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Athletic Participation in Severe Hemophilia: Bleeding and Joint Outcomes in Children on Prophylaxis

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KEY WORDS

hemophilia, athletics, arthropathy, bleeding, injury

ABBREVIATION

HTC—Hemophilia and Thrombosis Center

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WHAT'S KNOWN ON THIS SUBJECT: Children with hemophilia are often advised to limit athletic participation to activities that do not pose major bleeding or injury risk. There is not a uniform recommendation for appropriate activities and no research comparing outcomes for high- and low-impact activities.



WHAT THIS STUDY ADDS: This study of children with hemophilia, who are at high risk for obesity, demonstrates that risks for injury and hemophilic complications are not increased among participants who are in high- versus low-impact activities and are receiving clotting factor prophylaxis.

abstract

OBJECTIVES: We sought to determine joint outcomes relative to impact level of athletic participation among school-aged children who had hemophilia and were taking prophylactic factor replacement, as well as to investigate prognostic factors for joint outcomes.

METHODS: School-aged boys with severe hemophilia A or B at a single center were included in the study. Clinical data on baseline joint status, BMI, hemophilia treatment, bleeding episodes, joint assessments, athletic participation, and injuries were retrospectively reviewed. Data on athletic participation were supplemented, when incomplete in the medical record, via structured telephone interview.

RESULTS: Among 37 children with severe hemophilia A or B receiving factor prophylaxis, 73% participated in high-impact activities, whereas 27% participated in exclusively low-impact activities. The frequency of joint hemorrhages and new injuries did not appreciably differ between high- and low-impact athletics. In most instances, children developed <1 bleed or injury per season. A new target joint developed in 1 (3%) child. Sixteen percent of children met established BMI criteria for overweight, and 3% were obese. In logistic regression analyses with adjustment for prophylaxis frequency, level of athletic participation was not a significant prognostic factor for joint hemorrhage.

CONCLUSIONS: In the setting of regular prophylaxis and adult coaching and supervision, significant bleeding complications were uncommon and level of impact of athletic participation was not a prognostic factor for joint outcomes. Athletic participation with appropriate supervision and precautions should be encouraged in children with hemophilia receiving prophylaxis, given potential health benefits in an increasingly overweight pediatric population. *Pediatrics* 2009;124:1267–1272

In recent years in the United States, the prevalence of overweight and obesity in children has increased dramatically. According to the Centers for Disease Control and Prevention, the prevalence of obesity in US children is 12.4% for ages 2 to 5 years, 17.0% for those from 6 to 11 years, and 17.6% for adolescents up to 19 years of age.¹⁻³ Childhood obesity is caused, in part, by inactive lifestyles. From 1991 to 2003, the frequency of daily participation of school-aged children in physical education significantly dropped from 42% to only 28%.² In addition, when not at school, a significant percentage of children spend most of their leisure time engaged in sedentary activities such as watching television and playing video games instead of physical activities such as running, biking, swimming, and organized sports.^{2,3}

Children with hemophilia are particularly vulnerable to becoming overweight or obese as a result of the recommendation or perception that these children should limit their physical activity to avoid traumatic bleeding events. Children with hemophilia tend to be less physically fit than normal children. Engelbert et al⁴ reported that children with hemophilia have decreased aerobic capacity than normal children. Also, Hassan et al⁵ reported that children with hemophilia have a decreased achieved distance while participating in the 6-minute walk test. Although there seems to be considerable heterogeneity with regard to specific restrictions advised by pediatric hemophilia practitioners, children with severe hemophilia are generally strongly cautioned against participation in American football, rugby, lacrosse, boxing, basketball, soccer, wrestling, and ice hockey. In many instances, even limited contact sports such as baseball and volleyball are discouraged.⁶ It is hence not surprising that children with hemophilia have

even higher rates of overweight than observed in the overall pediatric population in the United States, at 20.6% among children with hemophilia between 2 and 12 years of age and 20.8% in affected adolescents.⁷ In addition to the usual risks for type 2 diabetes, low bone density, metabolic syndrome, and depression in obesity, obese patients with hemophilia are at increased risk for the development of hemophilic arthropathy.⁸⁻¹¹

