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Evaluation of cardiovascular disease risk factors, inflammatory markers and subclinical atherosclerosis in patients with hemophilia

Hemofili hastalarında kardiyovasküler hastalık risk faktörlerinin, inflamatuar belirteçlerin ve subklinik aterosklerozun değerlendirilmesi

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ABSTRACT

Aim: To assess and compare the risk factors of cardiovascular disease (CVD) between patients with hemophilia (PwH) and healthy controls in a single center cohort in Türkiye.

Materials and Methods: Anthropometric parameters including height, weight, and body mass index were recorded. Fasting glucose, HbA1c, high sensitive C-Reactive Protein (hs-CRP), adiponectin, lipid parameters (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) were assessed. International Physical Activity Questionnaires (IPAQ) and carotid intima media thickness (CIMT) measurements were performed. The data from PwH (n=80) and healthy controls (n=36) were compared. Independent associates of CIMT value were analyzed.

Results: Hypertension, diabetes mellitus, metabolic syndrome and smoking frequencies were remarkable in PwH. Family history of CVD was significantly more frequent (p=0.005) and when considered with IPAQ scores; PwH was much more sedentary than controls (p<0.001). Total cholesterol, LDL-cholesterol were significantly higher in the control group (p =0.003,=0.003) while hs-CRP levels were higher in PwH (p=0.009). Age and IPAQ score were significant independent predictors of CIMT (p=0.004 and 0.003, respectively).

Conclusion: As a result of aging; PwH exposure to the same CVD risk factors as the general population. Screening for CVD risk factors in PwH other than hemophilia evaluation will be essential.

Keywords: Hs-CRP, hemophilia, subclinical atherosclerosis, CIMT.

ÖZ

Amaç: *Türkiye'de tek merkezli bir çalışmada hemofili hastaları ile sağlıklı kontroller arasında kardiyovasküler hastalık (KVH) risk faktörlerini değerlendirmek ve karşılaştırmak.*

Gereç ve Yöntem: *Boy, kilo ve vücut kitle indeksi gibi antropometrik parametreler kaydedildi. Açlık glukozu, HbA1c, yüksek duyarlıklı C-Reaktif Protein (hs-CRP), adiponektin, lipid parametreleri (total kolesterol, HDL-kolesterol, LDL-kolesterol, trigliserit) değerlendirildi. Uluslararası Fiziksel Aktivite Anketi (IPAQ) ve karotis intima media kalınlık (KIMK) ölçümleri yapıldı. Hemofili (n=80) ve sağlıklı kontrollerden (n=36) elde edilen veriler karşılaştırıldı. KIMK değerinin bağımsız değişkenleri analiz edildi.*

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Bulgular: *Hipertansiyon, diabetes mellitus, metabolik sendrom ve sigara içme sıklığı hemofili hastalarında dikkat çekiciydi. Ailede KVH öyküsü anlamlı olarak daha sıktı (p=0,005) ve IPAQ skorları ile değerlendirildiğinde; hemofili hastaları, kontrollere göre daha sedantardi (p<0,001). Total kolesterol, LDL-kolesterol kontrol grubunda anlamlı olarak daha yüksekti (p =0.003,=0.003), hs-CRP seviyeleri ise hemofili hastalarında daha yüksekti (p=0.009). Yaş ve IPAQ skoru KIMK'nin anlamlı bağımsız belirleyicileri (sırasıyla p=0,004 ve 0,003).*

Sonuç: *Yaşlanma sonucunda; hemofili hastaları genel popülasyonla aynı KVH risk faktörlerine maruz kalmaktadır. Hemofili değerlendirmesi dışında; KVH risk faktörlerinin taranması da gerekli olacaktır.*

