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Original Article

Evaluation of unfavorable cardiovascular and metabolic risk factors in children and young adults with haemophilia

Running title:Metabolic risk in haemophilia patients

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Abstract

Objective: Increased risk of unfavorable cardiovascular risk factors has been defined in the aging population of haemophilia however they were less investigated in young patients. The purpose of this study was to assess obesity, hypertension, metabolic variables, insulin resistance and metabolic syndrome in young patients with haemophilia (PwH).

Methods: Forty-eight haemophilia A and B patients and 35 age and sex matched healthy controls were included. Anthropometric measurements, blood pressure, fasting glucose and insulin levels, serum lipids and dietary intakes were evaluated. According to the criteria of International Diabetes Federation for pediatric and adult age groups, metabolic syndrome was defined.

Results: The mean age of PwH was 21 years (range, 6–40 years). Forty-six percent of the PwH ≥18 years-old were obese/overweight vs none <18 years old. Obesity was more prevalent in PwH with arthropathy (p=0.017). Seven percent of the PwH ≥10 and <18 years-old and 25% of ≥18 years old had metabolic syndrome. There was no difference in metabolic syndrome between PwH and controls >10 years-old (19.5% vs 10% respectively, p=0.34). Fifty percent of the PwH ≥18 years-old had elevated blood pressure or hypertension. Fasting blood glucose levels of PwH were higher compared to controls (p=0.02).

Conclusions: Our study showed that obesity, hypertension and metabolic syndrome are frequent problems especially in PwH with arthropathy. Early prevention and management of overweight, obesity, and their sequelae must be addressed in clinical practice in order to maximize the overall health of the haemophilia population.

Keywords: haemophilia, obesity, hypertension, metabolic syndrome

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What is already known on this topic?

Patients with haemophilia were reported to have a reduced cardiovascular mortality due to a protective effect of having lifelong deficiency of factor VIII or IX, however, there is an increasing evidence that this condition does not appear to be preventive.

What this study adds?

Cardiovascular and metabolic risk factors like overweight/obesity, elevated blood pressure/hypertension, prediabetes/diabetes and dyslipidaemia can be detected from early ages in patients with haemophilia.

Introduction

In recent years, cardiovascular and metabolic risk has been defined in the aging population of haemophilia however they were less investigated in young patients with haemophilia (PwH) (1, 2). With increasing life expectancy of heamophilia patients, mortality and risk determination due to cardiovascular diseases has become an issue. While cardiovascular mortality was reported to be reduced in PwH due to a protective effect of having lifelong deficiency of factor VIII or IX (3, 4), there is an increasing evidence that this condition does not appear to prevent cardiovascular disease (5). Furthermore, Sun et al. recently demonstrated a significantly inferior microvascular endothelial function in haemophilia patients compared to healthy controls (2). Besides atherosclerosis, which is the first origin of cardiovascular disease beginning in childhood and adolescence, other established risk factors including obesity, hypertension (HT), dyslipidaemia, diabetes mellitus (DM) and family history for cardiovascular diseases are also known to play crucial role in mortality and morbidity of these patients (1). Recently, Limjoco et al. studied these risk factors in a young haemophilic population and identified modifiable risk factors for cardiovascular diseases (6).

Severe obesity in children and young adults was reported to be associated with an increased prevalence of cardiometabolic risk factors, particularly among boys and young men (7). Since haemophilia is characterized by progressive arthropathy, functional impairment and chronic joint pain, barriers towards engagement in physical activity may limit an individual's ability to maintain a healthy weight (8, 9). Therefore, obesity becomes an issue in PwH as well as aggravating effect of obesity itself on joint health (9).

Prevalence of HT in adults with moderate to severe haemophilia was found to be increased (10). Alperstein et al. reported an increased prevalence of HT in a hospitalized pediatric hemophilia population compared to pediatric male population, although not statistically significant (1.52% vs. 1.22%, p=0.26) (11). Recently, Limjoco et al. reported high rates of overweight and obesity, (pre)hypertension and abnormal lipids in children and young adults with haemophilia (6).

