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Review Article

Ankle hemophilic arthropathy: literature review

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Abstract: Hemophilia is a bleeding disorder characterized by the deficiency of a coagulation factors. The hemarthrosis is the most common and earliest manifestation. Repeated hemarthrosis over time causes the development of hemophilic arthropathy. Among most involved joints, the ankle is the one where much uncertainty remains about the best course of action in managing the various degrees of hemophilia manifestations. These manifestations range from simple acute swelling and pain to devastating deformity. The purpose of our review is to draw a comprehensive picture of ankle hemophilic arthropathy epidemiology, pathophysiology, clinical symptoms and signs, radiological features and all the treatments available at present days. This review confirms that the first line of treatment considered should be the replacement therapy of the coagulation deficient factors that, preventing hemarthrosis, stops the development and progression of ankle's joint damage. The treatments proposed in literature for advanced stage of arthropathy are many and vary according to the severity of the case. They range from conservative ones such as physiotherapy, orthosis, intra-articular injections, laser therapy, external beam radiation therapy, radio-synovectomy and oral drug to invasive surgical treatment such as ankle arthrodesis and total ankle replacement. Whatever is the chosen treatment, according to the arthropathy severity we believe that it must be carried out in reference centers for foot and ankle surgery assisted by expert hematologists.

Keywords: Ankle, hemophilia, hemophilic arthropathy, hemarthrosis, total ankle replacement, ankle arthrodesis

Introduction

Hemophilia is a hemorrhagic disease characterized by the deficiency of coagulation factors. The most common forms are Hemophilia A and B respectively due to a deficiency of coagulation factor VIII and IX. Both these forms are recessive X-linked disease, so the majority of the affected population is male. The clinical manifestations are related to the quantity and/or the remaining activity of the deficient factor, so hemophilia is classified in severe if the percentage of functioning factor is below 1%, mild if it is between 2% and 5% and finally moderate if it is between 5% and 50% [1]. The lack of factors VIII and IX causes patients to easily bleed for minor events and these bleedings are harder to interrupt. The most common manifestation of hemophilia, which occur in 80% of patients, is intraarticular bleeding [2]. The recurrent hemarthrosis causes firstly pain and then the development of degenerative disorders. Disorders of the joint capsule are synovium hypertrophy, capsular inflammation and retraction. The articular surface involvement mostly consists of chondral erosion, osteophytes formation, and subchondral cists. All these alterations translate in the ankle and foot into dorsal and plantar flexion reduction, malalignment of talocrural articular surface and a fixed varus or valgus equinus foot. The ankle is the third most common sites of hemarthrosis, preceded by the knee elbow with 24% and 22% respectively [3]. The reason for the augmented risk in these joints resides in their high degree of mobility and in the stress they undergo during physical activity [4]. Treatments for ankle arthropathy are numerous and range from conservative ones such as physiotherapy and orthosis to definitive surgical treatment like arthrodesis and total ankle replacement [5]. The involvement of the foot joints, in

particular the sub-talar, talo-navicular and calcaneo-cuboid is less frequent and usually develops subsequent to the arthrodesis of the talocrural joint [6]. The purpose of this review is to establish the state of the art of the management of the hemophilic arthropathy of ankle because of both the high impact of this pathology on patients' quality of life and the lack of a clear and uniform treatment strategy. Statistical analysis was performed using the SPSS 20 statistical software. First, the results in terms of post-operative outcomes were extrapolated from the studies included in the review and where possible descriptive statistical methods were used which included arithmetic means, frequencies and percentages.

Epidemiology

Hemophilia is an X-linked recessive disease so most of the affected people are male, with rare incidence in female due to variance in inactivation of X chromosome. The incidence for hemophilia A is about 1 per 5,000 to 10,000 males at birth and around 1 per 50,000 males at birth for hemophilia B [7]. It has been estimated that the frequency of joint bleeding in hemophiliacs undergoing prophylactic treatment, with the administration of recombined factor VIII and IX, still occurs in high percentage [8]. In children with hemophilia A and B, mentioned percentages afore are as 33% and 47% respectively. While in adults they consist of 60% and 42% in hemophilia A and B, respectively. This also confirms that the hemarthrosis frequency tends to increase as patients ages reaching 60% for the ankle in adults [9].