Anahtar Sözcükler: *Hs-CRP, hemofili, subklinik ateroskleroz, KIMK.*

INTRODUCTION

Aging hemophilia patients are confronted with many chronic diseases apart from medical problems related to coagulation disorder; particularly atherosclerosis. In the past, it was believed that hemophilia is a protecting factor from cardiovascular disease (CVD) due to hypocoagulable state (1), but it is a fact that; atherothrombotic events also occur in patients with hemophilia (PwH) (2). Although different results have been reported on whether long-term hypocoagulation protects from atherogenesis, a multicenter and cross-sectional study found subclinical atherosclerosis findings in obese hemophilia A patients at a rate similar to the obese control group (3). CVD risk factors have also been reported to be common in PwH from a retrospective multicenter study; among 294 PwH only 72 of them (24.5%) had no risk factors while 151 patients (42%) had 1 or 2 risk factors (4). Also in the same study CVD events were reported in 24 patients which means 8.2 % of the population. Clinicians are expected to encounter an increased rate of CVD in practice, risk factors are needed to be clarified.

We hypothesized that CVD risk factors among PwH should be common similarly as non-hemophiliac populations. Therefore we aimed to determine the risk factors of CVD, CIMT measurement values as an early marker of atherosclerosis, their possible relationship with risk factors of CVD in PwH and to compare with non-hemophiliac controls.

MATERIALS and METHODS

Participants

Ethical approval for the present study was obtained from the ethics committee of Ege University Faculty of Medicine on 04.09.2012 (*B.30.2.EGE.0.20.05.00/OY/1362/ 552),* conducted in accordance with the Declaration of Helsinki and funded by Ege University Scientific Project Research Unit. Written consent was obtained from the patient (or legal guardian) that his medical data can be published. Data collection was performed for the male PwH aged 18 years and older visiting Ege Adult Hemophilia and Thrombosis Center at Ege University Hospital, Izmir.

The control group was recruited through placement of an advertisement in Ege University Hospital. Excluding criteria for the control group were having coronary artery disease, hypertension, diabetes mellitus or hyperlipidemia in medical history. Hemophilia type (Hemophilia A and B), severity of disease, age, medication history, priorly diagnosed hypertension, diabetes, serological and virus load test results of hepatitis C (HepC), serological test results of human immunodeficiency virus (HIV) and smoking were recorded from patients' electronic medical records. The PwH were divided into two groups. Those with mild hemophilia were grouped as non-severe; those with moderate and severe hemophilia were grouped as moderate-to-severe hemophilia. Weight and height were measured and body mass index (BMI) was calculated as weight divided by height squared (kg/m2). The overweight range is defined as if BMI is 25-29.9 kg/m^2 and obesity range is defined as if BMI is ≥ 30 kg/m^2 (5). International Diabetes Federation (IDF) criteria was used for the diagnosis of Metabolic syndrome (6).

Physical activity assessment

Validated Turkish short form of International Physical Activity Questionnaire (IPAQ) was used to assess leisure time physical activity, domestic and gardening activity, work-related physical activity and transport related physical activity. The physical activity score was calculated as metabolic equivalent, which is a measure of energy expenditure per week ;-minutes/week and classified in three levels. At least 3000 MET-minutes/week was classified as high activity, 600

MET-minutes/weeks was classified moderate activity and lower than 600 MET-minutes/weeks was low activity (7).

Laboratory assessment

Venous blood samples were drawn after 12-14 hours of overnight fasting. Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides, glucose, HbA1c, high sensitivity C-Reactive Protein (hs-CRP) were measured (Roche Diagnostics GmbH, Mannheim, Germany). Low density lipoprotein cholesterol (LDL-C) was calculated with Friedewald's equation, for TG levels less than 400 mg/dL. Dyslipidemia was defined as the use of lipid lowering drugs and/or LDL-C was more than 160 mg/dL and/or TC was higher than 240 mg/dL and/or fasting or nonfasting TG level higher than 500 mg/dL (8). According to American Diabetes Association criteria participants were considered diabetic if the fasting plasma glucose ≥126 mg/dL or HbA1c ≥6.5%. In the absence of unequivocal hyperglycemia, diabetes diagnosis required two abnormal test results from the same sample or in two separate test samples. Impaired fasting glucose was defined as fasting plasma glucose levels between 100 and 125 mg/dL (9). Inhibitors (neutralizing antibodies against FVIII or FIX) were documented as present if the patient was positive for inhibitors at any time point during data collection. Serum samples for adiponectin measurement were stored at -80°C until analysis was conducted. All patients' serum adiponectin was measured consecutively at the same day by sandwich enzyme immunoassay technique using ELISA kit (Assaypro LLC, St. Charles, USA, Catalog No: EA2500-1).