The primary aim of this study was to assess obesity, hypertension, metabolic variables, insulin resistance and metabolic syndrome in children and young adults with haemophilia. We hypothesized that increased risk for cardiometabolic diseases could start from younger ages in PwH.

Patients and Methods

Study design

This cross-sectional study was conducted in Istanbul University, Department of Pediatric Hematology and Oncology of Cerrahpasa Medical Faculty and Oncology Institute, from February 2010 to November 2010. Forty-eight PwH and 35 age and sex matched healthy controls were included. The study was approved by Istanbul Clinical Research Ethics Committee No:1 (No: C-009/2010). Informed consent was obtained from parents for age of 6-12 years, from both subjects and parents for age of 12-18 years, and from subjects for age of older than 18 years according to the Declaration of Helsinki.

Patients

During regular outpatient clinic visit, consecutive patients were asked to participate the study. Forty-eight male patients, aged 6-40 years, with hemophilia A and B were

included in the study irrespective of the severity of their disease. Patients with a coagulation factor level of less than 1% of normal were classified as severe, 1-5% of normal were classified as moderate, and 5-40% of normal were classified as mild (12). The past medical records of the participants who approved, were examined. Age of diagnosis, annual spontaneous or traumatic bleeding rate, annual factor consumption, presence of chronic arthropathy, whether physiotherapy or home exercise is applied, sports and dietary habits, presence of other systemic diseases other than complications of haemophilia such as carrier status of HBV, HCV, HIV or presence of inhibitor were recorded. Data elements also included self-reported family history for diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD) (male <55 years, female <65 years) and dyslipidaemia. The annual factor consumption per kilogram of body weight (in international units/kg) was determined for each patient from the 12-month period prior to enrollment. Factors used for elective interventional and surgical procedures were not taken into account. Patients with a history of known cardiovascular disease were not included in the study. Blood samples were taken as part of the clinical follow-up of patients.

Control group

The control group was consisted of age-matched 35 random male subjects, who were admitted to general children's and general internal medicine outpatient clinics, without a history of congenital or acquired bleeding disorder, cardiovascular disease or chronic disease. Age, sports and dietary habits, self-reported family history for DM, HT, CAD (male <55 years, female <65 years) and dyslipidaemia were recorded.

Assessment of exercise and nutritional status: In the study and control groups, for individuals under 18 years, at least 3 days and 30 minutes regular exercise a week; for individuals aged 18 years and older, at least 2 days and 30 minutes a week were classified as those who perform regular exercise and others were classified as non-performing.

Dietary intake was evaluated by an experienced dietitian with the 3-day food record. Subjects were also given detailed oral and written instructions regarding the completion of a 3-day food record, consisting of 2 midweek days and 1 weekend day. In order to determine the amounts of consumed foods correctly, information was given about measuring cups such as water glass, tea glass, teaspoon, tablespoon, serving spoon and bowl. Energy and nutrient intake was analyzed by a computerized food analysis program adapted to our country (BeBis4 software program, Turkish version, Stuttgart, Germany) and evaluated according to the recommendations of the Turkish Dietary Guidelines. Percentage of sixty-six or less of the references was used as the criteria for inadequate nutritional intake (13). Over 300 mg daily cholesterol intake was considered as upper intake.

