Associations between cardiovascular risk factors, hyper- and hypocoagulability

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Chapter 12

The impairment in daily life of obese haemophiliacs

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ABSTRACT

Introduction Obesity is a major health concern, not only in the general population but also in patients with hemophilia. Little is known about the consequences of obesity for hemophilia patients. Since obesity is an important risk factor for osteoarthritis, these effects may be even more pronounced in hemophilia patients who are prone to joint damage.

Aims The association between obesity and limitations in daily activities as well as the frequency of bleeds and use of factor VIII concentrate in obese and normal weight hemophilia patients was assessed.

Methods Fifteen obese (BMI≥30 kg/m²) and fifteen normal weight (BMI≤25 kg/m²) hemophilia A patients matched for severity and age were analysed. The Hemophilia Activities List (HAL) was used to assess the impairment in daily activities.

Results Compared to the normal weight hemophilia patients, obese hemophiliacs had a significantly lower sum score (88/100 and 98/100, respectively, p-value=0.02), which was mainly caused by an impaired lower limb function. All other components of the HAL also showed lower scores in the obese patients, but did not reach statistical significance. A higher frequency of bleeds requiring treatment with factor VIII concentrate occurred in the obese hemophiliacs (17 bleeds in 8 individuals) compared to the controls (3 bleeds in 3 individuals) (p=0.045).

Conclusion Compared to non-obese hemophilia patients, obese hemophiliacs had more joint bleeds and a lower overall HAL score, which was driven by a lower limb function score. Prevention of overweight and weight reduction requires special attention from physicians treating hemophilia patients.
INTRODUCTION

Obesity has become a major health concern in the Western world. In various parts of the United States the prevalence of obesity (body mass index (BMI) of ≥30 kg/m²) in males exceeds 30% and a similar proportion has overweight [1]. In patients with hemophilia, a similar number suffers from obesity and overweight [2]. In the last decade, the prevalence of obesity doubled from 4% to 8% in adult hemophiliacs in the Netherlands, while the prevalence of overweight increased from 27% to 35% [3].

In general, obesity is associated with an increased morbidity and mortality due to cardiovascular disease, chronic arthropathy, diabetes mellitus, physical complaints and numerous other medical conditions [4,5]. In hemophilia, pre-existing arthropathy due to bleeding may be further aggravated by obesity [6-8]. Furthermore, obesity may induce bleeding in hemophilia patients due to the increased strain on the joints.

Given the potential harm of obesity in patients with hemophilia and the way osteoarthritis may impair daily life, we compared the level of impairment in daily life, the number of bleeding complications and the use of factor VIII concentrate in obese and normal weight hemophiliacs.

METHODS

Fifteen adult hemophilia A patients with obesity (body mass index (BMI) ≥ 30 kg/m²) were matched for both age and severity of hemophilia to 15 hemophilia A subjects with a BMI ≤ 25 kg/m². All patients were treated in the Hemophilia Treatment Centre of the Academic Medical Centre (AMC) in Amsterdam, The Netherlands. The cases consisted of all obese hemophilia A patients known at the hemophilia treatment centre. The controls also came from the same hemophilia centre and were randomly selected if they matched the cases. We stratified severity of hemophilia in two groups: severe hemophilia was defined as a factor VIII deficiency of ≤0.01 IU/ml, non-severe hemophilia as a factor VIII level of more than 0.01 IU/ml.

A physical examination was performed in all patients, which included measurements of weight and height. BMI was measured at our Hemophilia Treatment Centre for each individual using the standards of the World Health Organization. Patients participated after written informed consent had been obtained. The study was approved by the local Medical Ethical Committee.

Data collection

A questionnaire was sent by mail, which included a validated Hemophilia Activities List (HAL). The HAL is a recently developed, hemophilia specific, questionnaire, evaluating the self-perceived abilities of patients with hemophilia in performing activities of daily life [9-11]. During a study visit, the outcome of this questionnaire was discussed with the participant. Since the HAL does
not contain any questions about localisation of the joint(s) or muscles responsible for the reported disabilities, additional questions were asked during the visit.

Various physical functions (e.g. sitting, standing and self care) are represented in the HAL and the outcome of all separate variables in the HAL is reflected by scores between 0 and 100, in which 100 represents a normal function and 0 an absent function. Some components of the HAL are represented in combined scores; i.e. the overall sum score, the ‘basic lower extremity activities’ score for basic activities involving the lower extremities such as standing, and the ‘complex lower extremity activities’ score, representing the complex activities of the lower extremities, such as walking up the stairs, running and jumping.

Information on the number of bleeding episodes requiring treatment with factor VIII concentrate in 2008 and 2009 was obtained from participants during the visit. This information was verified by data from medical files and factor VIII transfusion data from the electronic database of the hospital.

The diagnosis of osteoarthritis was considered likely if a combination of symptoms (pain and stiffness), clinical features (tenderness to palpation, crepitus or decreased mobility), and radiographic features (joint space narrowing, subchondral sclerosis, marginal osteophytes, subchondral cysts) was present. Data on the presence of osteoarthritis was obtained from medical charts and radiology reports.