Physiopathology

Hemophilia has as a common complication joint damage in the form of a characteristic chronic arthropathy that develops consequent to recurrent intraarticular bleeding. The mechanisms that generate hemophilic arthropathy in foot and ankle are the same as every other joint involved. As acute hemarthrosis occurs the amount of blood degradation products exceed the capacity of the synovial membrane to absorb and eliminate them. So, these products, especially iron and hemosiderin, irritates the synovium that starts to produce proinflammatory cytokines. This induces a proliferation of the synovial tissues and blood vessels that characterizes hemophilic synovitis. Blood degradation products and inflammation also contributes to pathological reabsorption and remodeling of bone and cartilage. All these factors make the joint more prone to bleed, giving birth to a vicious cycle of deformity, bleeding, destruction, remodeling and worsen deformity.

Clinical presentation

The first manifestations of ankle and foot hemophilic arthropathy are swelling of the joint and pain that disappear as the acute event fades away. In the studies analyzed pain was mostly measured with Visual Analogue Scale (VAS) and the mean value was 5.04 and ranged from a minimum of 0.6 to a maximum of 8.5. Pain causes patients to assume an antalgic equines posture that is the first alteration. Even if this posture is correctable at the beginning, it becomes fixed as the disease progresses [10, 11]. The second modification for frequency is the reduction of ROM with a mean value of 21.3° ranging from 9.9° to 31.7° compared to the 70° of normal adults.

Another frequent sign in the ankles of hemophiliacs is a valgus hindfoot deformity [12] but is also possible a varus hindfoot deformity. Varus hindfoot is caused by the malalignment of subtalar joint and valgus rotation subsequent to either the overgrowth of the medial malleolar in adolescence or the development of arthrosis in adulthood [10]. The fixed plantar flexion derives from the degeneration of tibiotalar joint and osteophytes growth on the anterior part of tibia's articular surface. This joint remodeling locks the foot in an equines-valgus position facilitating the retraction of the Achilles tendon, that itself participate in the final deformity [13]. All these manifestation, especially sudden pain without trauma, can make it difficult to determine the cause of patient discomfort, so differential diagnosis with other atraumatic diseases of the foot [14-16] may be necessary.

The most used scale to evaluate functional status of the ankle and foot was the American Orthopedics Foot and Ankle Scale (AOFAS). Among the studies considered the AOFAS mean value at clinical presentation is 31.76 and ranges from 22.0 to 40.2.

Imaging

Radiological imaging, especially X-Rays, plays a fundamental role in the evaluation of joints.

Table 1. Ankle joint radiological evaluation: Pettersson score

Radiological alteration	Finding	Score
Osteoporosis	Absent/Present	0/1
Epiphysis enlargement	Absent/Present	0/1
Subchondral face irregularity	Absent/Slight/Pronounced	0/1/2
Joint spaces narrowing	Absent/<50%/>50%	0/1/2
Subchondral cist formation	Absent/one cist/>1 cist	0/1/2
Joint marginal Erosion	Absent/Present	0/1
Incongruence between joint surface	Absent/Slight/Pronounced	0/1/2
Deformity	Absent/Slight/Pronounced	0/1/2

Standard radiographs of the ankle (anteroposterior and lateral view) can be used to evaluate a series of alterations such as osteoporosis, enlargement of epiphysis, subchondral surface irregularity, joint space narrowing, subchondral cyst, joint margins erosion, incongruence between joint surfaces, anterior and posterior osteophytes. It can also determine the valgus tilt due to medial tibial overgrowth and the flattering and collapse of talus dome due to avascular necrosis and deformity in general. The most common radiographic score used to classify joint damages is the Pettersson score (**Table 1**) [17, 18].

The radiographic changes of the foot are mostly similar to those of the ankle and the most involved joints are the subtalar and the talonavicular. A useful tool evaluate them is the Kellgren-Lawrence scale (**Table 2**) [19, 20]. Even thanks to lower costs and easier accessibility X-rays are the most commonly used to evaluate the degree of joint disease, but the gold standard for articular imaging is MRI. This technique also allows to evaluate soft-tissues damages, the quantity of hemarthrosis, synovial hyperplasia, hemosiderin deposits and cartilage loss [21]. Along with MRI also Ultrasound (US) can be used to evaluate both bone and soft tissues damages in particular Musculoskeletal ultrasonography (MSKUS) allowed clear visualization of synovial lesions, effusion, cartilage modification and bone surface damage [22]. CT does not seem to be used much, probably because X-Rays are sufficient to determine bone involvement, while US and especially MRI are more useful to stage soft tissues.

