Pediatr Pol 2023; 98 (3): 203-207
DOI: https://doi.org/10.5114/polp.2023.131760
Submitted: 20.02.2023, Accepted: 25.04.2023, Published: 27.09.2023

PEDIATRIA Polska
Polish Journal of PAEDIATRICS

ORIGINAL PAPER

Analysis of the correlation between body weight, body composition, and factor VIII recovery in paediatric patients with severe haemophilia A – a single-centre study

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ABSTRACT

Introduction: Haemophilia A (HA) is a rare bleeding disorder. Patients with severe HA have a factor VIII activity of < 1%. The clinical picture of severe HA consists of a propensity for spontaneous haemorrhages to the skin, muscles, joints, and internal organs. To prevent severe complications of bleeds, patients with severe HA receive prophylaxis with deficient clotting factor. Obese people have larger absolute fat free mass (FFM) as well as fat mass than non-obese individuals of the same age, gender and height. Factor VIII (FVIII) concentrates are typically confined to the vascular space. Although the pharmacokinetics (PK) based FVIII dosing is becoming a standard in tailoring the prophylaxis for HA patients, the majority of them are still dosed according to total body weight and this may result in an overdose of FVIII. This study aimed to evaluate the PK of FVIII considering patients' body weight and body composition using electrical bioimpedance.

Material and methods: Twenty-one boys with severe HA undergoing plasma-derived factor VIII prophylaxis were enrolled in the study. Patients underwent physical examination, body weight and height measurements, had body composition assessed using electrical bioimpedance, FVIII concentration was measured before and 30 min after FVIII administration, and FVIII recovery was evaluated. Patients completed a questionnaire regarding treatment, physical activity, and bleeding.

Results: Of the patients who underwent the study, 47.6% had a normal body mass index (BMI), 42.8% were overweight, and 9.5% of patients were underweight. There was a correlation between patients' BMI and FVIII recovery, FFM and FVIII recovery, and fat mass and FVIII recovery. No relationship was found between FVIII recovery and bleeding rate.

Conclusions: Determining factor VIII dosage according to FFM requires further study.

KEY WORDS:

severe haemophilia A, FVIII recovery, overweight, obesity.

INTRODUCTION

Haemophilia A (HA) is a genetically determined bleeding disorder resulting from factor VIII (FVIII) deficiency. Inheritance of HA is recessive, linked to the X chromosome – almost only men are affected, while women are carriers of the defective gene [1].

Haemophilia is a rare disease. There are more than 400,000 patients with the severe form of haemophilia worldwide [2]. The prevalence of haemophilia in Poland is estimated at 1 : 12300, of which approximately 80–85% of cases are HA [3, 4]. There are approximately 300 paediatric patients with severe HA (305 patients enrolled in the bleeding prevention program in June 2018) [5].

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Clinically, HA, like other haemorrhagic diatheses, is characterized by a propensity to bleed. The most characteristic symptom of severe haemophilia is spontaneous as well as traumatic articular bleeding, which eventually lead to joint destruction. In addition, patients with haemophilia may bleed into the muscles, gastrointestinal tract, oral cavity, urinary tract, as well as into the central nervous system. 80% of bleeding events, however, occur in the musculoskeletal system [1]. Articular bleeding is not always symptomatic, but it can damage a joint. Prophylactic treatment with FVIII may prevent insidious arthropathy development [6].

Lack of physical activity is one of the causes of excessive body weight. This involves two concepts relevant to this article: overweight is excessive accumulation of body fat, not yet fulfilling the criteria for a diagnosis of obesity, but exceeding the physiological value (body mass index – BMI, 85–95th percentile for sex and age), while obesity is the abnormal and/or excessive accumulation of body fat leading to deterioration of health (BMI > 95th percentile for sex and age) [7].

The calculation of drug dosages to obese patients is a subject of concern. The main factors that affect the tissue distribution of drugs are body composition, regional blood flow and the affinity of the drug for plasma proteins and/or tissue components. Obese people have larger absolute fat free mass (FFM) as well as fat mass than non-obese individuals of the same age, gender and height. Factor VIII concentrates are typically confined to the vascular space, so the problem of accumulation of the drug in adipose tissue is not a concern in patients with haemophilia [8]. But it has some other impact.

Although pharmacokinetics (PK) based FVIII dosing is becoming a standard in tailoring the prophylaxis for HA patients, the majority of them are still dosed according to total body weight.

The purpose of this study was to investigate the role of excessive fat content for the FVIII pharmacokinetic. This is the first publication concerning this problem in children with haemophilia in Poland.

MATERIAL AND METHODS

The cross-sectional study was performed by Clinical Department of Paediatric Oncology, Haematology, Clinical Transplantology and Paediatrics of Medical University of Warsaw.