Cardiovascular examination

Physical examination determined the body mass index, waist circumference and blood pressure. Systolic and diastolic blood pressures were measured at the right brachial artery at a sitting position after ten minutes of resting. The mean of 2 measurements was used. Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg and a diastolic blood pressure of ≥ 90 mmHg, or use of antihypertensive medication; as reported for previous reports on hypertension in PwH (10).

Carotid intima-media thickness (CIMT) measurement was performed for both main carotid arteries with the patient in a supine position and head tilted backwards as described previously (11). CIMT measurement was obtained with Philips En Visor C device, using a 7.5-11 MHz phased array linear probe by a blinded cardiologist. From the main carotid artery bulb, a 1cm segment was identified within the first 2 cm distal region and the acquired images were transferred to the computer system. From these images, a special intima-media thickness measurement program (M' Ath ver. 2.0; Metris, Argenteuil, France) was used to determine the maximum and average CIMT values of the segment. The mean CIMT values of both carotid arteries were calculated and then these values were evaluated separately. Extreme CIMT as an independent predictor of potential coronary events was accepted ≥1 mm based on evidence from epidemiologic study (12).

Statistical Analyses

To summarize the data derived from the study, descriptive statistics were presented as mean ± standard deviation or median (min-max) depending on the normality distribution of the variables. Categorical variables were expressed as number and percentage. The Kolmogorov-Smirnov test and the Shapiro-Wilk test were used to check the normality of the numerical variables. In comparison of the two independent groups, independent samples t-test was used when the numerical variables distributed normally, whereas the Mann-Whitney U test was used when the numerical variables did not distribute normally. The differences between the categorical variables were compared with the Pearson chi-square in 2x2 tables where the expected cells ≥5, and the Fisher's Exact Test in tables where the expected cells <5. Depending on the distribution, correlations between the numerical variables were assessed by Spearman's Rho coefficient. To determine the independent associates of the CIMT value, univariate and multivariate linear regression analyses were performed.

"Jamovi project (2020), Jamovi (Version 1.2.22) [Computer Software] (Retrieved from https://www.jamovi.org) and JASP (Version 0.13) (Retrieved from https://jasp-stats.org) was used for the performance of the statistical analyses. A p-value <0.05 was accepted as statistically significant.

RESULTS

Overall, there were 80 hemophilia patients. Of these, 62 patients had hemophilia A (77.5%) and

the rest of the patients had hemophilia B. Thirty-six control subjects were included in the study. Based on the plasma factor level, 28 patients had non-severe (mild to moderate) hemophilia, whereas 52 patients (65%) had severe hemophilia. Only 2 patients (2.5%) had a factor inhibitor in the whole cohort. In the whole group, 61 patients (76.3%) were receiving prophylactic factor treatment. CIMT measurement was only completed by 66 patients and 22 controls.

The mean age of hemophiliacs and control subjects were comparable. Waist circumference and BMI values were similar in both groups. Although more patients had metabolic syndrome in the hemophilia group, there was no statistically significant difference between the hemophilia and the control groups. In terms of other major cardiovascular risk factors, only family history of cardiovascular disease was significantly more prevalent in the hemophilia group. Rates of diabetes mellitus, hyperlipidemia, hypertension and smoking were similar in the both groups. With regards to physical activity, the hemophilia group was much more sedentary. The median IPAQ score was 3552 [1080 – 9666] (met/minute/week) in the control subjects, whereas it was only 412 [165 – 5544] (met/minute/week) in the hemophilia patients ($p<0.001$). Interestingly, despite much more physical activity, the median total and LDL cholesterol levels were significantly higher in the control subjects compared with the hemophiliacs. Fasting plasma glucose and HbA1c values were similar in both groups. Again, there was no difference with regards to mean serum adiponectin levels between the groups. Serum hs-CRP values were significantly higher in hemophilia patients than that of the controls. Median CIMT were 0.6 mm [0.5 – 0.8] and 0.7 mm [0.4 – 1.3] in the control subjects and hemophilia patients, respectively ($P=0.117$). Table-1 summarizes the clinical and demographic characteristics and laboratory findings in the control and hemophilia groups.

