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Short review

Understanding cardiovascular risk in hemophilia: A step towards prevention and management

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ABSTRACT

Advances in hemophilia care have led to increased life expectancy and new challenges in the management of the aging hemophilia population, including cardiovascular risk. Despite the deep knowledge into cardiovascular disease in terms of pathophysiology, risk prediction, prevention, early detection and management gained over the last decades, studies in hemophiliacs are scarce and mainly descriptive. As a growing amount of evidence points towards a similar or increased prevalence of traditional cardiovascular risk factors in hemophilia compared to the general population, the role of non-traditional, disease-related and treatment-related cardiovascular risk factors remains under investigation. Better understanding of cardiovascular risk in hemophilia is mandatory for proper cardiovascular risk prevention and management. Therefore, this review aims to summarize current knowledge on cardiovascular risk in hemophilia patients focusing on a) cardiovascular risk factors (traditional, non-traditional, disease-related and treatment-related), b) cardiovascular morbidity and mortality and c) cardiovascular prevention and management.

1. Introduction

Factor replacement therapy is the cornerstone of modern hemophilia care leading to increased life expectancy of patients with hereditary hemophilia A (HA) and hemophilia B (HB) [1]. Aging hemophilia population presents a number of treatment challenges, including cardiovascular risk prevention and management. Although hemophilia patients have been traditionally considered protected from hypercoagulable states, cardiovascular risk assessment and management in hemophilia remain under study.

Several models have been proposed for cardiovascular risk prediction in the general population based on traditional cardiovascular risk factors, i.e. age, gender, hypertension, diabetes, dyslipidemia and smoking [2–4]. Beyond traditional cardiovascular risk factors, other pathogenetic mechanisms may account for excess cardiovascular risk in specific disease populations [5]. In patients with hemophilia reports on the prevalence of cardiovascular risk factors, cardiovascular risk, morbidity and mortality remain controversial. In addition, studies on pathogenesis of cardiovascular risk in these patients are scarce.

This review aims to summarize current knowledge on cardiovascular risk in hemophilia patients focusing on a) cardiovascular risk factors (traditional, non-traditional, disease-related and treatment-related), b) cardiovascular risk, morbidity and mortality and c) cardiovascular prevention and management. A PubMed search was performed using the following keywords: hemophilia, cardiovascular risk, hypertension, dyslipidemia, diabetes, obesity and smoking. Data presentation has been organized according to different cardiovascular risk factors.

2. Are hemophilia patients protected from thrombosis?

Traditionally, hemophiliacs were reported to have lower incidence of venous thromboembolism (VTE). Indeed, Mannucci and colleagues obtained data from 160 Hemophilia Treatment Centres worldwide concluding that VTE is very rare in hemophilia [6], with only two reported and published episodes of deep venous thrombosis (DVT) [7, 8]. More recently, Girolami et al. reviewed all non-catheter associated venous thromboembolic events in both HA and HB [9]. Among 27 cases of VTE, only one case occurred without any known risk factor. All other cases were associated with either exogenous risk factors such as orthopedic surgery, coagulation factor replacement therapy, severe infection or/and endogenous risk factors considering prothrombotic gene mutations [9]. Consequently, to that review there is solely one report of an unprovoked DVT case in a patient with severe HA [10]. These results are further stressed in a recent systematic review of prospective studies

Abbreviations: aPCC, activated prothrombin complex concentrate; aPL, antiphospholipid; FIX, factor IX; FMD, flow-mediated dilatation; FV, factor V; FVIII, factor VIII; HA, hemophilia A; HB, hemophilia B; HIV, human immunodeficiency virus; IMT, intima-media thickness; MTHFR, methylenetetrahydrofolate reductase mutations; rFVIIa, recombinant activated factor VII; VIII:C, plasma factor VIII coagulation activity; VTE, venous thromboembolism; VWD, von Willebrand disease.

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(1990–2011) by Coppola et al. [11]. In this study, safety data of factor concentrates in patients with HA, HB and von Willebrand disease (VWD) were reported aiming to identify the incidence and type of thrombotic adverse events. In 71 studies (45 in HA, 15 HB, 11 VWD) enrolling 5528 patients treated with 27 different concentrates, 20 thrombotic adverse events (2 HA, 11 HB, 7 VWD) were reported, including only two major VTE episodes. Moreover, both major VTE episodes occurred in VWD patients who had received prolonged coagulation factor replacement for surgery and were associated with abnormally increased FVIII levels. It should be noted that according to Girolami et al. estimation, the prevalence of VTE is 1 out of about 27000 patients while in the normal male population it is about 1/1000 or 1/2000 per year [9]. Overall, these data confirm the low risk of VTE in HA and indicate that thrombotic complications in these patients have a multifactorial pathogenesis, depending on exogenous (coagulation factor replacement therapy, replacement surgery, central-vein catheter, infections) and/or endogenous (prothrombotic gene mutations) risk factors [12–14].

On the other hand, arterial vascular events in hemophilia have not been adequately studied and characterized. There is still conflict in the pertinent literature regarding the possible protection from arterial thrombosis in patients with either HA or HB [15, 16]. Further prospective, large-scale, high-quality studies as well as long-term pharmacovigilance programs such as EUHASS [17, 18] could provide stronger data concerning both the incidence and the risk factors of arterial thrombotic events in this otherwise hypocoagulable state. This review will focus on current knowledge regarding arterial thrombotic events in the cardiovascular system.