Treatment

Since hemophilia is a pathology characterized by the deficiency of coagulation factors, the first line of treatment is intravenous administration of deficient factors substitutes which prevent recurrent bleeding and, consequently, the arthropathy establishment. Treatment of the arthropathy represents a second-line therapy to be undertaken when hemophilic hemarthrosis has resulted in joint degeneration and deformity [23].

Conservative treatments

Many types of conservative approaches have been proposed to treat hemophilic ankle arthropathy, most of which are specific for mild-to-moderate conditions (**Table 3**).

Physiotherapy: When arthropathy is already overt and prophylactic treatment is not enough anymore, patients need physiotherapeutic procedures to maintain joint function and range of motion. Treatment of the ankle with physical therapy is complicated because it involves a small joint surface that bears significant body weight, and the joint limitation alters biomechanical movement during walking.

A group of patients, that underwent manual therapy, registered an improvement of gastrocnemius muscle circumference, ankle pain perception, marginal improvement of the gastrocnemius muscles' strength along with increased dorsal ankle flexion, when compared to a control group that participated in educational sessions and home exercises [24]. Moreover, fascial therapy can improve ROM loss due to fibrous tissue formation made of cross-liked collagen resulting from intraarticular degenerative process. This treatment, along with the reduction of ankle joint bleeding [25], is aimed at removing fascial tissue restriction through mechanical stimuli. Direct myofascial release and indirect myofascial release technique, if duly administered over the fascia for 3-5 minutes, can promote cellular communication in the crystalline matrix of the fascia through mechanotransduction and piezoelectric effect.

Orthoses: In symptomatic treatment of hemophilic arthropathy, ankle-foot-orthoses (AFO), ankle-orthoses (AO), insoles, modifications in footwear and orthopedic shoes can be helpful [26]. They can be used to reduce the load stress on the ankle, resist or facilitate motion of arthritic joints, reduce plantar fascia strain by minimizing arch deformation, decrease joint

Table 2. Hindfoot radiologiacal evaluation: Kellgren-Lawrence score

Grade of alteration	Radiological finding
0	No radiological sings of osteoarthritis
I	Uncertain narrowing of articular space and possible osteophytic lipping
II	Definite osteophytes and possible narrowing of articular space
III	Moderate multiple osteophytes, definite narrowing of articular space, small pseudocystic areas with sclerotic walls and eventual deformity of bone contour
IV	Large osteophytes, marked narrowing of articular space, severe sclerosis and definite deformity of bone margins

loading, acting as a cushioning interface between the ground and foot. Also, orthoses can delay surgery because they improve walking comfort and stability sensation by altering the proprioception that controls muscle activity regulation, reducing pain and improving quality of life of people.

Intra-articular injections: Like in other types of arthritis, intra-articular injections can be used too. Yearly hyaluronic acid injections with physical therapies and muscular tone maintenance programs, are effective and safe when adopted as second-line therapy in patient with hemophilia affected by early- and mid-stage arthropathy with pain and functional impairment [27].

Laser: Nd:YAG laser with a wavelength of 1064 nm can penetrate and spread easily through the tissue, with a very low histolesive risk. Thus, it gives the chance to treat deep tissues and structures. Pulse intensity and frequency can be modulated to gain the desired results. Photo stimulation promotes tissue repair by accelerating the production of collagen and promoting connective tissue overall stability, with positive effects on pain management and postural control [28].

External beam radiation therapy (EBRT): EBRT reduces the frequency of bleeding in ankle joint, which is important to avoid synovium hypertrophy, release of proteolytic enzymes and hemosiderin deposits. It is important to underline that the mechanism responsible for such reduction is not completely understood. Even with very low administered doses, EBRT treatment resulted in a complete remission in patients with hemophilic pseudotumor, which is a progressive cystic swellings caused by recurrent hemorrhage [29]. All patients enrolled were considered to have a high probability to not respond to conventional therapy, such as arthroscopic or synovectomies with radioisotopes, and may develop profound disabilities. A decrease of the average number of bleedings per month was observed, dropping from 3.6 during one year prior to radiation therapy to 2.1 during the first year after therapy. It was maintained in the range of 1.0 to 1.5 until the tenth year, with a reduction of the 42% at the first year and maintained in the range of 58% to 73% from the second to the tenth year. Patients were also followed (from 1997 to 2006) to monitor any effect on bone growth and any development of neoplasia, but these effects were not found.

