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The effect of the Dietary Approaches to Stop Hypertension (DASH) diet on body composition, complete blood count, prothrombin time, inflammation, and liver function in hemophilic adolescents

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This randomized clinical trial was registered at IRCT.ir (IRCT20130903014551N6).

Details of the roles of the authors: H.M and M.H.R design the study. A.M and A.M prescribed diets to the participants and collected data. H.M and M.H.R analyzed data. S.F and N.S wrote the manuscript. C.C.T.C revised the manuscript and rechecked data analysis.

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Transparency Declaration: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported. The reporting of this work is compliant with CONSORT guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned (The Research Council and Ethical Committee of Isfahan University of Medical Sciences, Isfahan, Iran and Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran approved this study (Code: IR.MUI.RESEARCH.REC.1399.098). This randomized clinical trial was registered at IRCT.ir (IRCT20130903014551N6)) have been explained.

Abstract

There is no dietary strategy that has yet been specifically advocated for hemophilia. Therefore, we sought to assess the effect of the Dietary Approaches to Stop Hypertension (DASH) diet in adolescents with hemophilia. In this parallel trial, 40 male adolescents with hemophilia were dichotomized into the DASH group or control group for 10 weeks. The serum high sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), complete blood count (CBC), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), partial thromboplastin time (PTT), waist circumference (WC), percentage of body fat, fat-free mass (FFM), and liver steatosis were measured at the beginning and end of the study. Serum vitamin C was measured as a biomarker of compliance with the DASH diet. The DASH diet was designed to include high amounts of whole grains, fruits, vegetables, and low-fat dairy products, as well as low amounts of saturated fats, cholesterol, refined grains, sweets and red meat. Serum vitamin C in the DASH group was significantly increased compared to the control (P=0.001). There was a significant reduction in WC (P=0.005), fat mass (P=0.006), hepatic fibrosis (P=0.02), and PTT (P=0.008) in the DASH group, compared with the control. However, there were no significant differences regarding other selected outcomes between groups. Patients in the DASH group had significantly greater increase in the levels of red blood cell, hemoglobin, and hematocrit, as compared to control. Adherence to the DASH diet in children with hemophilia yielded significant beneficial effects on body composition, complete blood count, inflammation, and liver function.

Keywords: Hemophilia, Dietary approach to stop hypertension, body composition, complete blood count, inflammation, liver function, Adolescents.

Introduction

Hemophilia is a hereditary hemorrhagic disorder caused by a deficient or defective clotting factor VIII (type A hemophilia) or clotting factor IX (type B hemophilia) (1). The inheritance pattern of this disorder is X-linked recessive, therefore, hemophilia is exclusively transmitted through female carriers and affects only males (2). Recent evidence has shown that more than 1,125,000 men suffer from hemophilia around the world (3). The World Federation of Hemophilia has announced that Iran is among the top ten countries with the highest prevalence of hemophilia, globally (4).

When a male patient manifests unusual hemorrhagic episodes, with an elevated partial thromboplastin time (PTT) but normal prothrombin time and platelet count, the diagnosis of hemophilia is suspected (2). The extent of coagulation factor VIII or IX deficiency determines the probability and severity of internal and external bleeding (1). Depending on age, the predominant sites of hemorrhage are also varied; for instance, hemophilic newborns and toddlers are usually affected by head bleeding, while hemophilic adolescents typically experience intra-articular bleeding, known as hemarthrosis (5). Therefore, management of the disease becomes increasingly important in these subjects.

Prolonged hemorrhage, as evidenced by an elevated PTT, is a major concern in hemophilic patients (2). Due to recurrent bleeding and hemolysis, mild anemia is also a common complication in subjects with hemophilia (6). Moreover, recent evidence has suggested that hemophilic individuals have chronic low-grade inflammation, originating from increased levels of lipopolysaccharide in their blood circulation (7). Furthermore, hemarthrosis and subsequent synovitis and arthropathy make hemophilia sufferers less physically active in comparison to others (8). Therefore, overweight, obesity, and non-alcoholic fatty liver disease are prevalent comorbidities in this population (9). Unfortunately, no dietary approach has yet been designed or advocated to specifically manage the aforementioned problems in patients with hemophilia.

