Outcome measures analysis following total knee arthroplasty in patients with severe haemophilic arthropathy of the knee

KONSTANTINOS ZYGOGIANNIS[1], ANNA KOURAMBA[2], DIMITRIOS KALATZIS[1], STYLIANI-DESPOINA CHRISTIDI[1], OLGA KATSAROU[2], AGORITSA VARAKLIOTI[2] and GEORGIOS C. THIVAIOS[1]

[1]Department of Orthopaedics; [2]Blood Unit and National Reference Centre for Congenital and Bleeding Disorders, Laiko General Hospital, 11527 Athens, Greece

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Abstract. Total knee arthroplasty (TKA) has been the gold standard for treating severe haemophilic arthropathy of the knee when all conservative measures fail. However, performing a TKA in patients with haemophilic arthropathy is difficult due to severe joint deformity and destruction, and poor bone quality. The aim of the present study was to evaluate the short-term results of TKA in the treatment of knee haemophilic arthropathy in a tertiary referral centre, with an emphasis on health-related quality of life and knee function. A prospective study was conducted that included 19 male patients with end-stage haemophilic knee arthropathy who underwent TKA in a tertiary referral centre. Clinical outcome and health-related quality of life were assessed by the Western Ontario and McMaster Universities Arthritis (WOMAC) index and the Short Form-36 (SF-36) both pre-operatively and at 1-year post-operatively. The mean age of the patients was 50.37±7.63 years (range, 40-65 years). Pre-operative health-related quality of life was impaired in all patients in all SF-36 domains but was markedly improved after TKA. Knee function in all dimensions (pain, stiffness and physical function), as measured by the WOMAC questionnaire, significantly improved after TKA. Pre-operative pain, stiffness and function, along with total WOMAC score, were strongly and negatively correlated with pre-operative SF-36. Overall, the present study indicated a significant improvement in quality of life and clinical outcome after TKA in patients with advanced haemophilic arthropathy. More studies with longer follow-up periods in a larger population are needed to fully elucidate the mid- and long-term values of TKA in haemophilic patients.

Correspondence to: Dr Konstantinos Zygogiannis, Department of Orthopaedics, Laiko General Hospital, 17 Agiou Thoma, 11527 Athens, Greece
E-mail: zygogianniskonstantinos@gmail.com

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Introduction

Haemophilia is an X-linked recessive disorder of blood coagulation, which occurs almost exclusively in males, it is estimated that the responsible mutations originate at a ratio of ~3:1 more frequent in males than females (1). Heterozygous females are generally asymptomatic carriers of the disease. Haemophilia A (also known as classic haemophilia) is caused by a lack of factor VIII, and haemophilia B (also known as Christmas disease) is due to a lack of factor IX (2,3). Factor VIII is a 265-kDa protein that circulates bound to von Willebrand factor and activates factor X via proteinases in the endogenous blood coagulation system. Factor IX is a 55-kDa proenzyme, which is converted to active proteinase by factor IXa or by the tissue factor VI-Ia complex. Factor IX then activates factor X, in combination with activated factor VIII (4). The factor VIII and IX genes are located on the X chromosome. Approximately one in 10,000 males are born with factor VIII deficiency, while factor X deficiency occurs in approximately one in 100,000 male births, globally scale (5). Caused by either factor VIII or factor IX deficiency, haemophilia is characterized by bleeding into the soft tissues, muscles and joints. Spontaneous bleeding into the muscles or soft tissues can result in the formation of large haematomas or pseudotumours, causing muscle necrosis or compartment syndromes (6).

Bleeding within joints is the most common manifestation of haemophilia and it is seen in up to two-thirds of patients; it occurs spontaneously or after minor trauma, and manifests immediately with joint stiffness, pain, heat and swelling. Haemarthoses are the hallmark of haemophilia and one of the major causes of morbidity in affected patients. Haemarthoses develop in 75-90% of haemophilic patients, usually before the age of 2, and continue into adolescence and sometimes into adulthood, even after the age of 30 (7). The late complications of haemarthroses (deformities, contractures, and/or degenerative arthropathy) develop in adolescence or adulthood. The most commonly affected joints are the knees, elbows and ankles. The disease progresses into subacute and chronic arthropathy with synovial thickening, pain and deformity. Later manifestations also include chronic joint contracture and secondary osteoarthritis, particularly in the knees (7,8).