Radio-synovectomy (RS): RS, along with primary prophylaxis avoid joint bleeding and can help halt hemophilic synovitis. It consists in destruction of the synovial tissue by intra-articular injection of a radioactive agent like yttrium-90, phosphorus-32, and rhenium-186. Radiation causes fibrosis within the sub-synovial connective tissue of the joint capsule and synovium. It also affects the complex vascular system by obstructing some vessels, while it does not affect the articular cartilage. Radioactive substances, therefore, have a radio necrotic effect. Ideally, RS should be performed before the articular cartilage has eroded. The indication for RS is chronic hemophilic synovitis causing recurrent hemarthroses, unresponsive to hematologic treatment. On average, the efficacy of the procedure ranges from 76% to 80% and administrations can be repeated up to 3 times at 6-month intervals [30].

Oral D-Penicillamine: D-Penicillamine is effective in controlling hemophilic synovitis but its anti-inflammatory effect is not known. At the end of a study with 16 patients followed over a median period of three months, ten patients had an unequivocal response, 3 had a reduction in palpable synovium, and 3 had no response [31].

Surgical treatment

Surgical treatment of ankle arthropathy can be both arthroscopic and open.

Table 3. Conservative treatment

Author	Year	Treatment		Cases		Parameters	Values	
				Patients	Ankles		Preop	Postop
Cuesta Barriuso [24]	2014	Manual therapy group		11	20	ROM dors	8.55	8.05
						ROM plant	38.35	40.45
						VAS	2.95	1.10
		Educational group		10	19	ROM dors	3.58	4.89
						ROM plant	32	34.84
						VAS	2.95	0.0447
		Control group		10	17	ROM dors	10.12	9.88
						ROM plant	41.82	44.18
						VAS	0.618	0.441
Donoso-Ubeda [25]	2020	Fascial therapy	Experiment al group	33		Joint bleeding	1.56	0.27
						Joint status (HJHS)	7.20	6.02
						Pain, under load (VAS)	3.47	1.82
						Pain, no load (VAS)	0.64	0.14
			Control group	32		Joint bleeding	1.70	0.58
						Joint status (HJHS)	6.59	7.20
						Pain, under load (VAS)	3.61	4.14
						Pain, no load (VAS)	0.64	0.70
De La Corte Rodriguez-Merchan [26]	2015	Orthoses		-		-	-	-
Carulli [27]	2020	Viscosupplementation		14	21	NPRS	8	1
						HJHS	20	8
						Annual bleeding rate	3	0
Elnaggar [28]	2020	Pulsed Nd:YAG laser		35		NPRS	6.18	4.53
						Postural control (%)	DC 73.94	DC 81.41
							CoG-MV 4.50	CoG-MV 5.25
Kong [29]	2010	External beam radiation therapy		35		Bleedings per month	3.6	2.1 (1 y)-1.5 (10 y)
Rodriguez-Merchan [30]	2012	Radiosynovectomy		-		Efficacy of the procedure range	-	76-80%
Corrigan [31]	2003	D-Penicillamina		16		Synovitis		10 Complete Response 3 reduction in Palpable Synovium 3 no response

AOFAS: American Orthopedic foot and ankle society score; FFI: Foot Functional Index; NPRS: Numeric Pain Rating Scale; ROM: range of motion (dorsal and plantar); HJHS: Hemophilia Joint Health Score; SF-36: 36 Item short form health survey; VAS: visual analogue scale.

Table 4. Arthroscopic treatment

Author	Year	Treatment	Cases		Parameters	Values	
			Patients	Ankles		Preop	Postop
Kaya Bicer [32]	2018	Debridement	15		Bleeding		
					Frequency	18	1.5
					FFI score %	44.4	23.6
					AOFAS	70	-
Buda [33]	2017	Arthroscopic Bone Marrow-Derived Cells Transplantation	5		AOFAS	34.8	81
					VAS	4.8	2.2
					ROM	12	18
Bai [34]	2013	Arthrodesis	10		Fusion rate	100% in 10.5 weeks	
Tonogai, I; Sairyo, K [35]	2020	Arthrodesis	1	2	JFFS	24	87
					ROM	<20°	-
					dorsiflexion	5°	-
Tsukamoto [36]	2011	Arthrodesis	2	3	AOFAS	39	80

AOFAS: American Orthopedic foot and ankle society score; FFI: Foot Functional Index; ROM: range of motion; VAS: visual analogue scale; JSSF: Japanese Society for Surgery of the Foot ankle-hindfoot scale score.