Anthropometric measurements: All participants have undergone a complete physical examination including standardized measurement of weight, height and waist circumference, in-duplicate. BMI SDS were calculated for children <18 years, using Turkish national reference data (14). Subjects with BMI ≥95% were defined as obese and with BMI ≥85% as overweight. BMI was calculated for adults and classified as underweight, normal weight, overweight or obese based on WHO classification (15). Waist circumference was evaluated according to NHANES III reference limits

appropriate for age and sex (16). Blood pressure (BP) was interpreted according to three consecutive measurements. In children <13 years of age, hypertension was defined as systolic or diastolic BP ≥95th percentile on the new sex, age, and height tables (17). For adolescents ≥13 years and adults, hypertension was defined as systolic and/or diastolic BP ≥140/90mmHg and elevated BP was defined as systolic and/or diastolic BP ≥120/80mmHg according to 2017 guidelines (17, 18).

Biochemical assessment: In all subjects, fasting glucose, insulin, total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride and uric acid levels were evaluated. Hyperglycemia was defined as a fasting glucose level of ≥100 mg/dl. Insulin resistance was estimated by HOMA-IR (Homeostasis model assessment of insulin resistance) formula, fasting serum insulin (μU/ml) x fasting plasma glucose (mmol/l)/22.5, as described by Matthews et al (19). For adults, HOMA-IR lower than 2.7 was considered to be normal, while above 2.7 was considered as insulin resistance (20). For children and adolescents, insulin resistance was diagnosed with HOMA-IR values higher than ≥97th percentile for age and sex (21). According to the criteria of International Diabetes Federation, metabolic syndrome was defined for children above 10 years (22) and adults (23).

Statistical Analysis

The data was statistically analyzed using computer software SPSS version 18.0 (Chicago, IL, USA). For baseline characteristics, descriptive statistical analysis was performed using percentages for categorical variables, mean±standard deviation (SD) for normally distributed continuous variables, median and interquartile range for skewed

continuous variables. Differences between two groups were tested using two-sample t test or Mann-Whitney U test for continuous variables and chi-square test or Fisher's exact test for categorical variables, as appropriate. Results were evaluated at 95% confidence interval and a *p* value less than 0.05 was considered statistically significant.

Results

A total of 48 haemophilia patients and 35 age and sex matched healthy controls were included. The demographic characteristics between the groups were similar. The mean age of haemophilia group and control group was 20.5±9.1 years and 21.4±9.0 years, respectively (p=0.65). There was no difference in weight, height, BMI and waist circumference of PwH and controls (Table 1). Median age at diagnosis was 11 (1-129) months among haemophilia patients. Sixty-six percent of haemophilia A and 50% of haemophilia B patients were on prophylaxis, others were on demand therapy. Median annual factor consumption for haemophilia A and B patients were 1846 IU/kg (0-3600) and 840 IU/kg (318-2434), respectively. The frequency of PwH with inhibitors was 8.3% and they were mainly of severe type haemophilia A. Artropathy was present in 61.9% of haemophilia A and 66.7% of haemophilia B patients and mainly in patients over 18 years old, and of severe type. Only few of these were getting physiotherapy (5% of haemophilia A and none of the haemophilia B patients).

According to food consumption records, the intake amounts for energy, protein, fat, carbohydrate, fiber and cholesterol determined by age and sex were compared among haemophilia and control groups (Table 1). Energy intake was higher in control group (p=0.02), but other nutrient intakes were similar. Subjects were having similar amounts of

regular exercise in both groups. Haemophilia patients with normal weight were having less regular exercise compared to those with overweight or obesity, 14.3% and 23.1%, respectively (p=0.66).

Biochemical assessment of all participants is shown in Table 2. Fasting blood glucose levels of PwH were higher compared to controls (p=0.02). On the other hand, serum levels of triglyceride were significantly lower in haemophilia group (p=0.008). Total cholesterol levels were somewhat lower in haemophilia group, but did not reach statistical significance. Forty-six percent of PwH over 18 years old were overweight/obese, however none of the patients younger than 18 years old was. Obesity was more prevalent in PwH with arthropathy (p=0.017). When metabolic syndrome was assessed in different age groups, none of the patients <10 years old had metabolic syndrome, 7.7% of patients between 10 and 18 years old and 25% of PwH between 18 and 40 years old had metabolic syndrome. Fifty percent of PwH >18 years old had elevated BP/hypertension vs 23% of ≤18 years old (p=0.03). The frequency of elevated BP/HT remained higher in all haemophilia cohort, although not statistically significant, when compared to controls (35.5% vs. 28.6%, p=0.51). When PwH and controls over 10 years old were compared for metabolic syndrome, no significant statistical difference was found (19.5% and 10% respectively, p=0.34). Comparison of metabolic variables among haemophilia patients and controls are shown in Table 3. In addition, the Spearman correlation analysis did not show any correlation between annual factor consumption and any of the metabolic parameters in PwH.

