 14,000); $p=0.94$, but higher weight was correlated with higher total factor consumption ($cor=0.88$; $p<0.001$), up to 14,000 units/week in a patient weighing 81 kg (Figure 2). In the whole subject cohort, there was no difference in history of target joints based on weight category (30% in normal weight v. 25% in overweight or obese, $\chi^2=0.11$, $p=0.74$).

Discussion

We identified a significant proportion of children with haemophilia with overweight and obesity including 37% with BMI $\geq 85\%$ and 4.7% with severe obesity. Overweight and obesity are high in both our Hispanic and non-Hispanic populations and correlated with a FH of CVD. Additionally, 37% had abnormal WHtR consistent with higher cardiometabolic risk, 19% had borderline or high lipids, and 28% met criteria for (pre)hypertension. Factor consumption was positively correlated with weight. Overweight and obese subjects did not have a higher rate of target joints, but impact of overweight and obesity on joint disease may

have been off-set by the high rate of prophylaxis, or may manifest over longer periods of time.

Adams et al. conducted a survey of HTC practices to promote healthy weight. Ninety-eight percent indicated that the HTC should address obesity. Kahan et al. recently reviewed the prevalence and impact of obesity in people with haemophilia and possible interventions based on existing guidelines.[11] Overall, the authors recommended that the HTC play an active role in identification, management and prevention of obesity.

Height and weight should be measured at each visit to calculate BMI. Many EHRs have growth chart tools such that weight and BMI trends can be reviewed with the family. For those with BMI ≥ 95%, extended BMI growth charts may be utilized to identify if a patient is severely obese. Physicians, nurses and/or physical therapists (PTs) may discuss the impact of overweight and obesity on joint disease and collaborate with the patient to set weight-reduction and bleed-reduction goals. A recommended strategy is to help the family identify 1-3 shared goals which are specific, realistic, and measurable, to modify the goals based on known barriers and facilitators, and to devise a strategy for self-monitoring.

In this study, the dietician identified poor or fair diet for 37% of subjects and provided appropriate recommendations to improve diet intake and monitoring. If a dietician is available in the HTC comprehensive clinic, he/she may specifically review BMI with the family, assess current diet, and provide recommendations regarding healthy food and drinks, primarily water. There are a number of resources which may be shared at the clinic visits. The National Heart, Lung, and Blood Institute (NHLBI) has a program called “We Can!®” to promote childhood activity and nutrition.[32] Educational topics include calories needed each day, energy balance and BMI. There are additional resources for specific groups including Hispanics and materials are available in English and Spanish. Additionally, the US Department of Agriculture has a number of on-line resources at [chooseMyplate.gov](http://choosemyplate.gov). [31] Depending on the patient’s socioeconomic status, the family may live in a “food desert” with a lack of affordable and nutritious food, and the dietician may need to work with the family on how to find healthy options within their environment. The dietician may recommend that a patient and family participate in a behavioral intervention program focused on nutrition and physical activity.[11] Barkin et al. demonstrated that behavioral interventions which focus on skill building and optimizing use of resources results in weight reduction in already obese Hispanic preschoolers.[33] Patients may be referred to programs outside of the HTC, but as noted by Kahan et al. the comprehensive care model aligns well with behavioral intervention strategies. HTCs which are implementing telemedicine may even utilize this technology to conduct or reinforce interventions. Alternative strategies, such as Growing Right Onto Wellness (GROW), a family-centered, community-based obesity prevention program, are being tested to prevent obesity starting in young childhood.[34]

Although 93% of subjects participated in physical activity in the past 7 days, most did not meet the recommended minimum of 60 minutes per day. In addition, 56% have more than 2 hours of screen time per day. Opportunities exist within HTCs to educate about the benefits of physical activity. PTs should assess physical activity and exercise at comprehensive clinic visits and perform examinations and clinical history to determine if joint disease is limiting

physical activity. If joint disease is limiting physical activity, then medical providers may initiate or optimize prophylaxis, prescribe celecoxib to reduce pain and improve mobility, and encourage low-impact sports. Moreover, exercise plans may be developed with the patient based on clinical status, patient preferences, and patient goals. PTs may share haemophilia-specific guidelines from “Playing it Safe” to guide selection of safe sports. In addition, they may review the recommended 60 minutes of activity and review the positive impact of exercise on stress-reduction, sleep, self-image, and socialization. In addition to recommended safe activities, the PTs may review the importance of both strengthening large muscle groups including core muscles and varying activities to prevent injury. As part of the physical activity education, the HTC should identify barriers to participation including parenting practices and access to outdoor play space. The built environment is the “human made space in which people live, work, and recreate on a day-to-day basis.”[35] The availability and upkeep of the built environment may impact participation in physical activities.[36] Families may be scared to send their children out to play or may not be aware of accessible resources. The HTC may help families identify community centers or recommend home exercise videos or participating in the events sponsored by the HTC or local haemophilia association.

Since screen time often interferes with physical activity, the PT or other care provider should also assess time spent watching tv, playing video games, using hand-held devices and using computers for school or pleasure. WeCan! has excellent resources to target screen time reduction.

