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ORIGINAL ARTICLE

Obesity and overweight in patients with hemophilia: Prevalence by age, clinical correlates, and impact on joint bleeding

Chia-Yau Chang[a,b], Tsung-Ying Li[c,d], Shin-Nan Cheng[d,e,f], Ru-Yu Pan[d,g], Chao-Neng Cheng[h], Hung-Jung Wang[b,i], Shu-Hsia Hu[d], Yeu-Chin Chen[d,j,*]

[a]Department of Pediatrics, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, ROC; [b]Division of Pediatric Hematology/Oncology, Hemophilia Center, Taipei Medical University Hospital, Taipei, Taiwan, ROC; [c]Department of Rehabilitation, Tri-Service General Hospital, Taipei, Taiwan, ROC; [d]Hemophilia Care and Research Center, Tri-Service General Hospital, Taipei, Taiwan, ROC; [e]Department of Pediatrics, Tungs' Taichung MetroHarbor Hospital, Taichung, Taiwan, ROC; [f]Department of Pediatrics, National Defense Medical Center, Taipei, Taiwan, ROC; [g]Department of Orthopedics, Tri-Service General Hospital, Taipei, Taiwan, ROC; [h]Department of Pediatrics, National Cheng Kung University Hospital, Taichung, Taiwan, ROC; [i]Department of Medical Imaging, Taipei Medical University Hospital, Taipei, Taiwan, ROC; [j]Division of Hematology/Oncology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC

Abstract

Background: The prevalence of obesity in patients with hemophilia (PWH) varies among different ethnicities, and its influence on joint bleeding and hemophilic arthropathy has not been studied in Taiwan population. We explored the prevalence and clinical correlates of obesity and the impact of body mass index (BMI) on annual joint bleeding rate (AJBR) and hemophilic arthropathy in PWH in Taiwan.

Methods: We retrospectively collected clinical information on 140 severe/40 moderate PWH from 2006 to 2014. The patients' median age was 31.5 years, ranged from 6 to 73 years. Their BMI, 6 index joints score by Pettersson scoring, AJBR, and other clinical data were analyzed.

Results: The prevalence of overweight and obesity by age group was 7.1% in PWH aged ≤10 years, and rapidly increased to 34.5% in PWH aged 11 to 18 years, 46.7% in PWH aged 18 to 29 years, 61.8% in PWH aged 30 to 39 years, 60.6% in PWH aged 40 to 49 years, and 48% in PWH aged ≥50 years, respectively. Two peak rates were 72.7% in PWH aged 35 to 44 years and 66.7% in PWH aged >65 years. Age, HCV infection, knee score, elbow score, and total 6 index joints scores were found to correlate positively with BMI. However, subtype and severity of hemophilia, ankle scores, HBV and HIV infection did not correlate with BMI. Finally, BMI was found to correlate positively with AJBR in both adult and pediatric PWH.

Conclusion: The prevalence of overweight and obesity in adolescent and adult PWH was higher than those in the general male population in Taiwan, which rapidly increased with age to peak in PWH aged 35 to 44 years and >65 years. High index joint score, with the exception of ankle scores, positively correlated with high BMI. Further, BMI and obesity also had positive correlation with AJBR in PWH. To our knowledge, this is the first study examining these associations in PWH in Taiwan.

Keywords: Annual joint bleeding rate; Body mass index; Hemophilia; Hemophilic arthropathy; Obesity; Pettersson score; Prevalence