Haemophilic arthropathy is the ultimate result of recurrent intra-articular bleeding, with repeated inflammation and subsequent joint destruction. The radiographic findings of haemophilic arthropathy include the typical findings of osteoarthritis: Narrowing of the joint space, subchondral sclerosis and subchondral cyst formation (9). The Arnold-Hilgartner classification is a plain radiograph grading system for haemophilic knee arthropathy (10). The pathogenesis of the condition is not fully understood but may result from excessive deposition of iron in the synovium and cartilage, leading to increased peri-articular soft-tissue density. As prothrombin and fibrinogen are normally absent within the joints, the blood remains in a watery state, with no clotting potential. The plasma is gradually reabsorbed, and the remaining red blood cells are phagocytosed by synovial cells and macrophages. Haemosiderin, found in synovial cells, can be toxic and cause chronic hyperplasia of the synovium, consisting of few lymphocytes and mostly fibrous tissue (11,12).

The current management of patients with severe haemophilia includes prophylactic administration of coagulation factors. When chronic synovitis is established, radiosynovectomy may be used in order to delay and avoid progression to arthropathy (13,14). Total knee arthroplasty (TKA) is the gold standard used for treating severe haemophilic knee arthropathy when all conservative measures fail (15). However, performing a TKA in patients with haemophilic arthropathy is difficult due to the anatomical impairment with physeal overgrowth, excessive arthrofibrosis and poor bone quality (10). Moreover, it has been observed that TKA for the treatment of severe haemophilic knee arthropathy is generally performed in young and active male patients due to the nature of the disease, this is mainly attributed to the fact that former medication was not as advanced as current treatment options and a severe joint arthropathy was more likely to appear at an early age (16). The aim of the present study was to evaluate the short-term results of TKA in the treatment of knee haemophilic arthropathy in a tertiary referral centre, with an emphasis on health-related quality of life and knee function.

Patients and methods

Study design. This prospective study included 19 male patients with end-stage haemophilic knee arthropathy (Arnold-Hilgartner stage V) who underwent TKA at Laiko General Hospital (Athens, Greece) between February 2015 and December 2021. Patients with previous knee surgeries, recent knee infections and with follow-up <1 year were excluded from the study. All patients read and signed an informed consent form allowing publication of their data in the present study. The study was approved by the local Institutional Review Board of Laiko General Hospital (Athens, Greece; approval no. 702/1128). Pre-operative planning was based on recent knee x-rays in the anteroposterior weight-bearing and lateral views. Coagulation factors were delivered pre-operatively with regular level monitoring and further administration if needed. All patients wore compression stockings, but no other antithrombotic prophylaxis was necessary.

Surgical technique. TKA was performed with the use of a tourniquet until skin closure. A standard midline incision and a medial parapatellar approach were used. A synovectomy was performed in all patients. Different types of implants were used, depending on the severity of the arthropathy and the presence of axial deformity, stiffness and intraoperative instability. In total, 6 patients (31.6%) with moderate joint deformity and adequate range of motion received a cemented posterior stabilized (PS) prosthesis (United U2 Knee™ Total Knee System, implantcast GmbH). In 8 patients (42.1%) with severe axial deformity, decreased range of motion but no intraoperative instability, a semi-constrained prosthesis (condylar constrained knee) was used (ACS Knee System; implantcast GmbH) (Fig. 1). Finally, in the remaining 5 patients (26.3%) with severe angular deformity, stiffness with flexion contracture and intra-operative instability, a fully constrained prosthesis (rotating hinge) was implanted (MutarsGenuX Revision Modular Knee System; implantcast GmbH). Patella resurfacing was performed in 14 out of 19 patients (73.7%).