Discussion

Our study showed that obesity, hypertension and metabolic syndrome are frequent problems especially in PwH over 18 years old with arthropathy. Early prevention and management of overweight, obesity, and their sequelae must be addressed in clinical practice in order to maximize the overall health of the haemophilia population. Therefore, assessment of cardiovascular and metabolic risk factors, beginning from early childhood is crucial for this specific patient population.

The relationship between haemophilia and cardiovascular risk is not yet well understood (24). Haemophilia has traditionally been regarded as a protective state for thrombosis due to hypocoagulability in several cohort studies (3, 4). On the other hand, some studies indicated a potential negative effect of haemophilia (25), while some found no substantial effect (26). Because of the important role of obesity as a risk factor for cardiovascular disease, impact of obesity in haemophilia population was reviewed (9). The authors recommended implementing general guidelines for weight management in the context of the haemophilia care team.

Overall life expectancy and quality of life among people with haemophilia have increased in recent years, primarily because of the reduction in infections by viral diseases and the advances in factor replacement therapy. However, older patients who had been treated with on demand therapy still have a variety of orthopedic problems. In our study, overweight and obesity were frequent in subjects over 18 years old with target joints. This finding may be attributed to reduced engagement in physical activity to prevent bleeds and preserve joint health. Besides, target joints progressively leading to pain, restriction of movement and potentially irreversible structural damage that form the hallmark of

haemophilic arthropathy may also reduce physical activity and result in weight gain. Furthermore, the reduced mobility and loss of muscle function leads to subsequent muscle atrophy, which may in turn increase the risk of weight gain (27). On the other hand, in a Dutch haemophilia cohort, it has been reported that overweight and obesity itself increased the number of joint bleeds and reduced function of the lower limbs (28). Recently, Limjoco et al. reported high rates of overweight and obesity in a relatively younger haemophilia cohort (mean 12 years, range 5-20 years). However, authors identified no difference in target joints based on weight category (30% in normal weight vs. 25% in overweight or obese, p=0.74). They suggested that impact of overweight and obesity on joint disease may have been offset by the high rate of prophylaxis or still it may manifest over longer periods of time in follow-up (6).

Another outcome of increase in life expectancy of PwH is experiencing cardiovascular complications of older age. HT is one of the most relevant cardiovascular risk factors that has gained attention, since it is also a major risk factor for intracranial hemorrhage in PwH (29). Although there are some studies documenting an increased rate of HT in adults with hemophilia (10, 30), little is currently known about the prevalence and severity. Increased prevalence may be the result of the regular visits of these patients to clinics and getting the diagnosis of HT or due to intraparenchymal hemorrhages in the kidneys (31). Recently, slightly increased prevalence of HT was reported in a pediatric hemophilia population, thus raising awareness for assessment of blood pressure also in young PwH (11). Our study showed that the prevalence of elevated BP and HT was higher especially in PwH over 18 years old, although not statistically significant.

Nevertheless, the clinical difference noted in the hemophilic group demonstrates a trend and warrants further study. Blood pressure measurements should be a part of standard care in PwH early in their life, with the possible consideration of early intervention.