Anthropometric measurements were comparable in both groups. There was no difference in terms of major cardiovascular risk factors between patients with hemophilia A and patients with hemophilia B. HbA1c levels and blood lipids were also similar in both groups.

There was no significant difference between two hemophilia groups' physical activity measured as IPAQ score ($p<0.8$), CIMT ($p<0.4$), serum hs-CRP ($p<0.7$) and adiponectin ($p<0.06$). Median BMI and mean waist circumference in patients and control groups were 26.2/24.9 kg/m^2 ($p=0.443$); 95.5/92.6 cm ($p=0.2$), respectively.

The severe cases were significantly higher in patients with hemophilia A than patients with hemophilia B. On the other hand, no difference was observed regarding the rate of prophylactic factor treatment or the presence of factor inhibitors between the groups. When we look at the potential differences between non-severe (mild to moderate) and severe patients in terms of cardiovascular risk factors; the frequency of metabolic syndrome was significantly higher in the moderate-severe hemophilia group than the mild ones. Median CIMT values in addition to other laboratory parameters were similar in both groups. Physical activity evaluated by IPAQ score among severe hemophilia patients was not different from patients with nonsevere hemophilia. Table-2 summarizes the clinical and laboratory findings in hemophilia patients that were classified into severity groups.

Carotid intima-media thickness was positively correlated with serum hs-CRP values. There was a moderate negative correlation between the IPAQ score and the CIMT thickness as well. Waist circumference and BMI also showed significant positive correlations with the CIMT. Correlation coefficients are shown in Table-3.

Univariate and multivariate linear regression models to determine the independent associates of CIMT among hemophilia patients were applied. Only age and IPAQ score were left significant predictors of CIMT. Table-4 demonstrates univariate and multivariate linear regression analyses showing independent associates of CIMT.

There was a remarkable result among patient characteristics which we need to mention in detail. None of the participants was HIV positive. Approximately one-fifth (26%) were hepatitis C infected, but none had the existence of structural liver disease.

Table-1. Comparison of the clinical and demographic characteristics and laboratory findings between the control and hemophilia groups.

	Control Group (n=36)	Hemophilia Group (n=80)	*P-value*
Age (years)	36.1±11.2 34 [23 – 69]	36.7±11.5 36 [18– 64]	0.707
Waist circumference (cm)	92.6 ± 11.1	95.5 ± 11.4	0.201
BMI (kg/m^2)	24.9 [19.4 – 37.4]	26.2 [17.4 – 39.8]	0.443
Smoking, *yes* (%)	21 (58.3)	36 (45)	0.184
Hypertension, *present* (%)	1 (2.8)	10 (12.5)	0.169
Diabetes mellitus, *present* (%)	0 (0)	8 (10)	0.056
Family history of CVD, *present* (%)	12 (33.3)	49 (61.3)	**0.005**
Metabolic syndrome, *present* (%)	5 (13.9)	19 (23.8)	0.225
Hyperlipidemia, *present* (%)	1 (2.8)	8 (10)	0.270
Systolic blood pressure (mmHg)	120 [100 – 150]	120 [100 – 210]	0.076
Diastolic blood pressure (mmHg)	80 [65 – 90]	80 [60 – 120]	0.316
CIMT (mm)	0.6 [0.5 – 0.8]	0.7 [0.4 – 1.3]	0.117
IPAQ score (met/minute/week)	3552 [1080 – 9666]	412 [165 – 5544]	**<0.001**
Total cholesterol (mg/dL)	198.5 [152 – 337]	178 [96 – 275]	**0.003**
LDL cholesterol (mg/dL)	122 [84 – 228]	107 [37 – 227]	**0.003**
Triglycerides (mg/dL)	136.5 [56 – 501]	111.5 [39 – 1018]	0.22
HDL cholesterol (mg/dL)	39 [31 – 80]	41 [30 – 75]	0.643
Fasting plasma glucose (mg/dL)	83 [62 – 148]	85.5 [15 – 340]	0.230
HbA1C (%)	5.3 [4.9 – 6.4]	5.4 [4.4 – 9.7]	0.489
hs-CRP (mg/dL)	0.1 [0 – 1.5]	0.2 [0 – 2]	**0.009**
Adiponectin (µg/mL)	9.4 [1.9 – 19.8]	8.2 [3.2 – 40]	0.487

