

Bone Density Status in Bleeding Disorders: Where Are We and What Needs to Be Done?

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Bleeding disorders, including hemophilia, can be seen in every ethnic population in the world. Among various bleeding disorders, reduced bone density has been addressed in hemophilia A. In recent years, there has been an increasing interest in addressing osteopenia and osteoporosis in hemophilia A. There is little or no study about the possible susceptibility of other individuals with bleeding disorders to reduced bone density. Questions have been raised about the role of blood coagulation factors in bone mineralization. This review provides new insight and ideas for further survey in the field of bleeding disorders and reduced bone density.

Key Words: Hemophilia A, Hemophilia B, Osteoporosis, Reduced bone density, von Willibrand diseases

INTRODUCTION

Hemophilia is a male bleeding disorder with worldwide distribution. Affected individuals have no or reduced levels of coagulation factor VIII and IX in plasma (Hemophilia A and Hemophilia B respectively). Hence, they encounter unusual bleeding pictures spontaneously or after trauma and surgery. The spectrum of bleeding manifestations varies from superficial ecchymosis to lethal hemorrhage in central nervous system.[1,2]

Extensive research over the past two decades have provided important information on tendency of hemophilia to reduced bone density in comparison with the control group. Hemarthrosis, infection with hepatitis C virus, low physical activity, etc. are common reported causes of susceptibility of hemophilia to reduced bone density.

To date, there are few studies that have investigated the status of bone mineral density (BMD) in rare bleeding disorders (RBD). However, much uncertainty still exists and need to be investigated. This review provides new insights into further surveys in this field.

COMMON BLEEDING DISORDERS: HEMOPHILIA

Hereditary deficiency of each coagulation factor in hemostatic cascade has been

explained. Among them, hemophilia A, von Willebrand’s disease (vWD) and hemophilia B are the most common coagulation factor deficiencies around the world. They can be found in all ethnic population.[1] While, the prevalence of hemophilia A varies among different countries, its prevalence has been estimated to be about 3 to 20 per 100,000 population. Hemophilia B is seen as 1 case among 5,000 male births in the European countries and United State.[3] It is estimated that the total number of hemophilia to be about 500,000 in the universe.[4] Among 77 countries in the world, the total number of individuals with hemophilia has been estimated 100,000.[5] Hemophilia A or classic hemophilia comprises about 80% of all cases with hemophilia. Individuals with hemophilia A and B have no or reduced levels of coagulation factor VIII and IX in circulation respectively. Lack or reduced levels of coagulation factors VIII and IX results in impaired clot formation and tendency to bleeding episodes. These lifelong disorders are categorized as severe type (<1%), medium type (1-5%), and mild type (5-30%) of a relevant coagulation factor in blood circulation.[6] Hemarthrosis is regarded as a hallmark of severe hemophilia that is associated with long immobility period.[7] Recurrent hemarthrosis are considered as the main cause of joint deterioration in hemophilia (arthropathy).[8] Replacement therapy using plasma derived or recombinant coagulation factor concentrates are base of treatment of bleeding episodes and prophylaxis regimens.[9]

vWD

It is the most common inherited bleeding disorder worldwide that is associated with defect in adhesion and aggregation platelets.[10] After vascular injury, von Willebrand’s

factor (vWF) mediates attachment of platelets to the sub-endothelium. Also, it acts as carriers of coagulation factor VIII in plasma.[11]

The prevalence of vWD varies based on the definition of disease and on the studied population, nevertheless is about 1 in 10,000 in symptomatic patients who has visited in a hemophilia treatment center.[10] This bleeding disorder characterized by bleeding after trauma and surgery and also mucosal tissues, hemorrhage. The history of bleeding tendency in the patient and his/her family with a laboratory pattern of abnormalities in vWF is necessary for diagnosis and categorizing the disease.[12] On the whole, if we consider the estimated numbers of individuals with common and RBD, there are a noticeable number of patients with bleeding disorders in the world.[13]

RBD

RBD comprise an important cluster of coagulation disorders.[14] They are usually inherited as an autosomal recessive genetic pattern with an estimated prevalence of about 1 to 2 cases per 1,000,000 population (Table 1).[15] They include factor I deficiency, factor II deficiency, factor V deficiency, factor VII deficiency, factor X deficiency, factor XI deficiency, factor XIII deficiency, and combined factor V and VIII deficiency. Affected individuals with RBD have no detectable level or reduced level of relevant coagulation factor in circulation that usually pay the way toward hemorrhage. One of the most important events in the two current decades in hemostasis field was remarkable findings in understanding the molecular basis that leads to each type of RBD.[16] One of the greatest challenges in working on RBD is the rarity of cases. This can be overcome by par-