Although none of the patients had DM in our cohort, higher levels of fasting blood glucose which predicts diabetes was observed. Same subpopulation was affected by both increased blood glucose levels and obesity, as expected. Biere-Rafi et al. identified higher number of PwH with hyperglycemia than controls, but differently in an older cohort of mean age 47 (1). Alperstein et al. reported a lower prevalence of DM in pediatric haemophilia population, contrarily (11). While prevalence of dyslipidaemia was similar among haemophilics and control group, mean serum levels of triglyceride were significantly lower in our haemophilia group. Additional research is required to determine whether blood glucose and lipid screening should start earlier for children with haemophilia.

The frequency of metabolic syndrome in our pediatric PwH (aged 10-18 years) was higher than Turkish data (schoolchildren, aged 10-19 years) according to the criteria of IDF (7.7% vs 2.3%, respectively (32). However, for the adult age group of PwH, frequency of metabolic syndrome was comparable with the previous public data (25% in PwH vs. 31.2% in Turkish adult males) (33).

Study Limitations

This study has several limitations. Our haemophilia patients were very heterogeneous with a wide age range (child, adolescent and adults), both types of

haemophilia A and B, and all types of severity. Therefore, most of subgroup analysis couldn't be performed and relation of cardiometabolic risk factors to severity of disease could not be revealed. Further studies should include a more representative study population and control group of all ages, types and severity of haemophilia. Furthermore, data were collected from the past medical records and at only one outpatient clinic visit rather than over time. Repeated blood pressure measurements on different days are needed for the accurate classification and diagnosis of HT, and the exclusion of white coat HT. Although we couldn't manage to have measurements on different days, we referred all subjects with once detected elevated BP/HT for further assessment. Another limitation of our study was that, we did not have information about smoking and alcohol uses, which have an impact on cardiovascular and metabolic parameters. Furthermore, we asked about subject's routine exercise status, but not questioned about how many hours they spend on watching TV, playing computer and mobile phone, which are risk factors for the development of obesity. Further studies should be designed to follow-up patients longitudinally.

Conclusion

In conclusion, cardiovascular and metabolic risk factors like overweight/obesity, elevated BP/HT, prediabetes/DM and dyslipidaemia can be detected from very early ages in PwH. Since adult patients do not have a lower prevalence of cardiovascular risk factors as historically known, screening from the early ages and considering early intervention and management might help to ameliorate general health status of this specific patient group and reduce morbidity.

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Ethics

Ethics Committee Approval: The study was approved by Istanbul Clinical Research Ethics Committee No:1 (No: C-009/2010).

Informed consent: Informed consent was obtained from parents for age of 6-12 years, from both subjects and parents for age of 12-18 years, and from subjects for age of older than 18 years according to the Declaration of Helsinki.

Authorship Contributions

Concept: Melek Yildiz, Bulent Zulfikar, Hasan Onal, Data Collection or Processing: Melek Yildiz, Nihal Ozdemir, Beyza Eliuz Tipici, Bulent Zulfikar, Analysis or Interpretation: Melek Yildiz, Nihal Ozdemir, Beyza Eliuz Tipici, Hasan Onal, Literature Search: Melek Yildiz, Nihal Ozdemir, Basak Koc, Writing: Melek Yildiz, Basak Koc, Nihal Ozdemir

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Table 1. Clinical and anthropometrical data for PwH and healthy controls.