Descriptive statistics were presented mean ± standard deviation / median [Min. – Maks.] in metric variables, and number (%) in categorical variables. Bold p-values were accepted as statistically significant (p<0.05). BMI: body mass index, CVD: cardiovascular disease, CIMT: Carotid intima-media thickness, hs-CRP: high sensitive C-reactive protein, IPAQ: International Physical Activity Questionnaires

Table-2. Comparison of the clinical and demographic characteristics and laboratory findings according to severity of hemophilia.

	Severity of Hemophilia		*P-value*
	Non-severe (n=28)	**Moderate-to-severe** (n=52)	
Age (years)	38.9 ± 12.7 38.5 [18 – 64]	35.6 ± 10.7 35 [18– 59]	0.287
Waist circumference (cm)	95.1 ± 12.6	95.7 ± 10.9	0.816
BMI (kg/m^2)	26.4 [17.5 – 39.8]	26.2 [17.4 – 35.5]	0.972
Smoking, *yes* (%)	16 (57.1)	20 (38.5)	0.109
Hypertension, *present* (%)	5 (17.9)	5 (9.6)	0.308
Diabetes mellitus, *present* (%)	3 (10.7)	5 (9.6)	0.999
Family history of CVD, *present* (%)	18 (64.3)	31 (59.6)	0.683
Metabolic syndrome, *present* (%)	3 (10.7)	16 (30.8)	0.044
Hyperlipidemia, *present* (%)	3 (10.7)	5 (9.6)	0.999
Systolic blood pressure (mmHg)	120 [100 – 210]	130 [90 – 180]	0.552
Diastolic blood pressure (mmHg)	80 [60 – 120]	75 [60 – 110]	0.600
CIMT (mm)	0.7 [0.4 – 1.3]	0.6 [0.5 – 1.1]	0.197
IPAQ score (met/minute/week)	462 [165 – 4108]	338 [165 – 5544]	0.703
Total cholesterol (mg/dL)	175.5 [109 – 275]	179 [96 – 260]	0.880
LDL cholesterol (mg/dL)	109 [61 – 227]	106.5 [37 – 181]	0.743
Triglycerides (mg/dL)	113.5 [39 – 1018]	111.5 [43 – 1018]	0.916
HDL cholesterol (mg/dL)	41 [25 – 66]	40 [30 – 75]	0.545
Fasting glucose (mg/dL)	83.5 [15 – 139]	86 [59 – 340]	0.762
HbA1C (%)	5.5 [4.8 – 7]	5.3 [4.4 – 9.7]	0.167
hs-CRP (mg/dL)	0.2 [0 – 2]	0.2 [0 – 2]	0.880
Adiponectin (µg/mL)	7.5 [3.2 – 14.6]	8.5 [3.7 – 40]	0.112
İnhibitor, *present* (%)	0 (0)	2 (3.8)	0.539
Prophylaxis			
Yes (%)	21 (75)	40 (76.9)	0.847
No (%)	7 (25)	12 (23.1)	

Descriptive statistics were presented mean ± standard deviation / median [Min. – Maks.] in metric variables, and number (%) in categorical variables. Bold p-values were accepted as statistically significant (p<0.05). BMI: body mass index, CVD: cardiovascular disease, CIMT: Carotid intima-media thickness, hs-CRP: high sensitive C-reactive protein, IPAQ: International Physical Activity Questionnaires

Table-3. Correlations of carotid intima-media thickness (CIMT)

