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COMMENTARY

The imperative to prevent joint bleeding in everyone living with hemophilia

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People with hemophilia continue to experience bleeding and hemorrhage, including in their joints, resulting in arthropathy, disability, and decreased health-related quality of life (HRQoL). Little has been learned in the last 15 years to explain the biological processes by which bleeding into the joint space leads to chronic joint disease [1]. Higher levels of baseline factor (F)VIII or FIX in people with hemophilia A or B were associated with a lower occurrence of joint bleeding [2]. However, 36% of those with severe hemophilia, despite factor replacement therapy, reported 5 or more episodes of joint bleeding in the prior 6 months [3]. This remains true today despite innovations in treatment regimens and products. Real-world data from an observational, noninterventional, prospective, multicenter study of FVIII prophylaxis in all severity forms of hemophilia A demonstrated that only 34% to 56% reported no bleeding [4]. Similarly, across the emicizumab clinical development program (HAVEN 1-4), 46% of children, adolescents, and adults with hemophilia A, with or without inhibitors directed to FVIII, experienced no bleeding [5]. The burden of disease [6] and the burden of treatment in high-income countries, along with healthcare expenditures for people with hemophilia, remains substantial [7]. In low- and middle-income countries, the situation is even more pronounced because of budgetary constraints [8]. While the situation is modestly better among those with moderately severe hemophilia, in which 61% reported no joint bleeding in the prior year [9], pain and functional limitations persist in this population [10,11], and it is recommended that those with a more severe bleeding phenotype receive regular prophylaxis [12,13].

Van Heel et al. [14] assessed the long-term development of arthropathy using the Pettersson score [15] in 363 people with hemophilia born between 1935 and 2005. Several findings are not unexpected, including the initiation of prophylaxis at successive earlier ages and a decrease in the occurrence of arthropathy in successive birth cohorts (<1970, 1970-1980, 1981-1990, and >1990) as access to treatment and its intensity increased in the Netherlands (and all high-income countries worldwide). Despite access to prophylactic treatments and the gains realized over more than 4 decades, the occurrence of arthropathy was evident in more than 75% of those with severe hemophilia and more than half of those with moderately severe hemophilia, indicating the morbidity of the condition despite its moniker [16]. Among those with severe hemophilia, the most frequently affected joint was the ankle, followed by the elbow, then the knee. While in those with moderately severe disease, the knee was most often affected, closely followed by the ankles and elbows. Unexpectedly, the presence of inhibitors to FVIII or FIX was not associated with the development of arthropathy.

The implications of the breadth and depth of arthropathy documented by van Heel et al. [14] are profound and include acute and chronic pain, physical disability, and reduced HRQoL. In a review of the English literature, the prevalence of chronic pain was 40% among people with hemophilia. Most (61%) reported the intensity of the pain to be moderately severe using the EQ-5D-3L, but 1 in 8 reported extreme pain [10]. Foot and ankle arthropathy results in not only pain and disability but also lower HRQoL scores [17].

We all might be well served by recalling the words of the nursery rhyme, “Dem Bones” (James Weldon Johnson [1871–1938]), which goes something like this, “The toe bone’s connected to the foot bone, the foot bone’s connected to the ankle bone, the ankle bone’s connected to the leg bone, now shake dem skeleton bones!”

Varus or valgus deformity of the knee can influence the tilt angle and tibiotalar angle of the ankle on not only the affected knee side but also the contralateral side [18], and nearly two-thirds (60%) with ankle arthropathy have hindfoot malalignment, all creating a vicious acute or chronic pain cycle [19]. Addressing these issues is often not simple

since even experienced musculoskeletal radiologists fail to identify hindfoot malalignment on ankle magnetic resonance imaging [20].

The lesson here from the excellent work of van Heel et al. [14] is that prevention is key, but how to optimally prevent joint bleeding and subsequent arthropathy? There are a plethora of new and innovative options currently available and more potentially coming to correct the deficit in thrombin generation and rectify the bleeding tendency in people with hemophilia, but these are likely to only be available to those living in countries with the ability to pay. Those in low- and middle-income countries are unlikely to have access to these innovations and are destined to repeat the lessons we have learned from our Dutch colleagues. In addition, underserved and marginalized populations such as women with bleeding disorders and people with inherited bleeding disorders beyond hemophilia (eg, von Willebrand disease, rare factor deficiencies, and platelet disorders) can only hope for a future with innovative therapies to prevent complications of their disease [21].

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