	Haemophilia patients (n=48) (%)	**Controls (n=35) (%)**	***p* value**
Age groups			0.99
6 – 9.9 years	7 (14.6%)	5 (14.3%)	
10 – 17.9 years	13 (27.1%)	9 (25.7%)	
18 – 40 years	28 (58.3%)	21 (60.0%)	
For children	**(n=20)**	**(n=14)**	
Weight (SDS)	0.1 (-2.7 – 2.4)	-0.1 (-2.7 – 1.6)	0.29
Height (SDS)	0.1 (-2.1 – 2.4)	-0.1 (-1.5 – 1.3)	0.56
BMI (SDS)	-0.1 (-2.9 – 1.8)	-0.6 (-2.7 – 1.4)	0.28
For adults	**(n=28)**	**(n=21)**	
Weight (kg)	74 (52 – 95)	81 (55 – 105)	0.06
Height (cm)	175 (166 – 187)	175 (158 – 190)	0.63
BMI (kg/m^2)	24.0 (17.9 – 30.0)	25.1 (18.8 – 30.0)	0.10
Waist circumference (cm)	89 (70 – 111)	92 (71 – 106)	0.27
Regular exercise	8 (16.7%)	6 (17.1%)	0.95
Energy and nutrient intakes			
Energy (Kcal)	1318 (496 – 2530)	1572 (900 – 2573)	0.02
Protein (%)	15.9 ± 2.8	16.7 ± 3.3	0.29
Lipid (%)	36.1 ± 5.2	35.4 ± 3.7	0.51
Carbohydrate (%)	48.1 ± 6.3	47.8 ± 4.5	0.80

Fiber (gr)	12.7 (5.9 – 27.0)	15.2 (6.5 – 23.5)	0.06
Cholesterol (mg)	176.0 (18.7 – 378.7)	178.0 (81.3 – 365.7)	0.18
Haemophilia type			
A (%)	42 (87.5%)	N/A	N/A
B (%)	6 (12.5%)	N/A	N/A
Haemophilia severity			
Mild	4 (8.3%)	N/A	N/A
Moderate	2 (4.2%)	N/A	N/A
Severe	42 (87.5%)	N/A	N/A
Arthropathy	30 (62.5%)	N/A	N/A
Annual factor consumption (IU/kg)	1796 (0 – 3600)	N/A	N/A

Data were presented as mean ± standard deviation, median (range) or n (%). SDS = standard deviation score; BMI = body mass index; N/A = not applicable.

Table 2. Biochemical profile of PwH and healthy controls.

	Haemophilia patients (n=48)	**Controls (n=35)**	***p* value**
Fasting glucose (mg/dl)	93.9 ± 9.9	88.1 ± 12.5	**0.02**
Fasting insulin (μIU/ml)	7.2 (3.2 – 21.9)	7.2 (0.7 – 29.8)	0.71
HOMA-IR	1.8 (0.7 – 5.5)	1.7 (0.2 – 8.3)	0.32
Total cholesterol (mg/dl)	153.2 ± 36.9	165.1 ± 32.6	0.13
LDL-cholesterol (mg/dl)	84 (36 – 162)	95 (60 – 160)	0.09
HDL-cholesterol (mg/dl)	41.5 (24 – 75)	40 (27 – 65)	0.21
Triglyceride (mg/dl)	66.5 (31 – 261)	93 (42 – 372)	**0.008**
Uric acid (mg/dl)	5.0 ± 1.3	5.4 ± 1.5	0.23

Data were presented as mean ± standard deviation, median (range). HOMA-IR = homeostasis model assessment of insulin resistance

Table 3. Frequency of metabolic syndrome components.

	Haemophilia patients (n=48)	**Controls (n=35)**	***p* value**
Overweight/Obese	13 (27.1%)	11 (31.5%)	0.66
Central obesity*	3 (6.3%)	3 (8.6%)	0.68
Elevated BP/HT	17 (35.5%)	10 (28.6%)	0.51
Dyslipidaemia			
Hypertriglyceridemia	5 (10.4%)	6 (17.1%)	0.28
Low HDL-cholesterol	2 (4.2%)	3 (8.6%)	0.35
Insulin resistance	11 (22.9%)	5 (14.3%)	0.33
Hyperglycemia	14 (29.2%)	3 (8.6%)	**0.02**
Family history of CVD	28 (58.3%)	21 (60.0%)	0.88

BP = blood pressure; HT = hypertension; CVD = cardiovascular disease; *According to waist circumference