1. INTRODUCTION

Obesity and being overweight are common and increasing health problems in modern society, and may constitute a major risk for serious chronic diseases and comorbidities such as chronic musculoskeletal disease, cardiovascular disease, cancer, etc.[1–3] In recent decades, advances in hemophilia care such as prophylaxis therapy and inhibitor management have improved the quality of life and prolonged the survival for patients with hemophilia (PWH). As a result, comorbidities of PWH such as obesity and overweight, which were a secondary concern in the past, are getting more attention.[4,5] Increasing prevalence of obesity in PWH has been reported and is an emerging challenge for the care of PWH.[4–6] From western countries, there have been some studies on prevalence of obesity in PWH and its impact on bleeding.[5–9] Repeated joint bleeding and impaired joint function can lead to a reduction in physical activity in PWH and consequently increase their risk of obesity. Wong et al.[6] demonstrated that hemophilic arthropathy (HA) occurred more commonly in obese PWH and the corresponding decrease in joint range of motion (ROM) correlated with increased body mass index (BMI). On the contrary, obesity can result in overload of joints and muscles in PWH and make them more vulnerable to joint bleeding and consequent joint damage. Biere-Rafi et al.[7] reported that obese PWH had a significant lower score of Hemophilia Activity List than

*Address correspondence: Dr. Yeu-Chin Chen, Division of Hematology/Oncology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, 325, Section 2, Chenggong Road, Taipei 114, Taiwan, ROC. E-mail address: yeuchin99@gmail.com (Y.-C. Chen).

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nonobese PWH, mainly caused by impaired lower limbs function. It was also reported that as BMI increases in PWH, ROM decreases, especially active ROM of lower limbs.[10,11] Some investigators reported that increased BMI led to more joint bleeding and more consumption of clotting factor treatment for PWH.[7–9] Prevalence of overweight and obesity in PWH vary among different countries and reports from Asian countries are very limited. Our aims were to investigate the prevalence of obesity and overweight in PWH in Taiwan and its clinical correlates, and explore the impact of BMI on annual joint bleeding rate (ABJR) and HA, which can impair quality of life and increase medical cost for PWH.

2. METHODS

2.1. Subjects and clinical correlates

We retrospectively collected data on 180 PWH including 140 severe and 40 moderate type hemophilia from two hemophilia centers of Tri-Service General Hospital and Taipei Medical University Hospital, both being referral centers for PWH, from 2006 to 2014. Among the 180 PWH, majority of patients regularly followed up at their respective hemophilia center and received comprehensive care including roentgenograms of the 6 index joints for evaluating progression of joint function. The data such as body weight, body height, and other clinical information including hemophilia type and severity, inhibitor status, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and human immunodeficiency virus (HIV) infection were obtained by chart review and analyzed. This study was approved by the ethics review board of both institutions and all enrolled patients signed an informed consent.

2.2. BMI in children and adults

According to World Health Organization (WHO) criteria, BMI was categorized into four levels comprising underweight, normal, overweight, obesity, which were classified by <5th percentile, 5th-85th percentile, 85th-95th percentile, ≥95th percentile, respectively. BMI ranging from 25 to 30 kg/m^2 represents overweight and BMI ≥ 30 kg/m^2 represents obesity by the standard of WHO.[1] However, as Asians have higher comorbidities and fat mass at lower BMI levels than Caucasians, the cut-offs are different from Caucasian standards.[12] For Taiwanese adult BMI, the risk-based standard by the mortality and morbidity for categorization is underweight as BMI < 18.5 kg/m^2, normal as BMI of 18.5 to 24 kg/m^2, overweight as BMI ≥ 24 kg/m^2, and obesity as BMI ≥ 27 kg/m^2.[12] For Taiwanese pediatric BMI for age, the categorization is according to the BMI standard of children and adolescents in Taiwan bulletined on the website of the Ministry of Health and Welfare.[13] According to our Taiwanese criteria, we calculated the prevalence of obesity, overweight, underweight in adult and pediatric PWH by different age groups. We also retrieved the prevalence of overweight and obesity in general male population from the Ministry of Health and Welfare in Taiwan for comparison with those of PWH in the study.[14]

2.3. Joint scores of the 6 index joints

HA was assessed by conventional roentgenograms of elbows, knees, and ankles. The Pettersson scoring classifies plain roentgenograms of knees, elbows, and ankles, each calculated by Pettersson score on a scale from 0 to 13.[15] The minimum score is 0, signifying no bony change of arthropathy, and the maximum score is 78 points. Here, we defined any index joint with either arthrodesis or joint replacement as 13 points. Elbows score, knees score, and ankles score stood for the sum of bilateral elbow joints score, bilateral knees score, and bilateral ankles score, respectively. Lower limbs score represented the sum of knees score plus ankles score. Total score represented the sum of the 6 index joints score. Among the 180 PWH, there were a total of 142 PWH who had the complete medical records of the 6 index joints score. The relationship of joints score and BMI was analyzed.