The Dietary Approaches to Stop Hypertension (DASH) diet is a well-known eating pattern, with multiple, documented, beneficial effects on weight management, body composition, liver function, inflammatory biomarkers, and some other aspects of human health (10-12). Adherence to this multifunctional diet creates a unique balance between the consumption of plant-based foods, including whole grains, fruits, vegetables, legumes, and nuts, and animal-based foods, including poultry, fish, and dairy products. In addition, it limits the intake of salt, red meat, fatty foods, and sugar-sweetened beverages and foods (13). To the best of our knowledge, no study has yet been conducted to evaluate the efficacy of the DASH diet in

hemophilic children and adolescents. Therefore, we sought to conduct a randomized controlled trial to assess the effect of the DASH diet on hematological parameters, inflammatory biomarkers, anthropometric indices, body composition, and liver function in adolescents with hemophilia.

Method:

Participants:

The present parallel randomized clinical trial was conducted from March to June 2020. A total of 40 adolescents with hemophilia were recruited from Omid Hospital, Isfahan, Iran. Volunteers were eligible if they *1)* were male, *2)* were aged between 10 to 18 years old, *3)* had clotting factor (VII, VIII and IX) deficiency, *4)* had not used antioxidant supplements within the preceding 3 months, and *5)* were not on a specific diet. Also, incidence of a new chronic disease during the study has been considered as a premature withdrawal. The sample size was calculated by $n= 2[(Z_{1-\alpha/2} + Z_{1-\beta})^2\times S^2]/\Delta^2$ where α=0.05 (type one error) and β=20% (type two error). Body mass index (BMI) was considered as the main variable. A previous study showed that the standard deviation of BMI in hemophilic patients was 2.08 kg/m2 (14), and the minimal detectable difference of BMI was 1.34 kg/m^2. Accordingly, 40 hemophilia adolescents were recruited for the current clinical trial. An introductory session was set up to clarify plans and details regarding the study. Written consent was completed by parents and adolescents, and the study was ethically approved by The Research Council and Ethical Committee of Isfahan University of Medical Sciences, Isfahan, Iran, and Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran (Code: IR.MUI.RESEARCH.REC.1399.098). This randomized clinical trial was registered at IRCT.ir (IRCT20130903014551N6).

Study Procedure and Dietary Intervention:

In this current study, participants were randomly dichotomized into the DASH group (n=20) or control group (n=20) for 10 weeks. Each subject received a code and randomization was run using select random number in SPSS 20. As is was a dietary intervention, patients and their parents could not be blinded. In DASH group, energy requirements of each participant were calculated individually based on the Harris–Benedict equation (15). The DASH diet was determined based on the previously modified DASH diet for adolescents (16), where the macronutrient composition was as follows: 50-55% of total energy from carbohydrates, 16-18% of total energy from protein and 27-30% of energy from fat. The DASH diet was

designed to include high amounts of whole grains, fruits, vegetables, and low-fat dairy products, as well as low amounts of saturated fats, cholesterol, refined grains, legumes, nuts, sweets and red meat. A sample of one-day menu is demonstrated in **Table 1**. Also, the consumption of red meat and sodium was limited. In this way, limiting red meat was applied by reducing the amount of red meat per serving in the diet and replacing red meat with white meat and poultry. It is recommended to consume a maximum of 180 g of meat per day with emphasis on the consumption of fish and white meat. Following recommendations were used to limit sodium intake: 1) avoid using of table salt, 2) cooking low-salt food, 3) limit using sodium-rich foods such as pickles and processed foods, and 4) use of low-salt cheese and breads. A maximum sodium intake of 2300 mg per day was allowed. All adolescents and their parents attended the meetings to learn daily food menus. Adolescents in the control group received nutritional recommendations based on healthy eating behaviors, including chewing food completely, using low-volume frequent meals, using healthy snacks, drinking adequate water, avoiding deep frying, limiting added fat and sugar. Serum vitamin C was defined as a biochemical indicator of compliance with DASH diet (17). Accordingly, compliance with the DASH diet was assessed by measuring serum vitamin C at baseline and after 10 weeks of intervention. Serum vitamin C was measured using biochemical colorimetric analysis. All patients and their parents participated in meetings programmed at baseline and 2-, 4-, 6- and 8-weeks. Parents were required to complete a one-day food record in the 1st, 5th and 10th week of the study. So, three, one-day food records (two weekdays and one weekend day) were completed by each participant, and a researcher investigated the completeness of food diaries with parents. All collected food records were analyzed using the USDA database.