**Statistical analysis**

Baseline characteristics were summarised by means and standard deviations (SD) in case of normally distributed data and by medians and ranges in case of skewed distributed data. Student’s t-test was applied for continuous variables and the \( \chi^2 \) test was applied for discrete variables. Non-parametric tests were applied in cases of skewed distributed data. A linear regression analyses was performed to calculate the correlation between BMI and the outcome of the HAL. An ANOVA analysis was performed to calculate whether any association found was significant.

**RESULTS**

**Characteristics**

The study population consisted of 15 obese (BMI \( \geq 30 \, \text{kg/m}^2 \)) and 15 normal weight (BMI \( \leq 25 \, \text{kg/m}^2 \)) hemophilia patients. The median weight was 102 kg (range 90-180) in patients with obesity and 78 kilograms (range 62-98) in the normal-weight group (p<0.001). Mean BMI was 34 kg/m\(^2\) (range 30-50) in the obese and 24 kg/m\(^2\) (22-25) in the normal weight patients.

The mean age of the study population was 55 years (range 22-74). Two patients in both study groups had severe hemophilia A, while the thirteen other patients were non-severe hemophiliacs (range FVIII 0.02-0.30 IU/ml).
None of the patients was infected with HIV. One third (n=5) of both cases and controls had hepatitis C infection. In both groups one patient with non-severe hemophilia had a history of an inhibitor to factor VIII, but these inhibitors disappeared before the observation period. Recovery and half life of factor VIII were thus normal in these two patients.

**HAL score**

All individual scores of the HAL were assessed. Limb function was assessed by scoring activities involving the function of the upper extremities, the basic lower extremities and the complex lower extremities. The ability to perform activities such as use of transportation, self-care, household tasks, leisure activities and sports was also assessed. Finally the sum of these functions was calculated. The results were stratified for severity of hemophilia. Overall, patients with obesity had a lower sum score than the normal weight patients (88/100 and 98/100, respectively, p=0.02). This difference was mainly driven by a lower score for lower extremities (Table 1). Due to the small number of cases with a target joint we could not specify which joint (knee of ankle) caused the lower score of the HAL. However, the ankle was affected in two cases and the knee in one case. The function of the upper extremity, use of transportation, self-care, household tasks, leisure activities and sports also slightly differed between the two groups. Obese patients had lower scores for all separate components of the HAL (Table 1) than controls, but these differences did not reach statistical difference.

<table>
<thead>
<tr>
<th>Total population</th>
<th>Non-severe hemophiliacs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI ≥ 30</td>
</tr>
<tr>
<td><strong>SUM</strong></td>
<td>88.4</td>
</tr>
<tr>
<td>Upper Extremity</td>
<td>94.7</td>
</tr>
<tr>
<td>Basic Lower Extremity</td>
<td>80.4</td>
</tr>
<tr>
<td>Complex Lower Extremity</td>
<td>77.2</td>
</tr>
<tr>
<td>Lying/sitting/kneeling/ Standing</td>
<td>86.9</td>
</tr>
<tr>
<td>Leg functions</td>
<td>75.6</td>
</tr>
<tr>
<td>Arm functions</td>
<td>93.3</td>
</tr>
<tr>
<td>Use of transportation</td>
<td>92.2</td>
</tr>
<tr>
<td>Self care</td>
<td>95.7</td>
</tr>
<tr>
<td>Household tasks</td>
<td>94.9</td>
</tr>
<tr>
<td>Leisure activities and sports</td>
<td>91.5</td>
</tr>
</tbody>
</table>
The association between the HAL score and BMI is shown in figure 1. When assessing the association in a linear regression model, there was a significant inverse association between the HAL score and BMI. BMI influenced the HAL score by 21% ($r^2=0.21$, $p=0.012$). When excluding the single outlier, the $r^2$ increased to 0.28, $p=0.003$.

After exclusion of the patients with severe hemophilia, the HAL scores remained the same for all separate functions, although the scores were somewhat higher in both cases and controls. Also the sum score remained significantly lower for patients with obesity compared to the normal weight hemophilia patients (90/100 and 99.5/100 respectively, $p=0.02$) (Table 1).

The HAL score was also calculated separately for patients with severe hemophilia, but the number of patients was very small. The overall HAL score was lower for patients with severe hemophilia. The HAL sum score of the four patients with severe hemophilia was 77.5/100 in the cases and 87.5/100 for the controls ($p=0.44$).

Figure 1. Scatter plot assessing the association between BMI and sum score of the HAL

**Bleeding**

When assessing the number of bleeding complications in both groups, obese hemophilia patients suffered from significantly more bleeds requiring treatment with factor VIII concentrate over the past 2 years (17 bleeds in 8 individuals) compared to the normal weight control group (3 bleeds in 3 individuals) ($p=0.045$). A similar trend was noticed when specifically joint- and muscle bleeds were analysed (Table 2). When assessing the number of bleeding complications in patients with non-severe hemophilia the difference did not reach statistical significance ($p=0.10$). The number
of individuals with a target joint was greater in the group of normal weight hemophiliacs (5) compared to obese hemophiliacs (3). In obese hemophiliacs, usually multiple joints were affected.