Chemoprophylaxis. Intravenous administration of 1 g vancomycin and 1.5 g cefuroxime was performed every 12 h for the first 24 h post-operatively. A standardized multimodal blood loss prevention method was typically used to reduce the transfusion rates, with intra-articular infiltration of a mix of 80 cc normal saline with 3 mg epinephrine, 10 mg morphine, 200 mg ropivacaine and 2,500 mg tranexamic acid. Post-operative pain management included the implantation of a catheter for the adductor canal block for 48 h. Drains were removed 48 h post-operatively. Physical therapy was initiated on the first post-operative day, and the patients were allowed to walk with partial weight bearing.

Demographics and statistical analysis. Patient demographics (age and BMI) were recorded. Health-related quality of life before and 12 months after surgery were assessed using the Short Form-36 (SF-36) which takes into consideration the physical functioning and role, bodily pain, general health, vitality, social functioning, emotional state and the mental health in a median and interquartile range. It also includes a physical component summary (PCS) and a mental component summary (MCS) with a mean and standard deviation value (17). Clinical evaluation of knee osteoarthritis in all dimensions (pain, stiffness and physical function in a median and interquartile range) was performed with the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pre-operatively and 1-year post-operatively (18). The WOMAC takes into consideration five items for pain (score range, 0-20), two for stiffness (score range, 0-8) and 17 for functional limitation (score range 0-68). While SF-36 is a self-reporting survey consisting of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly converted into a 0-100 scale on the assumption that each question carries equal weight. Lower scores indicated a patient who is more incapacitated. The values of the variables are presented using the mean and the standard deviation. The normality of the distribution of the measurements was checked using the Kolmogorov-Smirnov test. Paired t-test was used to compare SF-36 and WOMAC values before and after surgery. The Pearson correlation coefficient was used to detect

Table I. Comparison of SF-36 domains, before and after total knee arthroplasty.

	SF-36 score				
	Pre-operative		Post-operative		
Domains	Median	IQR	Median	IQR	P-value
Physical functioning	25.0	20	80	15	<0.001
Physical role	0	25	100	25	<0.001
Bodily pain	22.0	29	74	38	<0.001
General health	32.0	25	67	35	<0.001
Vitality	45.0	30	80	30	0.001
Social functioning	37.5	25	87	25	<0.001
Emotional role	0	33.3	100	33.3	<0.001
Mental health	40.0	44	84	24	0.001
	Mean	SD	Mean	SD	P-value
PCS-12	29.2	5.1	48.4	5.8	<0.001
MCS-12	37.6	10.8	53.3	9.4	<0.001

SF-36, Short Form-36; SD, standard deviation; PCS, physical component summary; MCS, mental component summary.

any correlations between SF-36 and WOMAC values while Spearman's correlation coefficient was used to assess both continuous and ordinal variables. All statistical analyses were performed with the statistical software SPSS, version 17.00 (SPSS Inc.). Also, as this study aimed to examine the effect of surgical treatment, *a priori* power analysis using a paired t-test was performed to confirm that the recruited sample size was adequate to perform this study with a statistical power of 80%. $P<0.05$ was used to indicate a statistically significant difference.

Results

Comparison of SF-36 domains before and after TKA. The present study included 19 male patients with a mean age of 50.37±7.63 years (range, 40-65 years) and a mean BMI of 24.52±1.48 (range, 22.03-27.57). As shown in Table I, health-related quality of life was found to be impaired in all SF-36 domains, with markedly lower scores demonstrated pre-operatively compared with post-operatively, and all differences being statistically significant. Notable improvement in physical functioning (the ability to perform basic activities), pain and physical role (the measured limitations in various roles including daily activities and work) can markedly improve aspects of everyday life such as emotional status, social functioning and general health.

Comparison of WOMAC score, before and after TKA. The average WOMAC score was 56 [interquartile range (IQR), 24] before the operation and 4 (QR, 4) after TKA (Table II). As shown in Table II, knee function in all dimensions (pain, stiffness and physical function) as measured by the WOMAC questionnaire significantly improved after TKA. Such differences could be attributed to the fact the haemophilic arthropathy is characterized by severe destruction of the joint (Fig. 1).