Measurement of Biochemical Variables:

Blood samples were drawn after 12 h of fasting, in the early morning, from the antecubital vein, and all of the related concentrations were prepared on the day of blood sampling. Samples were centrifuged at 3000×g for 10 min to separate the serum. High sensitivity C-reactive protein (hs-CRP) was measured using the Inm.turbid method by Audit kit (Delta treatment, Ireland-Iran), and interleukin 6 (IL-6) was measured by using the commercially available enzyme-linked immunosorbent assay kits (Siemens, Germany) by CLIA. Complete blood counts (CBC) were conducted using an automated procedure (Mindray apparatus). Serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) were measured by anzymatic system with a Pars Azmon kit (Pars Azmon, Iran).

Partial thromboplastin time (PTT) tests were performed using the turbidometry method by IL kits (Instrument Lab, Germany). In the present study, serum vitamin C was measured using vials previously treated with meta-phosphoric acid based on a biochemical colorimetric analysis.

Measurement of Anthropometric Variables and Body Composition:

Weight was measured to the nearest 100 g, with participants minimally clothed and unshod, whilst height was measured using a standard stadiometer according to standard protocols. BMI was calculated as weight in kilograms divided by the square of height in meters. Waist circumference (WC) was measured at the narrowest level, over light clothing, using a non-stretchable tape measure, without any pressure to the body surface. Weight, height and BMI percentiles were calculated based on Centers for Disease Control and Prevention (CDC) growth charts for children and adolescents, aged 2 to19 years (18). Body fat and fat free mass (FFM) were measured using bioelectrical impedance analysis (BIA) (Bodyvis A_1c, China), which is highly correlated with dual X-ray absorptiometry (r=0.88) (19). All measurements were conducted at baseline and at the end of the trial.

Measurement of Fibrosis and Steatosis

Liver fat was measured using FibroScan, and accepted as the reference standard. All biopsy specimens were investigated by a circulatory expert who specialized in liver diseases. The probe transducer tip was located on the skin between the ribs and the level of the right lobe of the liver. The =depth was between 25 and 65 mm under the skin exterior (20). Stages were recognized according to the NASH Clinical Research Network scoring system (21).

Statistical Analysis:

The analyses were performed on the basis of an intention-to-treat (ITT) approach. Missing values were treated according to linear regression method. To evaluate the distribution of variables, we used the Kolmogrov-Smirnov test, which demonstrated that body fat, SGPT, and CRP, were not normally distributed. Therefore, log transformation was applied. Quantitative variables were analyzed between two groups utilizing an Independent Student t-test, whilst an analysis of covariance (ANCOVA) was conducted to set confounding variables, especially baseline values. Data were presented as means and standard deviations, unless otherwise stated. All statistical analyses were performed using SPSS (version 20) statistical software.

Results

Among the 40 subjects with hemophilia who enrolled in the study, three patients in the DASH diet group (due to medical conditions and personal reasons) and four patients in the control group (due to medical conditions and low adherence to intervention) were excluded from follow up data collection (**Figure 1**). During the study process, two subjects had low adherence and they did not want to continue participation. Therefore, they excluded according to their tendency and researchers had no role in excluding these subjects. Nevertheless, baseline measurements were performed for these patients and we run ITT analysis according to the baseline measurements.

We excluded two subjects from control group because they stated that they did not start being on the prescribed diet. Therefore, we did not follow them because they had no compliance with prescribed diet. At the end of the study, we included baseline data of the all subjects randomly assigned to the DASH or control groups using an intention to treat method

The analyses were performed according to ITT approach; therefore, all 40 participants were enrolled in the final analyses. There were no side effects following the DASH diet among the participants.

Table 2 indicates baseline characteristics of study participants in each group. There were no significant differences between the groups in terms of age, BMI percentile, and WC. However, at baseline, individuals in the DASH diet group had higher weight and height percentiles, compared to those in control group.

Dietary intake of the study participants as a sum of the three one-day food records are presented in **Table 3**. Based on food diaries, the mean intakes of energy, carbohydrate, protein, fat, vitamin A, vitamin E, vitamin C, vitamin K, vitamin B1, vitamin B2, selenium, zinc, iron and dietary fiber during the trial were not significantly different between groups. As expected, dietary intakes of sodium were significantly lower (1172.35 vs. 1580.94 mg/day, p = 0.002), while calcium intakes were higher (754.26 vs. 545.28 mg/day, p = 0.017), in the DASH, vs. control group. Individuals in the DASH group had higher intakes of potassium (1987.52 vs. 1624.36 mg/day, p = 0.040) as compared with those in the control group.