One patient in each study group used factor VIII prophylaxis. The total amount of factor VIII concentrate (both prophylaxis as well as on demand use) in the two-year time interval seemed to be higher in the cases (49,000 IU) than in the controls (21,600 IU; p=0.44). However, since obese patients may require a higher dose of weight-based factor VIII treatment compared to normal weight hemophiliacs, we also assessed the use of factor VIII adjusted for body weight. A trend for a higher amount of factor VIII concentrate used per kilogram (480 IU in the cases and 280 IU in the controls, p=0.527) remained (Table 2).

Table 2. Bleeding episodes and factor VIII concentrate use in 2008 and 2009

<table>
<thead>
<tr>
<th></th>
<th>Cases (BMI ≥ 30)</th>
<th>Controls (BMI ≤ 25)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Severe patients</td>
<td>Non-severe patients</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>N=2</td>
<td>N=13</td>
<td>N=15</td>
</tr>
<tr>
<td>Total Bleedings</td>
<td>8</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>Joint Bleedings</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Muscle Bleedings</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Total FVIII concentrate use (mean)</td>
<td>341.000</td>
<td>4077</td>
<td>49.000</td>
</tr>
<tr>
<td>FVIII concentrate use per kg (mean)</td>
<td>3331</td>
<td>42</td>
<td>481</td>
</tr>
</tbody>
</table>

*total bleeds= muscle bleeds+ joint bleeds+ other bleeds, *total factor VIII concentrate use = factor VIII prophylaxis and on demand use, *Total bleeds all cases compared to total bleeds all controls

Osteoarthritis

One third of the obese hemophilia patients (n=5) had osteoarthritis compared to 20% of the normal-weight patients (n=3), p=0.417. Of these patients only two patients had a severe form of hemophilia A, one obese patient and one patient with a normal weight. Osteoarthritis was diagnosed by a combination of clinical findings and radiology reports. However, in only three patients the radiology report mentioned specific abnormalities on which the diagnosis was based (i.e. complete absence of cartilage, joint space narrowing with presence of subchondral cysts, narrowing of joint space with presence of marginal osteophytes). Symptoms consisted of pain and stiffness, decreased mobility and pain on palpitation.

Osteoarthritis was present in either the knees or ankles in 6 of the 8 individuals with osteoarthritis. These results seemed consistent with the lower score of the HAL for the lower extremity. One obese hemophilia patient had osteoarthritis of the hips and one normal-weight subject had osteoarthritis of the elbow.
DISCUSSION

The aim of the present study was to evaluate the influence of obesity on daily impairment, bleeding complications and factor VIII concentrate use in patients with hemophilia. Using the HAL score, hemophilia patients with obesity had an impaired functional ability compared to hemophilia patients with normal weight. A higher frequency of bleeds and a trend towards a higher use of factor VIII concentrate was also observed.

The prevalence of obesity is rapidly increasing, not only in the general population, but also in patients with hemophilia. In the present study BMI was inversely related to impairment in physical activities. In a large study in 274 obese subjects in the general population, osteoarticular pain was one of the main determinants of a poor health related quality of life [12]. Since obesity induces athropathy in the general population, it is logical to assume that obesity will have at least the same, but probably even more consequences for hemophilia patients. Strain on already fragile joints could potentially induce spontaneous joint bleedings, which could in turn further aggravate arthropathy. At present, more than 43% of the hemophilia population is obese or has overweight [3], which implies that a substantial number of patients will have an increased risk of osteoarthritis. In this small study a higher frequency of osteoarthritis in the obese patients was observed, but this did not reach statistical significance due to the small sample size. Since the majority of the patients in whom osteoarthritis was diagnosed consisted of non-severe hemophiliacs, osteoarthritis was most likely caused by obesity (which was generally present for several years) and not by frequent joint bleeds. The number of patients with severe hemophilia was too low to discriminate between bleeding and obesity as a cause of osteoarthritis. Nevertheless, it is important to actively prevent obesity, starting at childhood. Moreover, more attention and support is needed to help obese hemophiliacs to reduce weight. Low intensity sports (e.g. golf, swimming, walking, and sailing) that carry a low bleeding risk, should be promoted. Furthermore, a higher frequency of bleedings might be an additional consequence of obesity in this specific population, further impairing physical ability.

Some limitations need to be addressed. First, in the HAL score patients had maximum points for specific questions even when the answer was marked as not applicable. Since activities such as gardening may not have been applicable for patients due to physical limitations, this could have led to an underestimation of the limitations in daily activities. Second, the small sample size of our study may have limited significant differences between the two groups.

In conclusion, obesity is associated with limitations in daily life activities in patients with hemophilia as shown by a lower overall score of the HAL, and likely increase the number of bleeds and use of larger amounts of factor VIII concentrate. Considering the high prevalence of obesity in hemophilia patients, preventive measures are strongly warranted.
REFERENCES