With the increased use of prophylactic clotting factor replacement regimens in children with hemophilia, there has been an opportunity to consider greater participation in physical activities, with the potential to decrease the risk for development of overweight and obesity in these children. To date, however, data on the degree and safety of athletic participation among children with hemophilia in relation to type of athletic participation and clotting factor replacement regimen remain highly limited.¹² Accordingly, the purpose of this study was to describe participation in team sports and organized physical activities, rates of overweight and obesity, and clinical joint outcomes (specifically, the development of target joints) among children who have severe hemophilia and principally are maintained on prophylactic factor replacement and to compare outcomes with respect to type of athletic participation and preparticipation baseline joint status. Data were retrospectively reviewed from a comprehensive cohort of school-aged boys who have severe factor VIII or IX deficiencies (hemophilia A or B, respectively) and receive care from the Mountain States Regional Hemophilia and Thrombosis Center (HTC) at the University of Colorado Denver. Our HTC cares for nearly all children with severe hemophilia in the northern Rocky Mountain States of Colorado, Wyoming, and Montana and so is representative of

children with severe hemophilia in this large geographic region.

METHODS

Population

Eligibility criteria for the study included active clinical status at the Mountain States Regional HTC at the University of Colorado Denver, male gender, deficiency of factor VIII or IX with activity <2%, student status from first through 12th grades between January 2005 and June 2007, and an age of 5 to 20 years during the study period. School age was chosen because children are most likely to participate in organized sports during these years of childhood. Of 50 eligible individuals, 10 were excluded because of lack of available information on athletic participation. Data on bleeding and clinical joint outcomes were uniformly available (see "Data Collection"). Three additional patients were excluded because of lack of adherence to recommended prophylactic regimen. The study was approved by the Colorado Multiple Institutional Review Board (COMIRB #05-1035), with waiver of consent granted for retrospective analysis of clinically derived data and oral consent/assent obtained for telephone interview of details on athletic participation.

Data Collection

Data extracted from the patient's medical record included factor deficiency type and baseline level, age, race, factor prophylaxis regimen (dosage, frequency) and episodic treatments for hemorrhage, BMI, number and sites of target joints both before and after the analyzed year of athletic participation (defined as the 12-month period before last comprehensive clinic visit), number of joint hemorrhages, other bleeding episodes and injuries sustained during this period, seasons of athletic participation (as defined by the calendar: winter, spring, summer,

fall, with minimum duration of 8 weeks), and specific types of athletic activities. Data were supplemented, when incomplete in the medical record, via structured telephone interview, which collected data on types of athletic activity, prophylaxis use, and injuries related to athletic participation. BMI percentiles were calculated from BMI raw data according to Centers for Disease Control and Prevention guidelines.¹³

Athletic activities were defined as those that were organized and supervised by adults, occurred at least twice per week, and consisting of a minimum of one half hour of physical activity for each practice or game. Athletic activities were classified by frequency/likelihood of impact, as determined by the US National Hemophilia Foundation¹⁴ and shown in Table 1. Specifi-

cally, activities of National Hemophilia Foundation category 2 and higher were classified as “high impact,” whereas those rated category 1 or 1.5 were classified as “low impact.” In cases in which a child met participation criteria for >1 athletic activity for a given season, each athletic activity was counted separately, such that some children had >4 seasons of participation in 1 year.

A target joint was defined as 1 in which all of the following 3 criteria were met: (1) synovitis present on clinical examination (as determined by thickened or boggy synovium); (2) range of motion persistently impaired on serial evaluation in the nonbleeding state over the course of a minimum of 6 months; and (3) history of recurrent hemarthrosis in the affected joint. These data were collected by review of the medical record, with data on the first 2 criteria extracted from clinical examination notes of a single physical therapist with extensive experience in hemophilic arthropathy.

Statistical Analyses

Descriptive analyses involved calculation of median values and observed ranges for continuously distributed data and of proportions (ie, frequencies) or percentages for categorical data. The distributions of 2 independent groups of continuous data were compared by Mann-Whitney *U* test, and 2-group proportions were compared using the χ^2 test or Fisher’s exact test, as appropriate. Univariate logistic regression was used to assess the relationship between putative risk factors and outcomes, and multiple logistic regression was used to ascertain adjusted risk for outcome among putative risk factors that were either hypothesized a priori to be of clinical significance or shown to be of potential statistical significance in the univariate analyses (using a threshold of

$P \leq .10$ and limited to 2 covariates given sample size considerations). Alpha was otherwise set at .05 for all hypothesis testing.

