Bone mineral density in Iranian patients with haemophilia: the first experience in southern Iran

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Osteoporosis is a common disease with major negative effects on mobilization and quality of life. Patients with haemophilia are at risk for developing low bone density, osteopenia and osteoporosis. Most patients do not attempt vigorous exercise because of joint pain, swelling, previous haemarthrosis and a fear of joint re-bleeding. Furthermore, they are often not on prophylactic factor replacement therapy, but only receive on-demand factor replacement during joint or muscle bleeding. Other risk factors are hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections and chronic liver disease [1]. Abdelrazik et al. demonstrated that patients with haemophilia may have reduced bone mineral density (BMD) compared with age- and gender-matched controls, and children with established arthropathy have the lowest BMD and BMD Z-scores [2].

We assessed BMD in haemophiliac patients to establish the prevalence of osteoporosis and low peak bone mass, and tried to determine whether osteoporosis correlated with severity of haemophilia, haemophilic arthropathy, HCV and HIV infection.

In this case-control study, 55 patients with haemophilia ranging in age from 16 to 35 years were selected randomly between July and December 2009 from records maintained by Fars Hemophilia Center, part of a major referral hospital for haemophiliac patient in Shiraz, southern Iran. Eighty-seven voluntary control participants ranging in age from 15 to 35 years also took part in our study. All of them were high school or university medical students. Lower limb joints (knees and ankles) were evaluated according to published guidelines for joint evaluation (Colorado Physical Examination-1, full point instrument) [3]. Bone mineral density was measured by dual-energy X-ray absorptiometry (DEXA) with a Hologic model Delphi W densitometer at the left hip and lumbar spine (L2–L4). Virology studies were performed for all patients and control participants. Patients with decompenesated chronic liver disease were excluded. The diagnosis of decompenesated chronic liver disease was based on clinical signs of chronic liver failure and abnormal laboratory findings in liver function tests (albumin, globulin, and bilirubin) or prolonged prothrombin time.

Mean age was 23.5 years in the case group and 25.1 years in the control group (P = 0.49). We found no correlation between hepatitis C status and osteoporosis (P = 0.05). However, Wallney et al. reported that haemophiliac patients with HCV infection had a significantly lower BMD than those without hepatitis C [1]. Similarly, we found no correlation between the severity of haemophilia and osteoporosis in haemophiliac patients (P > 0.05). The mean total joint evaluation score (sum of the scores for both knees and ankles) on the Colorado PE-1 instrument was 8.85 ± 2.25 (range 0–24). The patients consumed a normal traditional diet without calcium or vitamin D supplementation. Our results showed that 41 patients (74.5%) had at least one or more features of chronic arthropathy.

Bone densitometry as measured by DEXA showed significant bone mineral loss at the left hip and lumbar spine in haemophiliac patients compared with control participants (Table 1).

Our study shows a significant association between total joint scores and BMD of the lumbar spine (P = 0.004). Strategies are available to prevent or slow the reduction in BMD in haemophiliac patients. The most important approach to prevent haemarthrosis is prophylactic factor replacement therapy, but unfortunately in our region, patients are not placed on a prophylaxis programme. They receive on-demand factor therapy after joint bleeding, so the risk of haemarthrosis and chronic arthropathy is high. Khawaji et al. noted that the use of factor prophylaxis since early childhood may preserve normal BMD in severe haemophilia [4]. It is logical to assess BMD with a DEXA scan in young adolescents with haemophilia to detect the early stages of osteopenia and low peak mass. The use of bisphosphonates in children and adolescents at risk for low bone density is increasing worldwide, and this approach seems beneficial in enhancing BMD [5].