Arthroscopy debridement and synovectomy: It can be used in patients who do not respond to other treatments or have already developed arthritic changes.

The effects of debridement were evaluated in patients who had at least 50% of range of motion preserved and did not have varus or valgus malalignment and a reduction of bleeding frequency was found in all patients (**Table 4**) [32].

BMDCT: It has been tried to *associate* debridement and synovectomy with arthroscopic bone marrow-derived cells transplantation (BMDCT) to treat osteochondral lesions in hemophilic ankle arthropathy. BMDCT included the production and application of platelet rich plasma (PRP) in order to apply growth factors and a fibrin clot to improve biomaterial implantation and promote regeneration.

In a study of 5 patients with mild or moderate ankle arthropathy [33], BMDCT was withdrawn from the spongy bone of the posterior iliac crest and injected after removal of fibrous and osseous sites of impingements. Synovectomy and resection of damaged osteochondral tissue down to healthy bone were also performed. A 2-year mean follow-up showed: pain reduction, improvement of ROM and AOFAS, partial resume to sport activity, no progression of joint degeneration and signs at imaging of chondral and bony tissues regeneration.

Arthroscopic or open arthrodesis: It is considered the most useful and successful treatment to be performed for end stage arthritis, in patients that underwent conservative treatment for more than 6 months without success and for possible correction in the coronal plane of malalignment lower than 15 degrees.

Arthroscopic arthrodesis has several advantages compared with open arthrodesis, including smaller skin incision, lesser periosteal stripping and lower periarticular soft tissue damage. These factors should have positive influences on union rates. For the procedure two standard anterolateral and anteromedial portals are used.

The procedure was performed in a study with ten patients with end-stage hemophilic arthropathy, which complained of swollen ankles and significant mechanical ankle pain, at load and at rest. The radiographs showed a fusion rate of 100% in an average time to fusion of 10.5 weeks (8-20 weeks). After successful fusion, no patient reported pain from the operated ankle [34].

In a study was analyzed a case of bilateral ankle arthroscopic arthrodesis in a 23-years old man with severe hemophilia A [35]. His total ROM of the ankle was <20° and maximum dorsiflexion was 5°. Preoperative and postoperative functional levels were assessed using the Japanese Society for Surgery of the Foot (JSSF) ankle-hindfoot scale score. Preoperative JFFS score was 24/100. Ankle arthroscopy was performed by anteromedial and anterolateral portals. Arthrodesis was done first in left ankle and, after six months, in right

ankle. Three cannulated 6.0-mm screws were placed to compress the tibia onto the talus. The ankle was fixed in the neutral position. Bony union was confirmed 8 weeks after surgery. At the 1-year follow-up visit, bony union was adequate and there was no radiologic evidence of screw loosening. At the time of publication, he was pain-free and working without limitations in daily activities but had limitations in recreation activity because both ankles were fixed. The JFFS score improved to 87/100.

In another study, three arthroscopic ankle arthrodeses were performed in two patients. Case 1 was a 26-year-old man and case 2 was a 25-year-old man. The follow-up periods ranged from 2 year and 4 months to 6 years and one month. Union was obtained in all three ankles. All the arthroscopic ankle arthrodesis stopped or significantly reduced recurrent joint bleeding. The AOFAS ankle-hindfoot scale scores were 39 (range: 32-52) points preoperatively and 80 (range: 74-92) points postoperatively [36].

Open arthrodesis: Different approaches are feasible for open arthrodesis: anterior, lateral and posterior. The anterior one is characterized by incision between tibialis anterior and extensor hallucis longus tendons (the same of total ankle replacement, TAR). It allows a good access to both medial and lateral gutter. It is less invasive, spares fibula and, eventually, allows the conversion of the procedure into TAR. The lateral one allows an excellent anterior to posterior visualization, it frequently uses a previous incision, and it guaranties appropriate deformity correction. One negative aspect of the lateral approach is that it decreases surface area for fusion, making plate fixation more difficult as the conversion to TAR. It is also more invasive since fibula sacrifice is necessary. The posterior one is less common, but it can be useful in revision, particularly if anteriorly or laterally soft tissues are poor. The procedure is correctly done when the ankle is fixed in neutral dorsiflexion, 0°-5° of hindfoot valgus and 5°-10° of external rotation.