RESULTS

Four (11%) of 37 children studied had severe inherited factor IX deficiency, whereas the remaining 89% had inherited factor VIII deficiency. Thirty-six children had $\leq 1\%$ baseline clotting factor activity, and 1 child had 2%. Seven (19%) had a history of factor VIII or factor IX inhibitory antibodies, all of which were successfully tolerized. All participants used a prophylactic factor replacement regimen, with 92% receiving “routine” prophylaxis (defined as at least twice weekly). As shown in Table 2, the study population exhibited a broad age distribution, and 19% were overweight or obese according to Centers for Disease Control and Prevention norms for BMI percentile.

Table 3 presents data on bleeding frequency and development of target joints in relationship to athletic participation. The majority (73%) of the patients participated in high-impact (with/without concomitant low-impact) athletic activities, whereas 27% participated in exclusively low-impact activities. The prevalence of ≥ 1 preexisting target joint was similar between high-impact and low-impact activity groups

TABLE 1 Classification of Athletic Activities by Frequency/Likelihood of Impact

High Impact	Low Impact
Basketball (28)	Circuit weight training (7)
Baseball (5)	Cross country skiing (2)
Bowling (2)	Cycling (46) ^b
Flag football (3)	Frisbee golf (12)
Football (American) (14) ^a	Golf (17)
Gymnastics (1)	Hiking (20)
Hockey (4) ^a	Marching band (2)
Karate (8)	Recess/PE (19)
Kayaking (2)	Swimming (36)
Mountain biking (2)	Tee ball (3)
Rodeo (3)	Walking (16)
Rollerblading (11) ^b	
Running/jogging (11)	
Scooter (20) ^b	
Skateboarding (12) ^b	
Skiing (4) ^b	
Snowboarding (1)	
Soccer (16) ^c	
Softball (1)	
Tae kwondo (4)	
Tennis (11)	
Track and field (1)	
Trampoline (1)	

Adapted from US National Hemophilia Foundation criteria.¹⁶ Total number of seasons of participation for the study population are given in parentheses after each activity.

^a Competitive participation was against medical advice.

^b Routine helmet use was advised.

^c Contact of the soccer ball with one’s head, “header,” was discouraged.

TABLE 2 Participant Demographics on Age, Race, and BMI

Demographic	% (n)
Age, y	
6–10	41 (15)
10–15	27 (10)
15–21	32 (12)
Race	
White	92 (34)
Hispanic	8 (3)
Black	0 (0)
BMI percentile	
<84th	81 (30)
85th–94th	16 (6)
≥ 95 th	3 (1)

BMI is calculated according to Centers for Disease Control and Prevention guidelines.¹⁵

TABLE 3 Athletic Participation, Disease Characteristics, and Outcomes by Impact Group

Parameter	High Impact ^a	Low Impact	<i>P</i>
No. of subjects	27	10	—
No. of seasons of participation	299	46	—
Met criteria for participation in ≥2 athletic activities in a given season, <i>n</i> (%)	20 (74)	5 (50)	.24
Used prophylaxis ≥2 times per week, <i>n</i> (%)	26 (96)	9 (90)	.47
≥1 target joint before participation, <i>n</i> (%)	6 (16.2)	4 (10.8)	.41
No. of joint hemorrhages per each season of participation, median (range)	0.05 (0.00–4.00)	0.50 (0.00–2.00)	.06
No. of injuries per each season of participation, median (range)	0.00 (0.00–1.00)	0.00 (0.00–0.25)	.25
Developed ≥1 new target joint during participation, <i>n</i> (%)	1 (4)	0 (0)	.998

^a With or without additional low-impact activities.