2.4. Annual joint bleeding rate

AJBR was obtained from chart records of PWH who consecutively followed up at least for 1 year, received factor replacement therapy regularly, and had a complete annual joint bleed record. PWH who did not have such complete annual joint bleed records were excluded. Among the 180 PWH, there were a total of 82 PWH who had the complete documents of AJBR and correlation analysis of BMI and AJBR was performed in these patients.

2.5. Statistical methods

Univariate analysis of clinical variables associated with BMI was performed by using an analysis of variance (ANOVA) and the Mann–Whitney *U* test. ANOVA was also used to analyze the association of underweight, normal, overweight, and obesity on all joints score. Spearman's rho was used to analyze clinical correlates with BMI and this test was also used to analyze clinical correlates including BMI with AJBR. $p < 0.05$ was considered statistically significant.

3. RESULTS

3.1. Patient characteristics

Among the 180 PWH, there were 162 hemophilia A patients including 11 with inhibitors and 18 hemophilia B patients. Their median age was 31.5 years, which ranged from 6 to 73. There were 43 boys (aged <18 years) and 137 male adults (aged ≥18 years). The mean age of the 43 boys and 137 male adults was 11.9 years and 37.6 years, respectively.

3.2. Mean BMIs, prevalence of overweight and obesity by age group

The mean BMIs and the proportions of underweight, normal, overweight, and obesity by different age groups are summarized in Table 1. There was no patient who was under 10-years-old with obesity. However, obesity rate increased rather rapidly to 27.6% in teenagers. The prevalence of overweight and obesity combined was 7.1% in PWH aged ≤ 10 years and 34.5% in PWH aged between 10 and 18 years. The prevalence of overweight and obesity increased further with age from adolescence to adulthood. Of adult PWH, the mean BMIs of the three age groups of patients aged >30 years were more than 25, which meant overweight in our Taiwanese adult PWH group. The prevalence of overweight and obesity attained the highest level of 61.7% in PWH aged 30 to 49 years. This prevalence declined in PWH aged ≥50 years to 48% but it was still nearly half (Table 1). The prevalence of overweight and obesity in all adult PWH aged ≥18 years was 29.2% and 24.8%, respectively, with a combined total of 54%, which was higher than the 49.8% noted in the general Taiwanese male population in 2014.[13]

3.3. Comparison of prevalence of obesity and overweight between adult males in the general population and PWH by age group

According to the report from the Ministry of Health and Welfare in Taiwan, prevalence of overweight and obesity in general adult males by different age groups in 2014 is shown in Fig. 1.[14] To compare the prevalence of obesity and overweight between males in the general population and adult PWH, we recalculated the prevalence in adult PWH according to the same classification that is used for various age groups of males in the general population. The prevalence of overweight and obesity in general adult male population aged 45 to 54 years attained peak level of 57.6%, which then gradually declined after ≥55 years. However,

Table 1

Values of body mass index, prevalence of overweight and obesity among PWH by different age groups