The aim of this study was to evaluate the relationship of FVIII recovery to body weight in paediatric patients with haemophilia.

Eligible boys were identified by an author of the study from patients with haemophilia treated in the Department of Pediatric Oncology, Hematology and Transplantology of the Medical University of Warsaw.

Patients underwent physical examination, weight and height measurements, body composition measurements using electrical bioimpedance, and had FVIII levels assessed before factor VIII administration and 30 min after factor VIII administration.

Ethical approval was granted by the Bioethics Committee of the Medical University of Warsaw.

- STUDY GROUP
  - INCLUSION CRITERIA
    - Males with severe HA
    - Age 6–18 years old
    - No persistent inhibitor
    - Patients treated with pd FVIII
  - EXCLUSION CRITERIA
    - No consent to participate in the study
    - Haemophilia B
    - Mild and moderate HA
    - Patients taking medications that have a significant effect on weight gain (e.g. steroids)
    - Age < 6 years old
- INSTRUMENTS
  - Factor VIII PK
    - Patients were receiving the standard FVIII dose used in prophylaxis during the survey (20–30 IU/kg)
    - Assessment of FVIII level was performed before the administration of FVIII, assuming that the previous administration of FVIII was performed at least 48 h earlier
    - The second FVIII level was assessed 30 min after FVIII administration
    - Factor VIII recovery was calculated as follows FVIII rec = (FVIII 30´(%) – FVIII 0´(%)/dose of FVIII (IU) per kg of body weight (k)]
  - Weight and height measurements
    - Body weight measurements were taken with an accuracy of 0.5 kg
    - Body height measurements were taken with an accuracy of 1 cm
    - BMI was calculated with an accuracy of 0.01 kg/m^2
    - Body weight, height and BMI measurements were compared to OLAF percentile charts [9]
  - Body composition analysis
    - An AKERN BIA 101 device was used for body composition analysis
    - The following parameters were considered:
      - FFM in kg and as a % of body weight
      - Fat mass (FM) in kg and as a % of body weight
  - Questionnaire
    - Patients filled in a questionnaire that contained questions about:
      - their physical activity. Patients defined their physical activity as: low (less than 30 min of exercise/day), moderate (more than 30 min of exercise per day) or high (competitive sport, intense training);
      - factor VIII dose and frequency of its administration;
      - frequency of bleeding (once per week/once per month/once per six months/once per year or less frequent).

TABLE 1. Characteristics of the study group

Parameters	Mean	SD	Median	Min	Max
Age (years)	13.17	2.46	13	10	17
Body weight [kg]	62.56	22.44	58	26	86.9
Centile of body weight	66.79	33.29	77	0.1	98
Height [cm]	166	0.15	168	133	184
Centile of height	64.13	34.44	74	3	99.9
BMI [kg/m^2]	22.24	5.43	21.1	14.7	30.03
Centile of BMI	63.13	34.59	55	0.1	98
Fat free mass [kg]	48.34	12.47	50.3	24	78.6
Fat free mass (% of body weight)	83.45	9.74	85.8	65.5	98.5
Fat mass [kg]	10.39	7.48	8.9	0.7	26.2
Fat mass (% of body weight)	16.55	9.74	14.2	1.5	34.5

BMI – body mass index

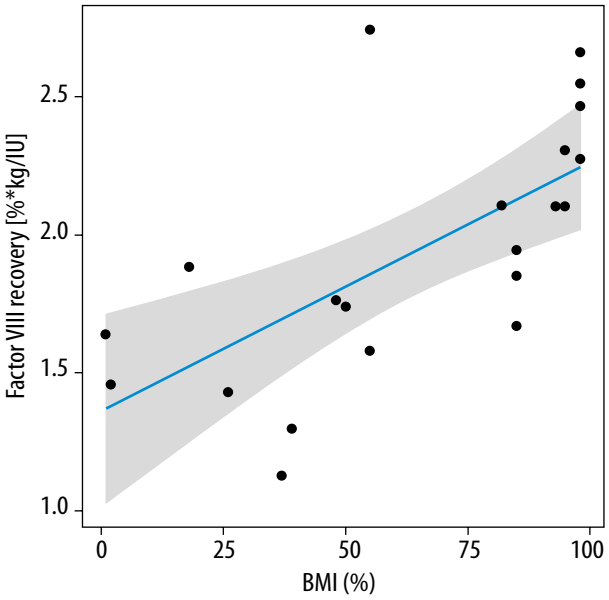

FIGURE 1. Correlation between patients' body mass index expressed in percentile and factor VIII recovery rate [%*kg/IU]