(16.2% vs 10.8%, respectively; *P* = .41). There was a median of 0.00 (range: 0.00–1.00) injuries per season of high-impact (with or without concomitant low-impact) athletic participation compared with 0.00 (range: 0.00–0.25) injuries per season of only low-impact activity. The median (range) of acute joint hemorrhages per season was 0.05 (range: 0.00–4.00) for high-impact athletics compared with 0.50 (range: 0.00–2.00) per season of low-impact activity. As is consistent with these averages, most children developed <1 bleed or injury per season of athletic participation. Only 1 child developed a new target joint during athletic participation. This was a 15-year-old who had normal BMI and received prophylaxis every other day and participated in golfing, swimming, hiking, and soccer for an average of 12 hours per week. He developed 7 joint hemorrhages as a result of trauma during soccer. Among 3 children who did not adhere to a prophylactic regimen and hence were not included in the analysis, 2 who participated in high-impact activities developed 0.23 and 1.40 hemorrhages per season, whereas the third child (who participated in low-impact activities only) had no joint hemorrhages.

The results of univariate analyses of putative predictors of frequent joint hemorrhage (defined as >1 joint hemorrhage per season, on average) are

shown in Table 4. None of the factors examined, including age, frequency of prophylaxis, number of injuries, and high- versus low-impact athletic participation, was significantly associated with the occurrence of frequent joint hemorrhage. To exclude negative confounding on impact level of athletic participation by frequency of prophylaxis, we performed multivariate analysis; after adjustment for frequency of prophylaxis, there remained no significant association between high-impact activity and occurrence of frequent joint bleeding (odds ratio: 0.32 [95% confidence interval: 0.04–2.70]; *P* = .30).

DISCUSSION

The purpose of this study was to investigate risk for hemorrhage and injury associated with athletic activity among school-aged children with hemophilia, according to frequency/likelihood of impact. Its findings demonstrate that, in the context of regular prophylaxis as well as adult coaching and supervision, significant bleeding complica-

tions were uncommon and frequency/likelihood of impact of athletic participation was not a prognostic factor for joint outcomes. Given the obesity epidemic that is particularly evident in individuals with hemophilia in the United States, these findings of acceptable safety of supervised athletic participation in children who have hemophilia and are on prophylaxis are of great importance. Furthermore, although a recent Dutch study did not demonstrate a relationship between physical activity and BMI among children with hemophilia,⁴ the myriad other benefits of physical activity—including improved strength and coordination, enhanced insulin sensitivity, vascular health, socialization, and self-esteem^{6,15,16}—give optimism that supervised athletic participation of children who have hemophilia and are on prophylaxis may have lasting favorable effects on health status in this at-risk population that carry into adulthood.

It is noteworthy that 10 (27%) of the school-aged children in this study had at least 1 target joint before attempting participation in organized sports and activities, despite use of aggressive treatment schedules and prophylaxis, and did not appreciably differ between high- and low-impact groups. This high prevalence of previous target joint underscores findings of the Joint Outcome Study, which suggested that chronic arthropathy is initiated very early in the preschool years.¹⁷ Although many of the joint hemorrhages began before participation in physical

TABLE 4 Univariate Findings for Putative Predictors for Bleeding Outcome (≥1 Bleed per Season)

Covariate	Odds Ratio	95% Confidence Interval	<i>P</i>
High vs low impact	0.32	0.04–2.65	.29
Age (per year increase)	1.04	0.81–1.32	.78
No. of injuries per season (per increase of 1), average	7.02	0.30–167	.23
No. of factor replacement doses per week, as part of routine prophylactic regimen (per increase of 1)	1.07	0.42–2.73	.89

activities, some boys experienced limited participation because of the injury. Only 1 child developed a new target joint while participating in contact sports (for details, see “Results”).

Until recent decades, individuals with hemophilia were kept as inactive as possible to prevent bleeding episodes, and this paradigm still persists, particularly among older generations of patients with hemophilia. On the 1 hand, progressive joint destruction related to repeated hemarthroses accounts for significant morbidity and cost in hemophilia, and there is a concern that athletic activity may exacerbate the risk for arthropathy. On the other hand, morbidity of arthropathy can be reduced by regular exercise, which builds muscle strength, increases joint motion, reduces pain, and reduces the frequency of joint hemorrhage.^{15,16,18} During the late 1970s, participation in physical activities became more favored. Home treatment programs were instituted and allowed for more freedom to participate in activities. Even athletics became accepted, although a consensus of appropriate sports participation in hemophilia has never been reached.¹⁹ In 2000, a Dutch survey of 293 patients with hemophilia showed that many participate in regular physical activity, but a large proportion of these individuals lament not being able to play sports such as soccer.²⁰ Subsequently, a survey among 71 individuals with hemophilia confirmed that these patients express considerable disappointment concerning restriction against high-risk, high-impact physical activities, particularly American football.¹⁸ von Mackensen et al²¹ demonstrated that athletic participation of individuals with hemophilia improves quality of life, causing optimism that if (as suggested by this work) such participation can be safely achieved from a young age, then long-term benefits will

be realized in these individuals with chronic disease.