2.1. Cardiovascular risk, morbidity and mortality

Robust assessment of cardiovascular risk has been the cornerstone of cardiovascular research over the last decades. Nevertheless, most studies in hemophilia patients were not designed to assess total cardiovascular risk. Supporting the notion of cardiovascular protection, the older study by Rosendaal et al. suggested that total cardiovascular risk in hemophilia patients is lower than that of the general population [19]. A more recent study however indicated significantly increased 10-year cardiovascular risk in patients with hemophilia in patients older than 40 years. The youngest age group (age 30–40 years) presented cardiovascular risk similar to the general population [20]. These data demonstrate the importance of aging in hemophilia population and its effect on cardiovascular risk.

Similarly, existing data on cardiovascular morbidity and mortality in hemophilia patients remain controversial. A recent scoping review revealed four studies reporting a protective cardiovascular effect in hemophilia patients [21–24]; whereas twelve studies documented cardiovascular morbidity similar to the general population. Interestingly, the aging hemophilia population showed different cardiovascular disease prevalence than the general population in seven studies [25]. Nevertheless, as pointed out by the authors, methodological concerns may account for the discrepancy between study results emphasizing the need of large, well-designed prospective studies. It should be also noted that a large retrospective study published after the scoping review, documented increased prevalence of cardiovascular disease in 2506 hemophilia patients compared to 7518 males in the general cohort. Moreover, cardiovascular morbidity appeared earlier in life in hemophilia patients [26]. Similarly, a most recent study of 1054 hemophiliacs from Taiwan confirmed cardiovascular morbidity at an earlier age but reported similar rates of cardiovascular morbidity in 10540 non-hemophiliacs [27]. Regarding cardiovascular mortality, initial studies have shown a low cardiovascular mortality in hemophilia patients compared to the general population [22, 28–31]. In 2010, the only systematic review in the field of cardiovascular mortality in hemophilia showed a non-significant reduction of mortality due to arterial thrombosis in patients with hemophilia [15]. It should be also noted that the middle-aged population of most studies is relatively young to develop fatal cardiovascular events. In addition, registry data often utilize death certificates to assess causes of death which is not the most reliable source of information. Therefore, lower cardiovascular mortality in this population does not necessarily correspond to protection from cardiovascular disease.

2.2. Incidence and prevalence of traditional cardiovascular risk factors in hemophilia patients

2.2.1. Hypertension

Hypertension has been long recognized as a prothrobotic state that leads to increased cardiovascular morbidity and mortality. Endothelial damage, vascular dysfunction, abnormalities in coagulation and fibrinolysis and platelet activation sustain the increased thrombotic risk observed in the general population with essential hypertension [32]. Assessment of subclinical target organ damage is considered essential in the evaluation of patients with hypertension and includes assessment of left ventricular hypertrophy, microalbuminuria, carotid atherosclerosis, arterial stiffness, fundoscopy and endothelial dysfunction [33].

Little is known about hypertension in hemophilia patients. Epidemiological evidence dates back to 1990, when Rosendaal et al. reported an increased rate of hypertension and antihypertensive treatment in hemophilia patients as compared to the general population [19]. The issue has been controversial since some studies found similar hypertension prevalence between hemophilia patients and the general population [24, 27, 34, 35]. However, a number of recent studies has confirmed the increased prevalence of hypertension ranging from 49% to 57% in large cohorts of hemophilia patients [20, 21, 26, 36–40]. Despite the plethora of epidemiological evidence, studies on the pathogenesis of hypertension in hemophilia are lacking. An early study of renal disease in hemophilia patients has associated acute and chronic renal disease with hypertension and HIV infection [41]. In particular, hypertension was more common in patients with hematuria suggesting that previous renal damage may predispose to increased hypertension prevalence in this population.

2.2.2. Other traditional cardiovascular risk factors

Except for hypertension, diabetes mellitus, dyslipidemia, smoking and obesity are well recognized modifiable traditional cardiovascular risk factors. Coexistence of two or more traditional cardiovascular risk factors results in higher cardiovascular risk stratification; while the presence of diabetes is considered equivalent to previous cardiovascular disease [33]. Results on the prevalence of traditional cardiovascular risk factors in hemophilia patients are conflicting. However, available evidence point towards prevalence similar to the general population.

In particular, diabetes mellitus was more common in hemophilia patients compared to controls in a small study by Walsh et al. [35]. Later reports on the prevalence of diabetes mellitus pointed towards a similar prevalence in hemophilia patients and the general population [20, 27, 42]. In addition, smoking has been documented in a similar percentage of hemophilia patients and controls [20, 27, 35, 42]. Unfortunately, the prevalence of dyslipidemia has not been reported by all relevant studies and therefore, available data are limited and controversial. The Dutch and UK cohorts have shown decreased total cholesterol and high-density lipoprotein levels in hemophilia patients compared to the general population; whereas no difference in dyslipidemia prevalence was found in a recent study of 1054 hemophilia patients [20, 27]. On the contrary, the large US cohort has shown an increased prevalence of dyslipidemia compared to the general population [26].

Among the other traditional modifiable cardiovascular risk factors, obesity may play a major role in hemophilia since it does not only impact cardiovascular health in these patients but also burdens bone and joint disease [43]. The prevalence of overweight and obesity appeared similar in hemophiliacs versus controls [35, 44]. Indeed, the only systematic review of obesity in hemophilia has shown that obesity and