Figure 2 presents serum vitamin C levels at baseline and at the end of trial in each group. At the end of the trial, serum vitamin C levels were significantly increased in the DASH diet

group (0.28 mg/dL) and control group (0.10 mg/dL) compared to baseline values. Between group comparison indicated a significant increase in serum vitamin C levels in the DASH group compared to control group (p=0.001), suggesting a relatively good compliance of the participants to the DASH diet.

Table 4 details the effect of the DASH diet on anthropometric indices, inflammation, and liver histology and enzymes. Within group comparison showed a significant reduction in WC (-2.25 cm), FAT (-0.52 kg), and PTT (-8.48), and a significant rise in FFM (1.25 kg), in the DASH diet group. Also, a significant increase was seen regarding FAT (0.88 kg), CRP (2.22 mg/L), and hepatic fibrosis (0.15 kPa) in the control group. Compared with the control group, adherence to the DASH diet led to significant reductions in WC (P= 0.005), FAT (P= 0.006), hepatic fibrosis (P= 0.02,) and PTT (P= 0.008). There were no significant differences regarding other selected outcomes between groups. To attenuate the difference in baseline values, the effect of baseline measurements were adjusted.

The effects of DASH diet on CBC profile are presented in **Table 5**. Whithin group analysis showed that WBC, RBC, HGB, HCT, and MCH were significantly increased after using DASH diet. Patients in the DASH group had significantly greater increase in the levels of RBC (P= 0.02), HGB (P= 0.005) and HCT (P= 0.006), compared to control group. To attenuate the difference in baseline values, the effect of baseline measurements were adjusted.

Discussion

In the current study, adherence to the DASH diet, for 10 weeks, among hemophilic adolescents resulted in a significant reduction in WC, fat mass, fibrosis, and PTT, in comparison to the control group. In addition, RBC, HGB, and HCT significantly increased, whilst steatosis and CRP levels were marginally reduced, in response to following the DASH diet, compared with the control group. However, changes in weight, BMI, FFM, IL-6, SGOT, SGPT, MCV, MCH, and MCHC were not significantly different between the two groups. To the best of our knowledge, this is the first study investigating the effects of the DASH diet on body composition, complete blood count, inflammatory markers, and liver function in hemophilic adolescents. It has previously been demonstrated that overweight and obesity are major issues when concomitant to hemophilia, and are associated with several metabolic abnormalities (9). With regard to the difficulties of these patients to be physically active (22, 23), following a healthy diet and decreasing calorie intake are suggested as key factors in the prevention or reduction of overweight and obesity among these patients (9). However,

currently, no dietary recommendation has been specifically advocated for these patients. Therefore, our findings, which indicated the beneficial effects of the DASH diet on several health aspects of hemophilia, might be useful in clinical settings to prevent and treat health complications of these patients.

The results of our study showed that serum vitamin C level significantly increased following the DASH diet, compared with the control diet. In addition, intake of soluble fiber and calcium were significantly higher, and sodium intake was notably lower, in the DASH group vs. control group. Currently, serum vitamin C level and dietary records represent the best tools to assess the compliance of study participants to the DASH diet (17). Concordant with our results, in a previous study conducted on children with metabolic syndrome, serum vitamin C significantly increased following the DASH diet, compared with the control group (17). Indeed, it has been suggested that consumption of vitamin C may be associated with lower blood pressure, by enhancing nitric oxide synthase activity (24, 25). Therefore, one of the possible explanations for the anti-hypertension effects of the DASH diet might be due to the high fruits and vegetable content of this diet. Indeed, the focus of the DASH diet is on vegetables, fruits, and low-fat dairy foods (26), thus, a significant increase in the soluble fiber and calcium intake is predictable among intervention participants, as compared to controls.