Although risk for injury cannot be eliminated, protective measures can be taken to mitigate the risk for injury that is associated with many types of athletic participation for individuals with hemophilia. These protective measures include the diligent use of helmets, facemasks, shin guards, kneepads, wrist/forearm guards, and other equipment that is appropriate to the type of athletic activity and mechanisms of injury. Proper footwear of good quality and fit is also very important to prevent injury.¹⁸ In addition, the risk for serious bleeding and number of hemorrhages can be radically decreased with the use of prophylaxis with factor VIII and IX concentrates.^{5,12,15,16} Nevertheless, the limit to which prophylaxis during seasonal athletic participation can prevent joint hemorrhage or overuse remains unknown, and patients with hemophilia still tend to be less physically fit than children without hemophilia,¹⁶ as exemplified by the high prevalence of overweight/obesity (19%) in our study population and similar to national rates²² despite the likelihood of a selection bias toward more athletically active individuals.

A few limitations of this study are apparent. Foremost among these are (1) the relatively small sample size, such that estimates of outcomes may be imprecise (as exemplified by 1 of the odds ratio confidence intervals in Table 4), and (2) the retrospective nature of the study, which cannot control for selection biases. In addition, there is potential for selection bias in this non-randomized study. For example, although children who participated in high-impact activities developed fewer hemarthroses per season than those who engaged in low-impact activities (median: 0.05 [range: 0.00–4.00] vs 0.50 [range: 0.00–2.00], respectively;

$P = .06$), it is possible that the latter group was more likely to have experienced frequent bleeding events before participation and therefore did not subsequently engage in high-impact activities during the study period. If this were the case, then it could have led to an underestimation of the risk for joint hemorrhage associated with high-impact athletic activities. Similarly, it is possible that high-impact athletic participation may identify children with a greater degree of joint fitness, as a result of either constitution or previous exercise behavior/ regimen. An additional limitation is the lack of a concomitant comparison group consisting of children who had hemophilia and received prophylaxis but did not participate in athletic activities; rather, we compared participants in high-impact and low-impact athletic activities, among children who had hemophilia and were on prophylaxis. Furthermore, this study did not address habitual physical activities outside of supervised athletic participation that could nevertheless have contributed to in-season joint hemorrhage and other injury. Last, it is possible that report of physical activity in studies such as this may not accurately reflect actual participation, as recently demonstrated by Engelbert et al⁵ for self-report. For this reason and particularly given the difficulty of assessing reliability of self-report in pediatrics, this study used parental report of child athletic participation.

It must be also emphasized that, because this study describes athletic participation that has occurred in the context of in-depth discussion involving parents and providers, fitness preparation, and reasoned decision-making, its findings should not be extended to children who have hemophilia and do not receive prophylaxis and for whom appropriate precau-

tions and supervision cannot be reasonably ensured. As was the case for patients in this study, adult supervision is important for children who have hemophilia and engage in athletic activities, to lessen the risk of injury and to provide an environment for rapid attention to injuries. Our HTC discourages children with severe hemophilia from participation in highly competitive contact sports, such as ice hockey and American football. Instead, moderate- to high-intensity low-impact athletic activities are encouraged, with consideration of higher impact activity in circumstances in which appropriate precautions (including prophylaxis and protective gear) and supervision

are in place. Future research should seek to compare prospectively among children who have hemophilia and receive factor prophylaxis the risks for clinically significant hemorrhage, injury, and development of new target joints between high- and low-impact athletic participants, as well as to compare these outcomes for patients who do versus do not participate in athletics.

CONCLUSIONS

Regular participation in high-impact athletic activity, supported by adult coaching and supervision, did not seem to increase the risk for development of joint hemorrhages or new

target joints in this population of school-aged children who had severe hemophilia and received routine prophylactic factor replacement. These findings have important implications in the context of recommendations for appropriate physical activities for children who have hemophilia and receive prophylaxis.

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