Age group, y	Cases number	BMI value (mean ± SD)	BMI status (four groups)				
			Underweight number, %	Normal number, %	Overweight number, %	Obesity number, %	Overweight or obesity, %
Children (<18)	43	20.4 ± 4.6	6 (14.0)	26 (60.5)	3 (7.0)	8 (18.6)	11 (25.6)
≤10	14	16.3 ± 2.5	3 (21.4)	10 (71.4)	1 (7.1)	0 (0)	1 (7.1)
18>y>10	29	22.3 ± 4.1	3 (10.3)	16 (55.2)	2 (6.9)	8 (27.6)	10 (34.5)
Adults (≥18)	137	24.6 ± 4.7	4 (2.9)	59 (40.1)	40 (29.2)	34 (24.8)	74 (54.0)
18-29	45	23.2 ± 4.4	4 (8.9)	20 (44.4)	16 (35.6)	5 (11.1)	21 (46.7)
30-39	34	25.3 ± 4.3	0 (0)	13 (38.2)	8 (23.5)	13 (38.2)	21 (61.8)
40-49	33	25.5 ± 4.5	0 (0)	13 (39.4)	8 (24.2)	12 (36.4)	20 (60.6)
≥50	25	25.5 ± 5.5	0 (0)	13 (52)	8 (32)	4 (16)	12 (48)

BMI = body mass index; PWH = patients with haemophilia.

the prevalence of overweight and obesity in PWH aged 35 to 44 years attained the highest level of 72.7% and declined to 42.9% at 45 to 54 years, but gradually rose up again and achieved another peak level of 66.7% when aged ≥65 years. The prevalence of overweight and obesity in PWH in all age groups was greater than that in general male population except in the age group of 45 to 64 years.

3.4. Relationship of BMI and Pettersson score with age in PWH

To see whether the joint deterioration preceded or followed rise in BMI of PWH, we plotted the relationship of BMI and total 6 index joints score with age in PWH as illustrated in Fig. 2. Both curves (BMI and Pettersson score) increased in parallel with age but it appears that the Pettersson scores rose before BMI. The curves eventually crossed at 45 to 54 years of age. Although these data are not prospectively looking at a single cohort over time but rather snap shots of different age groups, it seems that worsening joint disease appeared first and was followed by increasing BMI into overweight and obesity range.

3.5. Analysis of clinical correlates with BMI in PWH

By univariate analysis, PWH aged ≥ 18 years, positive HCV infection, elbows score ≥ 5 points, knees score ≥ 4 points, ankles score ≥ 9 points, lower limbs score ≥ 16 points, and total score ≥ 21 points were found to have significantly higher BMI than those patients without these parameters ($p < 0.01$), as shown in Table 2.

By correlation analysis, 142 PWH who had complete medical records including Pettersson score and other clinical correlates were analyzed. Both age and positive HCV infection had positive correlations with BMI ($p < 0.01$). All joint scores except ankles score were found to have positive correlation with BMI ($p < 0.01$). However, hemophilia subtype, severity of hemophilia, HBV infection, HIV infection, and ankles score were not found to have correlation with BMI, as shown in Table 3.

3.6. The impact of BMI on AJBR in PWH

There were only 82 PWH whose AJBR data could be completely recorded and analyzed. Total BMI and BMI of four different groups (obesity, overweight, normal, and underweight) were found to have positive correlation with AJBR (Table 4). Moreover, age, severity of hemophilia, HCV infection were also found to have positive correlation with AJBR.

4. DISCUSSION

Obesity and overweight can increase the risk of chronic musculoskeletal disease, diabetes, hypertension, hyperlipidemia, cardiovascular disease, stroke, and cancer.[1–3] Prevalence of obesity can vary in different ethnicities, being typically high in North America and Europe and relatively low in Asia and Africa.[1,16] It has been reported that prevalence of obesity in PWH varies among different countries and has conflicting comparison with the general population. In US and Canada, it was reported that there was high rate of overweight and obesity among PWH, but in India and Mexico, it was reported that there is a lower prevalence of obesity in PWH than those in the general population.[6] According to the data of Center for Disease Control (CDC) in 2005, for adult PWH in US, prevalence of overweight and obesity was high up to 58%, which was higher than 54.9% in the normal population.[17] The prevalence of overweight and obesity among adult PWH was also higher in the UK and Germany with reported rates of 64% and 62%, respectively.[6,18]