Fixation can be obtained with screws, plates, retrograde nail or external fixator. Controversy exists on the favored fixation method. Screws are often preferred due to high union rates, less soft-tissue dissection and ease of application, but plates achieve better stiffness and union rates then screw-fixation only. Nail, instead, is indicated where it is necessary to proceed with an additional subtalar arthrodesis. External fixation can be useful in case of increased infectious risk, poor quality of soft tissue or concurrent infection, common in patients with hemophilia. An article reported that all patients enrolled in the drawn study, were satisfied with the surgery and achieved bony fusion as confirmed by post-operative radiographs. At the final follow-up, the mean AOFAS scores and VAS scores were 81.4 ± 5.2 (range, 73-86) and 1.4 ± 1.1 (range, 0-3), respectively, which significantly improved compared with pre-operative 37.9 ± 11.2 (range, 20-55) and 7.0 ± 0.7 (range, 6-8), respectively [37].

In literature, there are many studies about open ankle arthrodesis in hemophilic arthropathy treatment [6, 38, 39]. This procedure, performed on a total of 89 patients, has shown good results in terms of long-term pain relief (mean VAS 1.05, range from 0.7 to 1.4), functional recovery of the ankle (mean AOFAS 80.27, with from 69 to 90.4), deformity correction, recurrent bleeding prevention and improvement of quality of life [5]. Open arthrodesis also showed low rate of complications such as delayed bone union, non-union, superficial or deep infection, recurrent bleeding episodes and degenerative changes in the surrounding joints [38] (**Table 5**).

In isolated ankle fusion, the subtalar and midtarsal joints have been implicated in providing sufficient movement of the foot postoperatively. The first joint fused, generally is the most painful; however, it is common to fuse adjacent joints because of the potential overload placed upon them after the previous surgery.

Total ankle replacement (TAR): It is indicated as primary procedure in the end-stage ankle osteoarthritis and as a conversion procedure in patients with painful ankle arthrodesis.

Literature analysis (**Table 5**), on a total of 68 TAR, shows an improvement in mean values of VAS (mean 1.33, range from 0.8 to 1.9), AOFAS (mean 80.87, range 69.0 to 90.4), ROM (mean 30.57, range from 26 to 37.3), SF-36 (physical and mental, respectively with a mean value of 62.35 and 67.95).

Table 5. Surgical treatment

Author	Year	Treatment		Cases		Parameters	Values	
				Patients	Ankles		Preop	Postop
Tsailas and Wiedel [38]	2010	Arthrodesis (anterior approach)		13	20	Symptom score	47.7	94.9
Bluth [6]	2013	Arthrodesis (anterior approach)		45	57	AOFAS	-	90.4
Eichler [39]	2017	Arthrodesis		9	12	AOFAS	22	69
						Olerud score	37	70
Asencio [23]	2014	Total ankle replacement		21		AOFAS	40.2	85.3
						Function score	23.6	35.9
						dorsiflexion	0.3	10.3
Preis [19]	2017	Total ankle replacement		14		VAS	8.5	1.3
						AOFAS	23.9	76.6
						ROM	9.9	28.4
						SF-36 physical	38.1	77.7
						SF-36 mental	51.4	78.9
						Petterson score	8.7	
Eckers [40]	2018	Total ankle replacement		14	17	VAS	-	1.9
						ROM	16	26
						AOFAS	-	81
						SF-36 physical	-	47
						SF-36 mental	-	57
						Implant survival %	-	94 (5 y), 85 (10 y), 70 (15 y)
Wang [37]	2020	Arthrodesis with Ilizarov external fixator		14		AOFAS	37.9	81.4
						VAS	7	1.4
						SF-36 physical	10	82.9
						SF-36 physical	59.2	72
Barg [41]	2010	Total ankle replacement		8	10	AOFAS	38	81
						Pain score	7.1	0.8
						ROM	18.3°	27.3°
						SF-36 physical	30.4	83.4
						SF-36 mental	56.9	82.8
Ahn [4]	2020	TAR vs AA	TAR	16		VAS	6.2	0.8
						FFI %	59.6	10.3
						ROM	30.8	37.3
						Plantarflexion range	28°	38.5°
			AA	13		VAS	4.5	0.7
						FFI %	61.5	23.7
						ROM	20.6	-

AA: Ankle Arthrodesis; AOFAS: American Orthopedic foot and ankle society score; FFI: Foot Functional Index; HJHS: Hemophilia Joint Health Score; NPRS: Numeric Pain Rating Scale; ROM: range of motion; SF-36: 36 Item short form health survey; TAR: Total Ankle Replacement; VAS: visual analogue scale.