	Mean CIMT	
	r	**P-value**
hs-CRP (mg/dL)	0.295	**0.006**
IPAQ (met/minute/week)	-0.564	**<0.001**
Waist circumference (cm)	0.305	**0.004**
Body Mass Index (kg/m^2)	0.302	**0.005**

Bold p-values were accepted as statistically significant (p<0.05). BMI: body mass index, CIMT: Carotid intima-media thickness, hs-CRP: high sensitive C-reactive protein, IPAQ: International Physical Activity Questionnaires

Table-4. Univariate and multivariate linear regression analyses showing independent associates of CIMT

	Crude Beta [95%CI]	crude P value	Adj. Beta [95%CI]	adj. P value
Age	0.01 [0.0.01]	**< 0.001**	0 [0.0.01]	**0.004**
Smoking: 1 vs 0	0.07 [-0.01.0.15]	0.072	0.04 [-0.02.0.11]	0.219
HT: 1 vs 0	0.18 [0.06.0.31]	**0.005**	-0.03 [-0.16.0.1]	0.659
DM: 1 vs 0	0.28 [0.16.0.4]	**< 0.001**	0.12 [-0.02.0.26]	0.099
Systolic blood pressure	0 [0.0]	**0.017**	0 [0.0]	0.598
BMI	0.01 [0.0.02]	**0.011**	0.01 [0.0.01]	0.064
LDL cholesterol	0 [0.0]	**0.002**	0 [0.0]	0.097
Adiponectin	0 [-0.01.0.01]	0.518	0 [-0.01.0]	0.435
IPAQ	0 [0.0]	**< 0.001**	0 [0.0]	**0.003**

BMI: Body mass index, DM: diabetes mellitus, HT: Hypertension, IPAQ: *International Physical Activity Questionnaires*

DISCUSSION

In this study we researched CVD risk factors in PwH and healthy controls. We reported that the PwH were more sedentary, had a higher frequency of family history and almost half of them were smokers. Also, an inflammatory marker; Hs-CRP, was significantly higher in PwH. CIMT, which is a subclinical atherosclerosis marker, was similar with controls. There was also a strong negative correlation between physical activity score and CIMT.

Hypertension is one of the modifiable risk factors that increase cardiovascular morbidity and mortality. Almost a quarter of PwH (n=17) were hypertensive while 12.5% of patients were using anti-hypertensive drugs and 7 patients were newly diagnosed in our study. Although there are few studies on this subject, the remarkable thing is that the prevalence of HT in hemophilia patients is similar to the general population and even increased in some countries ranging from 19.7% to 49.1% (4,10) (13-15). In our cohort; patients were diagnosed with essential hypertension and none were attributed to secondary causes. Another point to keep in mind is to screen for subclinical target organ damage with a diagnosis of hypertension.

Our findings showed also that obesity, diabetes mellitus and metabolic syndrome frequencies were also notably high in PwH. In our cohort 16.6% of patients (n= 11) were obese and 45% (n=36) of patients were overweighted. Obesity prevalence is alarming in PwH [4, 16, 17] and our study supports the literature on this subject. Type 2 diabetes mellitus was found in 10 % of PwH (n=8) and all of them were under anti-diabetic medication. Our results also showed that 21.2 % of PwH (n=14) had impaired fasting glucose. There are conflicting results on the prevalence of diabetes mellitus in PwH (16, 18) while it was similar to our findings in ARCHER study (4). The point to be emphasized here is that it should not be forgotten that diabetes mellitus is considered equivalent to coronary artery disease. The frequency of metabolic syndrome was found to be 23.8% in hemophiliacs whereas it was 13.9% in controls. Our findings were also compatible with the Turkish data (19) which has reported that 25% of PwH > 18 years old had MetS.