In the present study, WC and fat mass were significantly decreased in response to adherence to the DASH diet in comparison with the control diet. However, the differences between weight, BMI, and FFM did not significantly differ between groups. It has previously suggested that overweight and obesity, which are highly prevalent among hemophilia patients, are associated with annual joint bleeding rate and influence the joint health of these patients (27-29). It has also been widely demonstrated that overweight and obesity contribute to the reduction in motion of joints, acceleration of loss of joint mobility, and increasing chronic pain (29). Given that obesity in hemophilia patients is associated with an increasing prevalence of anxiety and depression and several other negative health consequences (29), prevention and treatment of obesity is necessary in these patients. However, generally, weight reduction during childhood is not recommended and the aim of the diet therapy should be the maintenance of weight among children and adolescents. Therefore, our results, which indicate that adherence to the DASH diet, for ten weeks, can maintain BMI and FFM, in addition to facilitating reductions in WC and fat mass, in adolescents with hemophilia, suggest that the DASH diet is a practical and safe dietary approach to help prevent obesity and its related complications among children and adolescents with hemophilia. Indeed, the

results of a systematic review and meta-analysis showed that, in comparison to the control diet, adherence to the DASH diet elicited a significant reduction in weight, BMI, and WC among adults (30). Moreover, the results of a cohort study showed that, after 3-years follow-up, the DASH diet had an inverse association with central and general obesity among adolescents (31). In another previous study, it was reported that, after 6 weeks adherence to the DASH diet, weight, BMI, and WC did not significantly change compared with usual dietary habits among children with metabolic syndrome (17). In Saneei et al, WC was significantly reduced in the DASH diet group compared with baseline, however, although the mean change of WC was higher in the DASH diet compared with control diet, it was not statistically significant (17). Thus, discordance in findings of some previous work and our study, in terms of WC, might be attributable to the difference in compliance and longer treatment time of our study (10 weeks vs. 6 weeks). Overall, the favorable effects of the DASH diet on WC and body composition in our sample might be due to the fact that the DASH diet is rich in fruits and vegetables, legumes, and low fat dairy products, as well as healthy vegetable oils, which provide a low-calorie dietary pattern and simultaneously provides suitable amounts of nutrients for the growth and development of children and adolescents.

In our study, fibrosis and steatosis were markedly decreased in the DASH diet group compared with the controls. Although Nonalcoholic fatty liver disease (NAFLD) is often associated with adulthood, recent studies have shown that the risk of developing NAFLD in adolescents has doubled in the past 20 years (32). Recent studies have presented NAFLD as one of the two most important complications of obesity in children and adolescents(33). Also, it should be noted that children with hemophilia have limited physical activity due to the risk of bleeding, which increases the risk of NAFLD. In a previous randomized controlled trial study, in comparison to controls, following the DASH diet for 8 weeks among adult Nonalcoholic Fatty Liver Disease (NAFLD) patients resulted in improvements in several metabolic factors, such as weight, BMI, triglycerides, markers of insulin metabolism, inflammatory, and stress oxidative markers of these patients (11). Similarly, observational studies have reported that consumption of the DASH diet has an inverse correlation with risk of NAFLD (34, 35). As mentioned above, hemophilia patients have several hindrances to being physically active and they are at high risk for obesity and related metabolic diseases. One the most important undesirable outcomes of being physically inactive and gaining weight, particularly enhancing visceral fat and central obesity, in both adolescents and adults

is insulin resistance, which has a bilateral association with fatty liver (36, 37). The beneficial effects of the DASH diet on the metabolic status of patients with hemophilia might be explained by the low amounts of simple sugar and higher fibre, magnesium, and calcium of this dietary pattern, which may reduce markers of insulin metabolism, triglycerides, and very low density lipoprotein (VLDL)-cholesterol levels (38). It has recently been shown that consumption of sugar-sweetened soda has a direct correlation with increased risk of NAFLD, since they possess high amounts of fructose and calories which both have a substantial role in the etiology of fatty liver (39, 40). Animal studies have shown that high calcium and magnesium diets, as exists in the DASH eating pattern, have a salient role in stimulating microsomal triglyceride transfer protein (MTP) in the liver (41), suppression of endothelial injury, reduction in the peroxidation of lipids, and enhancing the antioxidant capacity in both serum and tissues (42).

The findings of the present study demonstrated that consumption of the DASH diet yielded, albeit marginal, significantly reduced serum CRP levels compared with the control group. In accordance with our results, it has been shown that following the DASH diet significantly reduced hs-CRP among adolescents with metabolic syndrome (17), adult NAFLD patients (11), and Polycystic ovary syndrome (43) patients compared with control groups.