Standardized protocols should be utilized to measure BP in order to have accurate data. The NHLBI “A pocket guide to BP measurement in children” is a useful resource to readily identify children who meet criteria for (pre)hypertension. Patients who meet criteria for (pre)hypertension may be referred back to a primary care physician for confirmatory testing and referred for specialty evaluation and management if confirmed.[37]

The NHLBI provide guidance for lipid screening based on age and FH.[27] These guidelines, endorsed by the American Academy of Pediatrics, recommend screening once between 9-11 years and once between 17-21 years. Additional research is required to determine if lipid screening should start earlier for children with haemophilia. Lipid screening is traditionally performed at the primary care physician office, but HTCs may consider testing at the comprehensive clinic visit in conjunction with annual lab. If abnormal lipids are identified, then appropriate evaluation and management may be implemented.

Sixteen percent of participants reported a FH of CVD (myocardial infarction or stroke) in a male relative <55y and/or a female relative <65y. The role of the genetic counselor in the HTC is typically to guide genetic testing and counseling specifically related to bleeding disorders. However, the genetic counselor may also review FH of CVD to provide additional information about cardiovascular risk. Families may use on-line tools such as the CDC’s “Family Health Portrait” to gather and share FH information.

This study has several limitations. Data were collected at one HTC visit rather than over time. Since most patients are seen at least annually, future studies can be designed to include

longitudinal follow-up. This is particularly important to identify trends in BMI, and for confirming BP measurements for diagnosis of (pre)hypertension since a confirmed diagnosis is based on repeated measures and exclusion of white coat hypertension. In addition, future study should use updated guidelines on BP definitions which were published in 2017.[38] Future study should include follow-up of abnormal non-HDL-C levels plus longitudinal evaluation of lipid profiles. For both hypertension and hypercholesterolemia, the optimal means of communication between the HTC and primary care physician should be determined. In addition, smoking, physical activity and nutrition data were collected by self-report and without validated questionnaires. They provide some data on lifestyle factors which influence CVD, but future studies can include food logs to measure calorie intake and accelerometers to objectively measure physical activity. Importantly, future study should include a control group of healthy children matched for age, race, and ethnicity.

Conclusions

The analyses in this study demonstrate that cardiovascular risk factors can be identified within the context of comprehensive haemophilia care. HTC health care providers should be aware of the definitions of overweight and obesity and (pre)hypertension as well as the guidelines for managing these conditions.[27, 39] HTCs may utilize internal resources including dietitiansPT and child life specialists to recommend therapeutic lifestyle changes for a healthy diet plus avoidance of tobacco and alcohol use. In addition, if children are identified with overweight or obesity at a comprehensive clinic visit they may be referred back to the primary care physician for follow-up and/or to obesity and behavioral health programs as appropriate. PTs may perform targeted joint and muscle examinations and provide patient-specific recommendations to increase conditioning and sports participation. Children who have elevated BP may be referred back to their primary care physician for repeated BP measurements. Ultimately, resources will be required to monitor the impact of interventions on BMI, cholesterol, hypertension, and physical activity. Further study is warranted to determine if HTCs can partner with PCPs and appropriate specialists to promote cardiovascular health and risk reduction. Interventions should include shared decision-making strategies to set realistic goals and methods of self-monitoring.

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Figure 1.

Figure 2.

Table 1**HTC Medical Providers' Roles in Cardiovascular Risk Assessment and Intervention**

Provider	Evaluation	Intervention
Medical assistant	Measure height, weight, blood pressure; WHtR Draw blood for lab work	Information entered into electronic health record in real-time.
Genetic counselor	Obtain family history; identify family history of cardiovascular disease, diabetes, hypertension, and hypercholesterolemia	Construct family tree for sharing with patient and medical providers regarding CVD and risk factors.
Dietician	Assess BMI Obtain diet history	Review weight category with family using growth charts. Provide recommendations and resources to promote healthy diet. Establish goals with patient.
Physical therapist	Perform joint examination Obtain physical activity and injury history	Educate regarding conditioning and safe sports participation.
Child life specialist; social worker	Identify any developmental, social or psychological barriers to healthy lifestyle	Provide resources to overcome barriers; counseling if needed for anxiety or depression.
Nurse	Assess educational status of patient	Provide education regarding diagnosis and impact of cardiovascular risk factors on hemophilia and other health outcomes.
Physician/advanced practice provider	Obtain medical history Integrate information obtained from other providers	Optimize treatment plan to improve joint health and promote physical activity; discuss diagnoses of overweight/obesity, hypertension, and/or abnormal lipids; partner with PCP to manage cardiovascular risk factors.

Table 2

Cardiovascular risk factors

	Mean, range
BMI% for children	71, 12-99
BMI for adults	21.2, 20.7-35.4
WHtR	0.5, 0.3-0.6
Non-HDL-C	101, 57-175
Glucose	93, 74-169
	N (%)
<u>Weight category</u>	
Underweight	0
Normal weight	27 (63)
Overweight	9 (21)
Obese *	7 (16)
(Pre)hypertension in children (N=31 with BP measured in duplicate)	9 (29)
(Pre)Hypertension in adults (N=5 with BP measured in duplicate)	1 (20)
(Pre)hypertension in all subjects (N=36 with BP measured in duplicate)	10 (28)
WHtR >0.5	16 (37)
<u>Non-HDL-C</u>	
Normal	35 (81)
Borderline high	6 (14)
High	2 (5)

* Two subjects had class II obesity, BMI 120% of the 95%.