Serum total and LDL-cholesterol, was significantly lower in PwH than controls in our

study. Similar to our results, serum LDL-cholesterol was significantly lower in Japanese PwH than controls (10). Furthermore, in a recent Turkish study by Yildiz et al, PwH had lower total and LDL-cholesterol levels than controls (19). Although low LDL-cholesterol is associated with HCV infection (20), only one-fifth patients were hepatitis C infected in our study. Further studies are needed to clarify the reasons why total and LDL-cholesterol levels are lower in PwH. 45% of PwH were smoking among PwH and also in Canadians the smoking frequency was mentioned as 21.8 % (4). Smoking; a well-known risk factor for CVD was mentioned before that being a smoker in any time compared with non-smokers; increased the CVD risk 3.12 times (2).

IPAQ scores of PwH were significantly lower than the control group in the current study. In addition to hypertension, diabetes mellitus, dyslipidemia, obesity and smoking, sedentary life is one of the modifiable CVD risk factors. In the PURE study; higher physical activity (compared with < 600 Met/minutes/week, 600-3000 Met/minutes/week and >3000 (Met/minutes/week) was associated with lower risk of mortality and CVD (21). At least 500-1000 met/minutes/week was recommended to reduce CVD risk in current guidelines (22); in our study IPAQ scores of PwH were under the recommended range. While it was recommended to avoid physical activity in the past because of bleeding risk, nowadays physical activity seems essential for maintenance of health (23).

In addition to age and male gender, family history is another unfavorable risk factor and was found in 61.3 % of PwH which was also more frequent than controls. Although the lipid profile was significantly lower, strong family history of CVD, low IPAQ scores and smoking highlight the increased risk of CVD. No difference was determined in the CVD risk factors by treatment approach (prophylaxis vs on-demand therapy); similarly with current literature (2).

Hs-CRP was first mentioned by Sood et al as a risk factor in PwH for CVD (2). To the best of our knowledge we have not seen a study comparing the inflammatory marker hs-CRP between PwH and healthy controls. We found significantly higher hs-CRP levels in the hemophilia group than controls (p=0.009). Significantly low IPAQ score and significantly higher hs-CRP in our PwH is an important finding in terms of CVD risk. There has not been a recommendation in professional guidelines for the routine use of hs-CRP to screen the CVD risk in the general population; but it seems reasonable in selected populations who have family history of early ischemic heart disease, obesity, and/or sedentary lifestyle (24). Clinical use of serum biomarkers for the detection of cardiovascular diseases in PwH will be in the areas of research in the future, however adiponectin did not achieve a significant difference in our study.

CIMT showed no significant difference between PwH and healthy controls. However extreme CIMT with ≥1 mm was determined in 4 PwH, while it was less than 1mm in the control group. Important data from the literature come from Zwiers et al.(25); the mean CIMT in PwH was 0.8 mm which is similar to our study cohort. More importantly, in the same study it was mentioned that the mean CIMT; who had a major adverse cardiovascular event history, was 1.09 mm which reveals the importance of the risk that our patients are at.

One of the important points to be mentioned in our study is the negative correlation between the IPAQ score and CIMT. Physical inactivity was associated with increased CIMT by Kadoglou et al. (26) and in a study researching the use of CIMT for CVD risk prediction; 11% increased risk of myocardial infarction with each 0.1 mm increase of CIMT was determined (27). Factors affecting CIMT other than physical activity were mentioned as aging, hypertension, left ventricular hypertrophy, insulin resistance and metabolic syndrome (28). In our study weak correlations between CIMT and hs-CRP, waist circumference and BMI were found. Associations between CIMT and biological markers were also researched and high levels of hs-CRP were associated with increased CIMT (29). We also found that age and IPAQ scores were independent associates of CIMT in all participants.

CONCLUSION

This study determined the cardiovascular risk factors for PwH in Türkiye. In particular, we highlight that physical activity status is an important risk factor for CVD in PwH. Since joint dysfunctions are an important problem in PwH, increasing physical activity to reduce CVD risk factors should be carefully followed-up. PwH who are prone to be sedentary and overweight should be more closely monitored for traditional cardiovascular risk factors and receive counseling and preventive measures. Serial CIMT measurement as a non-invasive method for

early diagnosis of atherosclerosis would be beneficial in this population. As the risk factors are similar to the normal population, studies on the management of these risk factors will also be needed in the future.

Conflict of interest: The authors declare no potential conflict of interest.

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