However, adhering to the DASH diet for 4 weeks did not lead to reductions in hs-CRP in women with gestational diabetes, while it significantly increased plasma total antioxidant capacity (TAC) and total glutathione (GSH) (44). Several potential mechanisms have been posited regarding the anti-inflammatory effects of DASH diet, including high amounts of anti-oxidants, such as vitamin C, and high amounts of calcium, magnesium, and fibre present within this diet (45-47). It has previously been shown that magnesium inhibits nuclear factor kappa-light-chain-enhancer of activated B cells (***NF***-κB), and has a role in the down-regulation of the inflammatory response (48, 49).

One the most valuable findings of our study is that PTT significantly decreased after consumption of the DASH diet compared with the control diet. A prolongation in the PTT is occurrent in patients with hemophilia, even in some cases with severe hemophilia the PTT is 2 to 3 times longer than the normal range (50). However, to our knowledge, there is no study that has assessed the relationship between healthy dietary patterns and PTT, thus, more preclinical and clinical trials are needed to clarify our results and its underlying mechanisms. The DASH diet is rich in vegetables that are full of vitamin K. As a result, following this diet

increases vitamin K intake (51). In addition, DASH diet is a rich source of dietary fiber which can lead to more vitamin K production by altering gut microbiota (52). These suggested mechanisms should be investigated by additional studies. Similarly, our results indicated that adherence to the DASH diet significantly increased RBC, HGB, and HCT compared with the control group, which might due to the high antioxidant levels of the DASH diet, which are necessary in hematopoiesis (53).

The average age of the subjects in our study was 13-14 years. According to the WHO height-for- age percentile (54), the rate of height growth is about 6-7 cm/year (0.11-0.12 cm/week) in this age. The duration of the present study was 10 weeks. Therefore, the subjects had a maximum height growth of 1.1-1.3 cm. It should be kept in mind that the impaired growth is prevalent among children with chronic disease such as hemophilia (55). Therefore, it is unlikely that our findings on body composition were affected by the height growth of the subjects

Strengths and limitations

The strengths of our study included that; we utilized serum levels of vitamin C as a valid biomarker of diet compliance, and we applied the ITT approach for the analysis data, which permitted all of the study participants who participated in our study into data analysis. Evidence determined that the concentration of sodium and potassium in a 24-hour urine sample can be considered as a biomarker of compliance with the DASH diet. Although, collecting 24-hour urine samples is difficult, especially for children and adolescents. Additionally, day to day variation of 24-hour urinary sodium is high, and multiple samplings are required to attenuate day to day variation. [41]. Since it was not suitable for adolescents, we utilized vitamin C because it does not have these limitations. Moreover, to the authors' knowledge, this is the first study investigating the effects of the DASH diet, as one the most well-known healthy dietary patterns, on liver fibrosis and steatosis using a fibroscan, inflammatory factors, anthropometry, and body composition, as well as complete blood count among haemophilic adolescents. Nevertheless, as a main limitation of our study, blinding was not applicable due to the nature of our intervention. Dietary intakes were not assessed before the intervention and all the nutritional assessments were performed during the study. Also, dietary intake has been investigated during the study using 3 one-day food records. Due to the difficulty of obtaining food records from children with specific disease conditions, we could not convince participants to increase the number of food records. However, due to the fact

that the compliance with the intervention has been evaluated by biomarkers (serum vitamin C), these limitations had no serious unfavorable effect on the validity of the study.

Conclusion

Our findings showed that the DASH diet, which was primarily designed to control cardiovascular risk factors in healthy or unhealthy adults, has several beneficial effects on various health aspects of adolescents with hemophilia. Indeed, adherence to the DASH diet significantly reduced waist circumference and fat mass, in addition to eliciting beneficial effects on CRP, liver fibrosis, and steatosis, as well as RBS, HGB, and HCT, in hemophilic adolescents. However, more, well-designed and well-conducted, studies are needed to confirm the results of the present study.

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Authorship

HM, ATM, CTC, and MB : designed the study (project conception, development of overall research plan, and study oversight); MHR, : trained and supervised نام نویسنده مسزول in the administration and data extraction of assessments and performed the data-extraction reliability check and has primary responsibility for final content; SF, ME, : provided essential assessment techniques necessary for the research; MHR: conducted research (hands-on conduct of research, data collection and processing), performed baseline statistical analyses, and wrote the manuscript under the supervision of ALM, CTC and MB; ATM: designed and performed statistical analyses; and all authors contributed to the scientific interpretation of the analysis, commented on drafts of the manuscript, and accepted final responsibility for the manuscript.