In our study with a large series of patients, the prevalence of overweight and obesity in adult PWH was 54%, which was higher than the 49.8% seen in the general male adult population. The reason for that may be the impact of HA in our Taiwanese

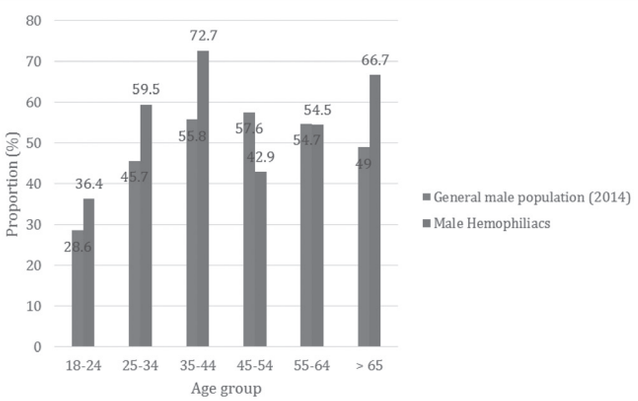

Fig. 1 Comparison of prevalence distributions of overweight and obesity between adult patients with hemophilia and general adult male population (in 2014) by age.

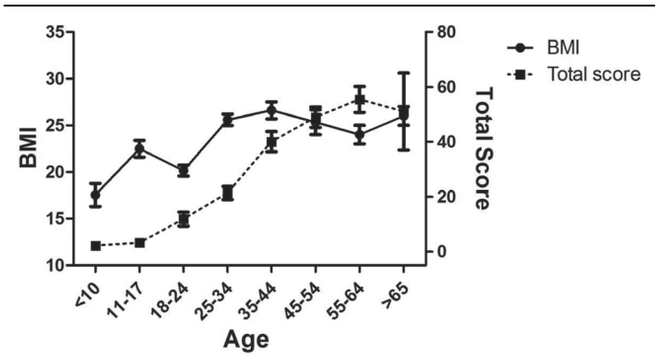

Fig. 2 Relationship of body mass index (BMI) and Pettersson score (total 6 index joints score) with different age groups in patients with hemophilia. The data of BMI and total joints score are expressed as mean ± SD.

Table 2

Pateint characteristics, clinical variables, and univariate analysis for BMI of PWH

Characteristics variables	Case number, %	BMI value (mean ± SD)	*p*
Age*	180		
<18 y	43 (22.8)	20.4 ± 4.6	$p < 0.01$***
≥18 y	137 (77.2)	24.6 ± 4.7	
Subtype**	180		
A	151 (83.9)	23.4 ± 4.9	NS
B	18 (10)	25.7 ± 5.6	
A+ inhibitors	11 (6.1)	22.9 ± 3.7	
Severity*	180		
Severe	140 (77.8)	23.9 ± 5.0	NS
Moderate	40 (22.2)	22.6 ± 5.0	
HBV*	159		
Negative	146 (91.8)	23.8 ± 4.8	NS
Positive	13 (8.2)	25.0 ± 3.7	
HCV*	165		
Negative	55 (33.3)	21.7 ± 4.8	$p < 0.01$***
Positive	110 (66.7)	25.0 ± 4.5	
HIV*	166		
Negative	157 (94.6)	23.9 ± 5.0	NS
Positive	9 (5.4)	23.8 ± 2.9	
Joint scores*			
Elbows score	142		
<5	69 (48.6)	22.7 ± 4.1	$p < 0.01$***
≥5	73 (51.4)	25.4 ± 5.1	
Knees score	142		
<4	71 (50)	22.7 ± 4.3	$p < 0.01$***
≥4	71 (50)	25.5 ± 5.0	
Ankles score	142		
<9	67 (47.2)	23.0 ± 5.0	$p < 0.01$***
≥9	75 (52.8)	25.0 ± 4.6	
Lower limbs score	142		
<16	69 (48.6)	22.8 ± 4.7	$p < 0.01$***
≥16	73 (51.4)	25.3 ± 4.7	
Total score	142		
<21	70 (49.3)	22.7 ± 4.3	$p < 0.01$***
≥21	72 (50.7)	25.4 ± 5.0	

*Mann–Whitney *U* test.