BMI – body mass index

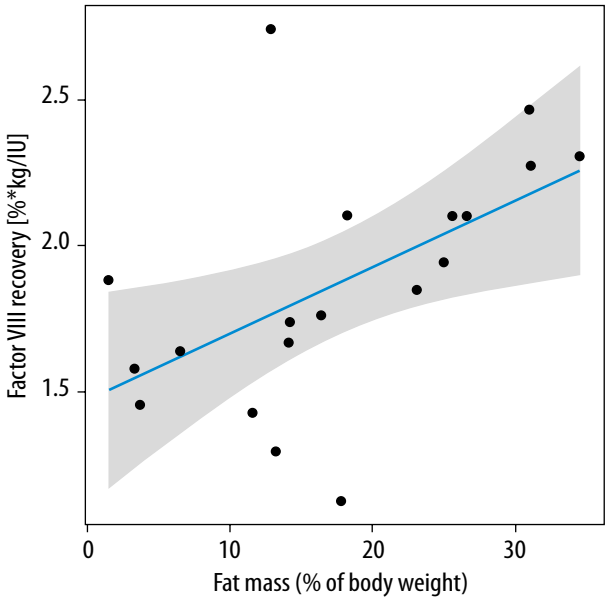

FIGURE 2. Correlation between patients' fat mass expressed as percent of body mass and factor VIII recovery rate [%*kg/IU]

- STATISTICAL ANALYSIS
  - The continuous variables were summarized using several statistics (median, mean, standard deviation and range)
  - The relationship between continuous variables was assessed using ordinary linear regression and between binary and continuous using logistic regression. These relationships were summarized using linear coefficient or odds ratio respectively, 95% confidence interval and *p*-value
  - Relationships were considered significant for $p < 0.05$
  - All analyses were performed using the R program language and statistical environment in version 4.2

RESULTS

From 65 patients with severe haemophilia, who were treated in the Clinical Department of Paediatric Oncology, Haematology, Clinical Transplantology and Paediatrics of Medical University of Warsaw during the survey, only 21 patients met the inclusion criteria.

Ten patients (47.6%) had BMI within the normal range, 8 patients (42.8%) were overweight or obese (overweight 6 [28.6%], obese 3 [14.3%]), and 2 patients (9.5%) were underweight according to OLAF centile scales. Further characteristics of the study group are presented in Table 1.

A correlation was found between patients' BMI and FVIII recovery (*p*-value: 0.0002).

Also a correlation was found between patients' BMI expressed in percentiles according to OLAF percentile charts and FVIII recovery (*p*-value: 0.0009) (Figure 1).

A relationship was found between FVIII recovery and patient's fat mass (FM%bw) expressed as % of body weight (*p*-value: 0.017) (Figure 2).

A relationship was found between FVIII recovery and FFM expressed as % of body weight (FFM%bw) (*p*-value: 0.017) (Figure 3).

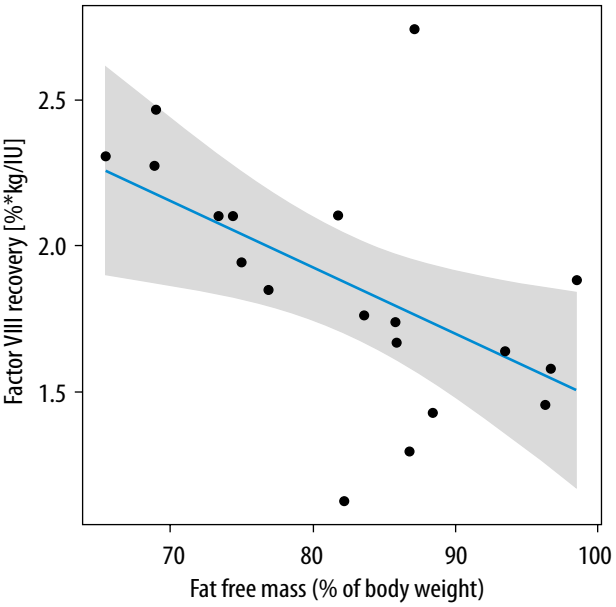

FIGURE 3. Correlation between patients' fat free mass expressed as percent of body weight and factor VIII recovery rate [%*kg/IU]

A relationship was found between patients' BMI and their lack of physical activity (p-value: 0.0088).

Also a relationship was found between patients' physical activity and FFM expressed as % of body weight (FFM%bw) (p-value: 0.047).

There was no statistically significant correlation between FVIII recovery and frequency of bleeding.

DISCUSSION

The latest 2020 guidelines of the World Federation of Haemophilia included a new definition of prophylaxis. According to the new definition it is regular administration of haemophilia patients with haemostatic drugs to prevent bleeding in order to enable them to lead a healthy and active lifestyle, including participation in physical and social activities on a comparable level to healthy people [2].