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Table 1. A sample menu of the prescribed diet to the DASH group (6276 kJ (1500 kcal), 55% from carbohydrate, 17% from protein, 28% from fats)

Food groups	**Serving size per day**	**Food item (g/d)**
Grains	6	Whole-Bread (60)
Vegetables	5	Whole-Cereals (150)
Fruits	5	Cooked peas (34)
Dairy	2	Cooked green beans (42)
Meat	2.5	Cabbage (93)
Nuts/Seeds	1	Tomato (60)
Fats/Oils	6	Green pepper (108)
		Cooked zucchini (78)
		Apple (200)
		Plum (65)
		Pear (170)
		Low-fat milk (230)
		Low-fat yogurt (230)
		Low-fat cheese (15)
		Cooked fish (45)

Table 2. Baseline characteristic of study subjects [a]

Variable	DASH diet (n=20)	Control diet (n=20)	P [b]
Age (year)	13.85±2.64	14.8±2.74	0.30
Weight (percentile)	76.02±25.66	73.98±16.04	0.03
Height (percentile)	50.75±34.48	39.46±23.69	0.006
Percentile BMI	85.45±14.17	80.76±15.29	0.88
WC (cm)	83.25±15.1	79.2±9.11	0.07
Serum Vitamin C (mg/dL)	0.42±0.21	0.36±0.21	<0.001

BMI; body mass index, WC; waist circumference

[a] Variables are expressed as mean ± SD.

[b] *p*-values resulted from independent t tests for quantitative and Chi-square for qualitative variables between the two groups.

Table 3. Dietary intake of the study participants as a sum of the three one-day food records [a]

Variable	DASH diet (n=20)	Control diet (n=20)	*P*[b]
Energy (Kcal/day)	1144.58±154.65	1293.71±310.73	0.067
Carbohydrate (g/day)	167.75±32.89	173.84±32.89	0.989
Protein (g/day)	49.74±18.59	50.71±18.59	0.882
Fat (g/day)	41.08±10.41	41.11±10.41	0.885
Sodium (mg/day)	1172.35±398.36	1580.94±398.36	0.002
Vitamin A (re/day)	613.74±383.34	501.35±383.34	0.386
Vitamin E (mg/day)	14.69±6.74	12.46±6.74	0.287
Vitamin C (mg/day)	72.55±38.66	54.43±38.66	0.140
Vitamin K (ug/day)	35.08±17.96	26.89±17.96	0.219
Vitamin B1 (mg/day)	0.9±0.22	0.83±0.22	0.355
Vitamin B2 (mg/day)	1.38±0.35	1.23±0.35	0.261
Vitamin D (ug/day)	1.91±1.38	0.75±1.38	0.021
Potassium (mg/day)	1987.52±574.08	1642.36±574.08	0.040
Calcium (mg/day)	754.26±246.96	545.28±246.96	0.017
Selenium (mg/day)	0.08±0.08	0.07±0.08	0.683
Zinc (mg/day)	6.11±1.78	5.52±1.78	0.261
Iron (mg/day)	8.48±3.08	8.66±3.08	0.717
Dietary Fiber (g/day)	14.43±4.42	12.10±4.42	0.139
Soluble Fiber (g/day)	0.52±0.17	0.38±0.17	0.022

[a] Variables are expressed as mean ± SD.

[b] Obtained from ANCOVA adjusted for energy intake

Table 4. The effects of dietary approach to stop hypertension (DASH) diet on anthropometric indices, inflammation and liver histology and enzymes [a]