**Analysis of variance (ANOVA).

***Significance at the 0.01 level (two-tailed).

BMI = body mass index; NS = not significant; PWH = patients with haemophilia.

PWH. HA was common in Taiwanese PWH with prevalence up to 64.3% for adolescents and 90% to 100% for adults,[19] which may lead to more physical constraint and limitation and consequent overweight and obesity.

In this study, it was shown clearly that PWH and Taiwanese general males had different distribution of the prevalence of overweight and obesity with age, with the former demonstrating a two-peak curve and the latter a one-peak curve. The distribution curves were in fact very similar to a report from a UK study in 2016, in which von Mackensen et al.[18] reported a similar distribution of prevalence of overweight and obesity in British PWH and general male population.

In 2010-2011, the prevalence of overweight and obesity in Taiwanese general male adolescents was reported as 27.6% in those aged 13 years, 29.8% in those aged 14 years, and 33.9% in those aged 15 years.[20] In this study, the prevalence of overweight and obesity in all teenagers was 34.5%, which was higher than those of early male adolescents in the general population. It has been reported that prevalence of overweight and obesity in pediatric PWH was usually higher than those in non-hemophilic boys because of overprotection by their parents and constrained physical activity for prevention of bleeding from trauma.[4,21] Revel-Vilk et al.[22] reported that among 170 boys with hemophilia, rate of obesity was 14.7%. In 2005, CDC reported rate of overweight in children with hemophilia was 20% to 21% when compared to 11.5% to 13.7% in general pediatric population.[17] Ross et al.[21] reported that among 37 severe pediatric PWH in USA, prevalence of overweight and obesity was 19%. In our study, the summed prevalence of overweight and obesity in 43 severe/moderate pediatric PWH was 25.6%, which was higher than those reported from USA. This discrepancy may be attributed to lower physical activity in pediatric PWH because of lesser use of prophylaxis therapy in Taiwan before 2014. The national health insurance for implementation of prophylaxis therapy in Taiwan was not allowed until middle of 2014 (which postdates the enrollment time frame of this study). Whether prophylaxis therapy helps with more physical exercise and reduces obesity rate in pediatric PWH in Taiwan is worthy of study in the future.

Our study showed the prevalence of obesity in pediatric PWH aged ≤10 years was 0% and 27.6% for patients aged 11 to 18 years, thereby implying that the obesity rate increased rapidly in the teenage group. A similar finding was reported by Majumdar et al. They found that children with hemophilia, aged <11 years, had a significant lower prevalence of overweight and obesity than those children, aged 11 to 20 years.[18] This observation of easy body weight gain during teenage years in PWH deserves clinical attention. Moreover, it has been reported that obesity in childhood is a risk for obesity in adulthood.[23] Serdula et al.[24] have reported that one third of obese preschool children, one half of obese school-age children, and two third of obese adolescences became obese in adulthood. Therefore, obesity prevention

Table 3

Correlation between clinical variables and BMI among PWH (n = 142)

Clinical variables*	BMI value
Age, y	r = 0.334***
Subtype of hemophilia[a]	NS
Severity of hemophilia	NS
HBV infection	NS
HCV infection	r = 0.330***
HIV infection	NS
Joints scores**	
Elbows score	r = 0.288***
Knees score	r = 0.245***
Ankles score	NS
Lower limbs score	r = 0.231***
Total score	r = 0.276***

[a]Including hemophilia A, hemophilia B, hemophilia A with inhibiters.
*Spearman's rho.
**Pettersson scoring system.
***Correlation is significant at the 0.01 level (two-tailed).
BMI = body mass index; NS = not significant; PWH = patients with haemophilia.