At present, a patient suffering from severe haemophilia has a chance to live a normal life. Due to widespread prophylaxis, a network of haemophilia treatment centres, training of medical staff, as well as education of patients' parents, haemophilic arthropathy and associated deformation of the musculoskeletal system are rare among paediatric patients. Children with haemophilia can play sports and participate in social life on an equal basis with their peers. On the other hand, the child's diagnosis with haemophilia significantly influences the organisation of family life. Parents learn to administer the FVIII concentrates on their own, recognize the symptoms of bleeding, and organize their children's activities on the days when the factor activity is the highest. Patients grow up with the need to undergo intravenous injections several times a week and attend visits in haemophilia treatment centres regularly. Any trauma at almost every step in childhood may not only require an additional dose of FVIII, but also creates the risk of another hospitalization. In the face of many challenges that await parents, it is difficult to avoid overprotecting.

Lack of physical activity is one of the causes of excessive body weight.

More than 20 years ago, the World Health Organization (WHO) officially recognized obesity as a disease that promotes the development of other diseases, increases the risk of death, and requires treatment [10]. It is estimated that there are currently more than 200 million children with excessive body weight worldwide [11]. In Poland in 2016, the percentage of school-aged children with excessive body weight was 22%. Within 4 years (between 2012 and 2016), this percentage increased by as much as 5%. The most recent (2018) preliminary results of a survey of adolescents aged 11–15 years (international Health Behaviour in School-aged Children survey) indicate that excessive body weight is present in 29.7% of boys and 14.3% of girls (according to WHO criteria, 2007). These percentages are several percent higher compared to the results of the 2014 edition of this survey. Between 2014 and 2018, the percentage of adolescents with excessive body weight increased 19.9–21.7% with a stronger deterioration observed in boys compared to girls and, considering age, in 13-year-olds of both sexes [12].

The epidemic of overweight and obesity also affects patients with haemophilia [13]. Worldwide, the percentage of haemophilia patients with excessive body weight is 17%. However, if only patients living in North America and Europe are considered, the percentage reaches 31% [14]. The prevalence of overweight and obesity in haemophilia patients compared to the healthy population varies depending on the country where the study was conducted. In the United States, Canada, Denmark, and Taiwan, haemophilia patients were more likely to be overweight than the healthy population, while in India, a smaller percentage of haemophilia patients suffered from overweight and obesity compared to the healthy population [15–17]. In Poland, no such statistics have been published to date. There are limited data on the paediatric population of haemophilia patients. It is known that children with haemophilia suffer much less frequently from excessive body weight compared to adults (26.9% vs. 43.3% worldwide). However, over 10 years of follow-up, the percentage of children with haemophilia and excessive body weight increased by as much as 40% [15]. Data on paediatric patients vary by part of the world. There are fewer obese and overweight children with haemophilia in Europe than in North America (18.8% vs. 30.6%) [16]. So far there are no such data in the Polish population of children with haemophilia. The study group was too limited to draw similar conclusions on its basis.

Obesity also comes with a higher risk for haemophilic arthropathy; joint range of motion has been shown to negatively correlate with BMI [18]. However, the intravascular compartment does not grow with the body mass. It

is the explanation of higher FVIII recovery rates in overweight and obese patients – patients with excessive weight receive higher weight-based doses that are distributed over similar volumes to those measured in patients whose BMI is within the normal range [19].

A limitation of this study is the size of the study group. Nevertheless, it should be taken into account that haemophilia is a rare disease, the study included patients from a single centre, and in the course of the study, the population of paediatric patients with haemophilia was heterogeneous in terms of clotting factor concentrate received. Taking into account the age of patients, we decided to include patients on plasma-derived factor prophylaxis so that the study group would be as homogeneous as possible.

According to the study results, patients with higher BMI and fat content had FVIII recovery that exceeds 2% /IU kg^{-1}. Factor VIII recovery rate is usually predetermined as 2%/IU kg^{-1} [20].

According to van Moort's study, using body weight to calculate the correct dose of FVIII is not optimal and especially in obese patients it may result in FVIII overdosing [21]. Taking the cost of FVIII concentrates into consideration, overdosing of FVIII concentrates may lead to unnecessary excessive cost for the healthcare system.

Not only patient weight can influence the PK of FVIII. Other factors affecting the PK of FVIII include: patient's age, VWF level and blood group [22]. In this study, only one of the factors affecting PK was analysed, and only one of the PK parameters was considered.

According to the new definition of prophylaxis in severe haemophilia, it should be tailored for the patient [2]. Therefore, factor dosing should not only be based on FVIII PK, but treatment planning should also take into account the state of the musculoskeletal system to maintain good quality of life and prevent joint damage.

CONCLUSIONS

Calculating the dose of FVIII concentrates using FFM rather than total body mass should be considered. The unjustified use of excessive doses of factor VIII concentrates for prophylaxis is a burden on the healthcare system. Pharmacokinetics of FVIII concentrates, depending on FFM, needs further investigations.

DISCLOSURE

The authors declare no conflict of interest.

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