Table 1. Frequency and types of rare bleeding disorders in population

Type of bleeding disorders	Inheritance	Incidence 1 in	References
Factor I deficiency	Autosomal recessive	2,000,000	Peyvandi et al. [47] Acharya and Dimichele [48]
Factor II deficiency	Autosomal recessive	1,000,000	Peyvandi et al. [49]
Factor V deficiency	Autosomal recessive	1,000,000	Mansouritorghabeh et al. [50], Lak et al. [51]
Factor VII deficiency	Autosomal recessive	500,000	Mansouritorghabeh et al. [52]
Factor X deficiency	Autosomal recessive	1,000,000	Brown and Kouides [53]
Factor XI deficiency	Autosomal recessive	1,000,000	Zucker et al. [54]
Factor XII deficiency	Autosomal recessive	1,000,000	Baldua et al. [55]
Factor XIII deficiency	Autosomal recessive	2,000,000	Dorgalaleh et al. [56]
Combined factor V and VIII deficiency	Autosomal recessive	1,000,000	Mansouritorghabeh and Shirdel [57]

participating in multicenter studies and also make use of the international database of RBD (<http://www.rbdd.org>), European Network of Rare Bleeding Disorders project (EN-RBD, <http://www.rbdd.eu>), or World Federation of Hemophilia database (www.wfh.org) that can facilitate the relevant studies.[17]

QUALITY OF LIFE (QOL) IN HEMOPHILIA

In the recent decade, the overall QOL in individuals with hemophilia has drawn more attention.[18-20] While, participation of individuals with hemophilia in the sport, activities is considered a beneficial and helpful factor for improving QOL, reduced physical activities in hopes of reducing the risk of hemorrhage, is considered as a destructive agent in the quality of everyday life in individuals with hemophilia and their families.[21,22] On the other side of the coin, reduced bone density is a silent disease without any sign and symptom until a bone fracture occurs. In the current decade, with the improvement of treatments in hemophilia, life expectancy has been increased in individuals with hemophilia.[23] Accordingly, femoral neck fracture in hemophilia due to impaired bone stability may occur subsequent trivial trauma in young patients, what is rarely seen in normal population.[24]

REDUCED BONE DENSITY IN HEMOPHILIA

A large and growing body of literature has investigated osteopenia and osteoporosis both in children and adults with hemophilia.[25-32] Reduced bone density in hemophilia can be explained by recurrent hemarthrosis, and lower physical activities that may have an influence on bone mineralization.[33] While, physical activity is considered as a central indicator of bone resorption, patients with bleeding disorders are less likely to engage in high impact activities and also weight-bearing exercises.[34] The exercises with the possibility of physical damages are not recommended for patients with hemophilia, due to increasing risk of bleeding episodes. Individuals with severe hemophilia are usually recommended being engaged in soft exercises such as tennis, swimming, golf, cycling and ping pong.[35] In developing countries due to limited sources of coagulation factor concentrates, children with hemo-

philia rarely engage in high impact sports to avoid risk of hemorrhage.[21] Those patients with hemophilia and arthropathy, characterized by swelling, pain, limited immobility and joint instability, may have a bigger risk of reduced bone density due to less likely to precipitate in exercise activities.[26-28]

Recently, a survey in hemophilia A, hemophilia B and vWD showed higher risk of bone health outcome in comparison with health control and has suggested a possible role of endogenous coagulation factors in maintaining bone mass.[36] A study on a mouse model of hemophilia B showed factor IX deficient mice have bone disease and coagulation factors have a direct impact on bone health.[37] On the other side of coin, the results of a study on the effect of prophylaxis in hemophilia on bone health indicate that replacement therapy as prophylaxis regimen since early childhood may reserve normal BMD in severe hemophilia.[38]

THE NEW HORIZON FOR FURTHER SURVEYS

For the first time Barnes et al.[28] reported reduced bone density in 10 severe hemophiliacs A in 2004. This confirmed by further surveys on individuals with hemophilia.[3,39-44] After that reduced bone density has been shown in two other bleeding disorders (hemophilia B and combined factor V and VIII deficiency).[3,44,45] There are gaps in status of bone density in vWD, factor VII deficiency, factor V deficiency, factor X deficiency, factor XIII deficiency, fibrinogen abnormalities, and platelet disorders. Also, our finding and understanding about the prevalence of osteopenia and osteoporosis in various types of bleeding disorders (severe, moderate, and mild), effective risk factors, pathogenesis of reduced bone density, influences of various treatments of osteopenia and osteoporosis in bleeding patients and possible influence of physical therapy and sports are limited and need to be investigated.

Furthermore, the effect of hemoglobin levels on susceptibility to reduce bone density has been reported by Oh et al.[46] recently. Hence, measuring of hemoglobin level and other indexes of red blood cells in patients with hemophilia and other bleeding disorders is another new horizon needs to be paid attention by further multinational collaborative efforts. Similarly, vitamin D levels in patients with

bleeding disorders and detection of haplotype of vitamin D need to be addressed by further surveys.

However, much uncertainty still exists about the relation between the lower level of each coagulation factor in blood circulation and reduced bone density.

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