	DASH Diet (n=20)				Control Diet (n=20)				P[c]	P[d]
	Baseline	End of trial	Change	P[b]	Baseline	End of trial	Change	P[b]		
Weight (percentile)	76.02±25.66	79.46±20.23	3.44±7.78	0.06	73.98±16.04	75.45±15.64	1.47±10.28	0.52	0.527	0.32
BMI (percentile)	85.45±14.17	85.56±11.50	0.11±4.44	0.91	80.76±15.29	81.94±16.08	1.18±16.61	0.75	0.404	0.72
WC (cm)	83.25±15.10	81±13.06	-2.25±3.32	0.007	79.2±9.11	79.61±8.91	0.41±1.89	0.33	0.659	0.005
FFM (kg)	49.68±12.69	50.94±13.04	1.25±1.01	<0.001	48.67±9.13	49.04±9	0.73±2.69	0.26	0.708	0.43
Fat (kg)	14.45±7.08	13.92±6.55	-0.52±0.99	0.03	12.12±4.16	12.73±4.41	0.88±1.33	0.02		0.006
IL-6 (pg/ml)	3.06±1.48	2.59±1.48	-0.46±1.28	0.09	2.15±0.56	2.3±0.56	0.15±0.68	0.32	0.512	0.30
CRP (mg/l)	2.72±2.54	2.26±2.38	-0.45±1.73	0.24	1.33±0.89	3.55±6.71	2.22±0.19	0.04	0.372	0.08
Fibrosis (kPa)	4.25±1.04	4.13±0.78	-0.11±0.69	0.45	4.54±0.95	4.69±0.92	0.15±0.24	0.01	0.520	0.02
Steatosis	204.20±55.	187.11±47.	-	0.11	200.10±53.	203.36±56.	3.25±9.4	0.1	0.07	0.06

	25	98	17.08±46.22		83	64	7	5	9	
SGOT (U/L)	19.60±4.44	19.67±3.28	0.07±3.47	0.92	24.3±11.36	24.59±11.2	0.29±3.63	0.72	0.061	0.47
SGPT (U/L)	16.58±8.85	17.23±6.93	0.38±4.33	0.38	21.2±8.19	22.06±8.92	0.86±4.91	0.48	0.056	0.43
PTT (1000/µl)	80.59±25.1	72.09±19.06	-8.49±14.31	0.01	72.86±25.07	76.92±22.43	4.05±12.91	0.17	0.547	0.008

BMI, body mass index; WC, waist circumference; FFM, fat free mass; IL-6, interleukin 6; CRP, C-reactive protein,. SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruic transaminase; PTT, partial thromboplastin time

[a] Variables are expressed as mean ± SD

[b] It shows the comparison baseline and final values in each group obtained from Paired T test

[c] It shows the comparison final values between DASH and control groups obtained from Independent t-test comparing endpoint measurements

[d] It shows the comparison final values between two groups after adjusting for baseline measurements obtained from ANCOVA, adjusted for baseline value

Table 5. The effects of dietary approach to stop hypertension (DASH) diet on complete blood count [a]

	DASH Diet (n=20)				Control Diet (n=20)				P[c]	P[d]
	Baseline	End of trial	Change	P[b]	Baseline	End of trial	Change	P[b]		
WBC (1000/µl)	6.32±1.49	6.84±1.40	0.51±0.86	0.01	6.06±1.04	6.34±1.34	0.27±0.77	0.12	0.342	0.30
RBC (mil/µl)	5.25±0.5	5.58±0.44	0.32±0.36	0.001	5.2±0.52	5.29±0.5	0.08±0.44	0.40	0.010	0.02
HGB (g/dl)	14.49±1.53	14.94±1.01	0.45±0.80	0.02	14.21±1.80	14.16±1.57	-0.04±0.77	0.8	0.054	0.005
HCT (%)	42.24±4.10	43.56±3.27	1.32±2.36	0.02	42.16±4.34	41.93±3.89	-0.22±1.47	0.49	0.130	0.006
MCV (fl)	80.97±3.68	81.43±4.39	0.46±2.12	0.34	78.3±7.13	78.26±7.30	-0.03±4.39	0.97	0.131	0.46
MCH (pg)	28.08±1.57	28.98±2.57	0.9±2.26	0.09	27.23±3.45	27.96±3.63	0.73±1.98	0.11	0.387	0.69
MCHC (g/dl)	34.5±0.94	34.29±1.27	-0.21±1.28	0.46	33.75±1.46	33.85±1.65	0.1±1.06	0.66	0.324	0.71

WBC, white blood cells; HGB, haemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration.

[a] Variables are expressed as mean ± SD

[b] It shows the comparison baseline and final values in each group obtained from Paired T test

[c] It shows the comparison final values between DASH and control groups obtained from Independent t-test comparing endpoint measurements

[d] It shows the comparison final values between two groups after adjusting for baseline measurements obtained from ANCOVA, adjusted for baseline value