A study with an observation period of over 15 years evaluated implant survival, through clinical outcome and radiographic assessment [40]. Seventeen TAR were performed in 14 patients. As a result of component loosening, 3 cases underwent revision surgery with component removal (one arthrodesis, 2 revision of TAR) at a mean postoperative interval of 7.5 ± 4.9 years. The estimated implant survival was 94%, 85% and 70% at 5, 10 and 15 years respectively.

A prospective study evaluated the mid-term outcome after implantation of an unconstrained, three-component total ankle prosthesis in patients with hemophilic ankle osteoarthritis [41]. Two female (two ankles) and six male (eight ankles) patients with a mean age of 43.3 ± 9.3 years (range, 26.7-57.5) were enrolled in the study. Five patients had frequent bleeding despite the previous arthroscopic synovectomy and debridement. In one of two patients treated with bilateral total ankle replacement, the bilateral procedure was performed as a one-stage procedure; in the other case the second ankle operation took place 1.8 years after the first surgery. In one patient treated with a bilateral procedure, a replace-

ment of ankle arthrodesis with total ankle arthroplasty was performed. No patient was lost until the last follow-up at 5.6 years ± 1.7 (range, 2.7-7.6 years). The AOFAS increased from 38 ± 18 (range, 8-57) preoperatively, to 81 ± 8 (range, 69-95). Four patients (50%) were completely pain free and there was substantial pain relief in all the patients.

Overall, average pain score decreased from 7.1 ± 1.6 (range, 4-9) to 0.8 ± 1.0 (range, 0-3). Physical examination of the affected joints at latest follow-up demonstrated no significant joint swelling, instability, or axial deformity of the affected joints. At latest postoperative follow-up, five (62.5%) patients had a normal level of sport activity and one patient (12.5%) a moderate level. At final follow-up, all patients were satisfied with the results of the total ankle replacement and stated that they would have the surgery performed again (**Table 5**).

Another study [4] analyzed clinical and radiological outcome comparing TAR and ankle arthrodesis in patients with end-stage hemophilic ankle arthropathy. Both TAR and ankle arthrodesis exhibited significant improvement in pain based on VAS and FFI (Foot Functional Index) scales. Compared to ankle arthrodesis, TAR resulted in superior outcomes in FFI disability and activity subscales, suggesting that TAR may be considered as a surgical option alongside ankle arthrodesis in end-stage hemophilic ankle arthropathy. Ankle arthrodesis alters the normal function of the hindfoot and adds strain to adjacent segments, which leads to degenerative changes in adjacent joints. TAR, instead, had a high probability of failure and poor results with early generation implants, in addition to higher infectious risk and bleeding possibility.

Conclusions

Hemophilic arthropathy is a rare disease that leads to progressive destruction of both cartilage and bone, resulting in severe painful symptoms and disability. The ankle appears to be the third joint in terms of involvement frequency. The first approach in the treatment of patients with hemophilic arthropathy of the ankle remains intravenous replacement therapy for deficient factors. However, other approaches, both conservative and surgical procedures (arthroscopic or open) have been proposed in order to obtain an improvement in the clinical picture of these patients. From the limited data available in literature analyzed in this review, it can be affirmed that treatment offered to the patient should start from the less invasive Fascial therapy and Orthoses for mild arthropathy. Secondary moderate arthropathy should be addressed with Nd:YAG laser, EBRT and RS. While surgical procedures like Open Arthrodesis and TAR are to be used in severe conditions.

Due to the multiple available treatments, a wide range of factors must be considered before choosing the best course of action. The factors to be considered are pain, functional status, patient's history and hematologic status, degree and extent of ankle osteoarthritis and deformity and patient's expectations. We believe treatment must be carried out in a reference center for foot and ankle surgery by a multidisciplinary team including expert hematologists able to guarantee adequate and safe pre- and post-surgical management.

Disclosure of conflict of interest

None.

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