In conclusion, this study documents a significant association between low BMD and osteoporosis in patients with haemophilia. Strategies available to prevent or reduce osteoporosis in these patients include at least a moderate increase in physical activity, weight-bearing

Table 1. Bone mineral density in patients with haemophilia and control.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BMD of lumbar spine (g m⁻²)</th>
<th>BMD of left femoral neck (g m⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>Mean</td>
<td>0.908</td>
<td>0.987</td>
</tr>
<tr>
<td>SD</td>
<td>0.13</td>
<td>0.19</td>
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<tr>
<td>P value (Unpaired t-test)</td>
<td>0.007</td>
<td>0.003</td>
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</tbody>
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BMD, bone mineral density.
Dengue virus infection in haemophilic patients: aggravation of bleeding risk


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Dengue infection is one of the most common mosquito-borne viral diseases of public health significance caused by any of the four dengue serotypes (dengue 1 to 4) and is expanding globally [1]. Paediatric patients and young adults including haemophiliacs in dengue virus endemic areas are particularly at risk. The clinical manifestations of dengue virus infection vary from the asymptomatic, mild degree of flu-like symptoms of dengue fever (DF), to a more severe degree of dengue haemorrhagic fever (DHF) and a serious condition characterized by haemorrhage and shock, called dengue shock syndrome. The case-fatality rate of patients with dengue infection was extremely high (13.7%) in 1958 and gradually decreased to 0.17% in 2000 and has remained unchanged (below 0.2%) during the last decade [2]. In cases of massive uncontrolled bleeding manifestations, the case-fatality rate would be higher than in those without serious complications.

The clinical diagnosis of DHF is based on four major characteristic manifestations [3]: high continuous fever lasting for 2–7 days; haemorrhagic tendency such as positive tourniquet test, petechiae and epistaxis; thrombocytopenia (platelet count ≤100 000 μL⁻¹); and evidence of plasma leakage due to increased vascular permeability manifested by haemoconcentration (an increase in haematocrit >20%) or pleural effusion. The three stages of DHF are, namely, febrile, toxic and convalescent. The febrile stage lasts 2–7 days followed by an abrupt fall to normal or subnormal levels of temperature; the toxic stage lasts 24–48 h; and finally, rapid clinical recovery without sequelae in the convalescent stage. The toxic stage is the most critical period requiring intensive supportive care. Optimal fluid therapy is essential to maintain vital organ function during the critical period. The severity of DHF is categorized into four grades [3]: grade 1, without overt bleeding but positive for the tourniquet test; grade 2, with clinical bleeding diathesis such as epistaxis and ecchymosis; grade 3, circulatory failure manifested by a rapid, weak pulse and narrowing pulse pressure (<20 mmHg) or hypotension, with the presence of cold, clammy skin and restlessness; and grade 4, profound shock in which pulse and blood pressure are not detected. The current WHO guidelines do not consider congenital bleeding disorder as a ‘high-risk’ condition in patients with suspected dengue infection. Moreover, virtually no data are available on the incidence and outcome of dengue infection in people with haemophilia [4].

We report six moderate (n = 4) and severe (n = 2) haemophilic patients (five haemophilia A, one haemophilia B) with dengue virus infection. They reported to the physician after having fever for 2–5 days. Five patients were referred to Ramathibodi Hospital after being admitted at their hometown hospitals for 3–6 days. Two patients were in the febrile stage, while three patients were in the toxic stage. Their ages ranged from 5 to 16 years. They presented with high fever for 6–10 days with lethargy, loss of appetite and bleeding manifestations of petechiae, ecchymosis, epistaxis, and bleeding of the gums, gastrointestinal tract and thorax as shown in Table 1. All patients were serologically confirmed as having dengue virus infection by dengue-specific IgM and IgG determined using ELISA. Secondary dengue infection was found in all patients.

Haemoconcentration with increased haematocrit ≥20% for age was evidenced in four of five patients with DHF, while the remaining patient had a low haematocrit of 34% due to massive haemothorax. Marked elevated alanine aminotransferase (1223–13 371 U L⁻¹) and aspartate aminotransferase (171–4201 U L⁻¹) indicating acute hepatic