Table 4

Correlation between clinical variables and annual joint bleeding rate

Clinical variables*	AJBR
Age, y	r = 0.352**
Subtype of hemophilia[a]	NS
Severity of haemophilia	r = –0.381**
HBV infection	NS
HCV infection	r = 0.443**
HIV infection	NS
BMI	r = 0.330**
BMI status (four subgroups)	r = 0.281**
Underweight	
Normal	
Overweight	
Obesity	

[a]Including hemophilia A, hemophilia B, hemophilia A with inhibiters.
*Spearman's rho.
**Correlation is significant at the 0.01 level (two-tailed).
AJBR = annual joint bleeding rate; BMI = body mass index; NS = not significant.

should be started during childhood because there was already a high obesity rate in teenagers with hemophilia.

With regard to clinical correlates with BMI, moderate and severe PWH had no difference in BMI value by either univariate or correlation analysis in our study. The association between hemophilia severity and obesity remains conflicted. Hofstede et al.[5] reported that nonsevere PWH were significantly more overweight than severe PWH. On the contrary, Revel-Vilk et al.[22] reported that prevalence of obesity was higher in severe hemophilia boys. However, CDC reported that prevalence of both overweight and obesity in severe PWH were lower than those in nonsevere PWH in 2005,[17] and von Mackensen et al.[18] reported mild PWH had a trend to have higher BMI compared to those with severe or moderate PWH. Majumdar et al.[23] reported that there was no significant difference in obesity rates between severe and nonsevere PWH. One of the possible causes of these varied observations may be that not every severe PWH has HA of joints and physical inactivity, especially under adequate factor replacement therapy. McNamara et al.[26] showed that muscle atrophy mediated at least part of the relationship between hemophilia severity and BMI.

With regard to the impact of HA on BMI, we found that elbows score ≥ 5 points, knees score ≥ 4 points, ankles score ≥ 9 points, lower limbs score ≥ 16 points, and total score ≥ 21 points were significantly associated with higher BMI. By further correlation analysis, all aforementioned joints scores except ankles score were found to have positive correlation with BMI. Obesity usually results from excess intake of calories and less physical activity, and HA of PWH may lead to marked physical limitation without prophylaxis therapy. Patients with more severe HA (high joints score) are usually with more restriction in terms of physical activity and therefore more vulnerable to increased body weight. In our study, when looking at the relationship of BMI and total 6 index joint score with increasing age in PWH (Fig. 2), it appears that joint score deterioration occurred before development of obesity in our patients.

Interestingly, hemophilia patients with HCV infection in our study were found to have higher BMI than those patients without HCV infection. It has been reported that chronic liver disease such as HCV was associated with chronic proinflammatory metabolic effects and may predispose to weight gain, although this does not explain why a similar association was not seen with HBV or HIV infection in our study.[27]

We analyzed the clinical correlates with AJBR and found that age, hemophilia severity, BMI value, and BMI status (underweight, normal, overweight, obesity) had positive correlations with AJBR. In our study, AJBR correlation with age of PWH may be due to high HA prevalence among PWH in Taiwan and more severe HA in older hemophilia patients.[19] McNamara et al.[26] reported that obesity was associated with more frequent bleeding in PWH, where 8 of 30 (26.7%) PWH had arthropathy. HA affects AJBR greatly without adequate treatment such as prophylaxis therapy. Majumdar et al.[28] reported association between weight loss and decreased joint bleeds in a 27-years-old severe hemophilia A patient, who achieved a marked reduction of the 6 index joints bleeds after successful reduction of body weight and BMI.

In conclusion, there was higher prevalence of overweight and obesity in adolescent and adult PWH than in the general male population in Taiwan. The prevalence rapidly increased from childhood to 34.5% in teenagers and the highest rate of 72.7% in adults aged 35 to 44 years. Six index joints score except ankles score, age, and HCV infection positively correlated with BMI value and obesity had a positive correlation with AJBR in PWH.

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