Correlations between SF-36 and WOMAC score before TKA. Pre-operative pain, stiffness and function along with total WOMAC score were strongly and negatively correlated with pre-operative SF-36 PCS, while pain and total WOMAC score were strongly and negatively correlated with SF-36 MCS (Table III), indicating that the pre-operative status of the patients was significantly lower comparing to the postoperative status. Even though stiffness was significantly improved, in comparison with the other parameters it presented the lowest rate of improvement. Which could be attributed to the fact that the initial preoperative values of stiffness were lower in comparison with the rest of preoperative values (Fig. 2).

During the 1-year follow-up time, the only recorded complication was one case of post-operative knee stiffness, treated with manipulation under anaesthesia and arthroscopic debridement.

Discussion

Health-related quality of life is widely accepted as a key outcome measure in chronic diseases, including knee osteoarthritis. Quality of life refers to how well individuals function in everyday life and their subjective perception of well-being. According to the World Health Organization's definition, health-related quality of life is considered multidimensional, encompassing physical, mental and social functioning, and well-being (19). The present study was conducted in a tertiary referral centre specializing in the treatment of haemophilic patients. All haemophilic patients were managed by a multidisciplinary team, including haematologists, orthopaedic surgeons and physiotherapists. The main finding of the present

Table II. Comparison of WOMAC score before and after total knee arthroplasty.

	WOMAC score				
	Pre-operative		Post-operative		
Dimension	Median	IQR	Median	IQR	P-value
Pain	11	8	0	2	<0.001
Stiffness	6	1	0	2	<0.001
Physical function	40	22	4	12	<0.001
Total WOMAC	56	24	4	14	<0.001

WOMAC, Western Ontario and McMaster Universities Arthritis; SD, standard deviation.

Figure 1. Representative pre-operative anteroposterior and lateral x-ray view of end-stage haemophilic arthropathy of the knee with significant axial malalignment. Scale bar, 63 mm.

study was that the short-term results of TKA in patients with end-stage haemophilic arthropathy were satisfactory in terms of health-related quality of life and functional improvement.

Regarding its use, the SF-36 is probably the most recommended and most frequently used quality-of-life measure for knee osteoarthritis in epidemiological studies and clinical trials. The SF-36 is a multipurpose, short-form health survey with 36 questions (20). The SF-36 consists of eight subscales that can also be summarized into two composite scores, a physical component score (PCS-12) and a mental component score (MCS-12) (21). Previous studies have shown moderate to large improvements in scores for most of the eight subscales of the SF-36 and for the PCS-12 in individuals who have undergone TKA (22,23).

While a plethora of studies have evaluated survival rate, rate of complications and clinical scores after TKA for haemophilic arthropathy (24-26), few of them have focused on patient quality of life. In a small study by Schick *et al* (27), 92% of patients were satisfied with the outcome of TKA, with a significant improvement in all WOMAC dimensions. However, the improvement in physical function ability was not notable, a finding that was attributed to the arthropathic affliction of other joints. Viliani *et al* (28) reported that at follow up, 28% of patients who underwent TKA mentioned that they experienced excellent quality of life while 72% of them referred their life as good. A large prospective study by Mortazavi *et al* (29), including 83 patients with haemophilic arthropathy who underwent TKA, detected similar improvements with regard to SF-36 and WOMAC scores; however, patients were markedly younger at the time of operation. According to Wang *et al* (30), patient satisfaction with pain relief was higher than satisfaction with functional improvement. In the present study, all patients reported a significant improvement in health-related quality of life and knee function.

The main aim of TKA is the reduction of knee pain and the improvement of knee function. While TKA is an established surgical method for primary knee osteoarthritis

Table III. Correlations between SF-36 and WOMAC score before total knee arthroplasty.

	WOMAC score			
SF-36 domains	Pain	Stiffness	Physical function	Total WOMAC
PCS				
Spearman's P-value	-0.698	-0.482	-0.753	-0.758
P-value	0.001	0.036	<0.001	<0.001
MCS				
Spearman's P-value	-0.531	-0.367	-0.411	-0.463
P-value	0.019	0.122	0.081	0.046

SF-36, Short Form-36; WOMAC, Western Ontario and McMaster Universities Arthritis; PCS, physical component summary; MCS, mental component summary.

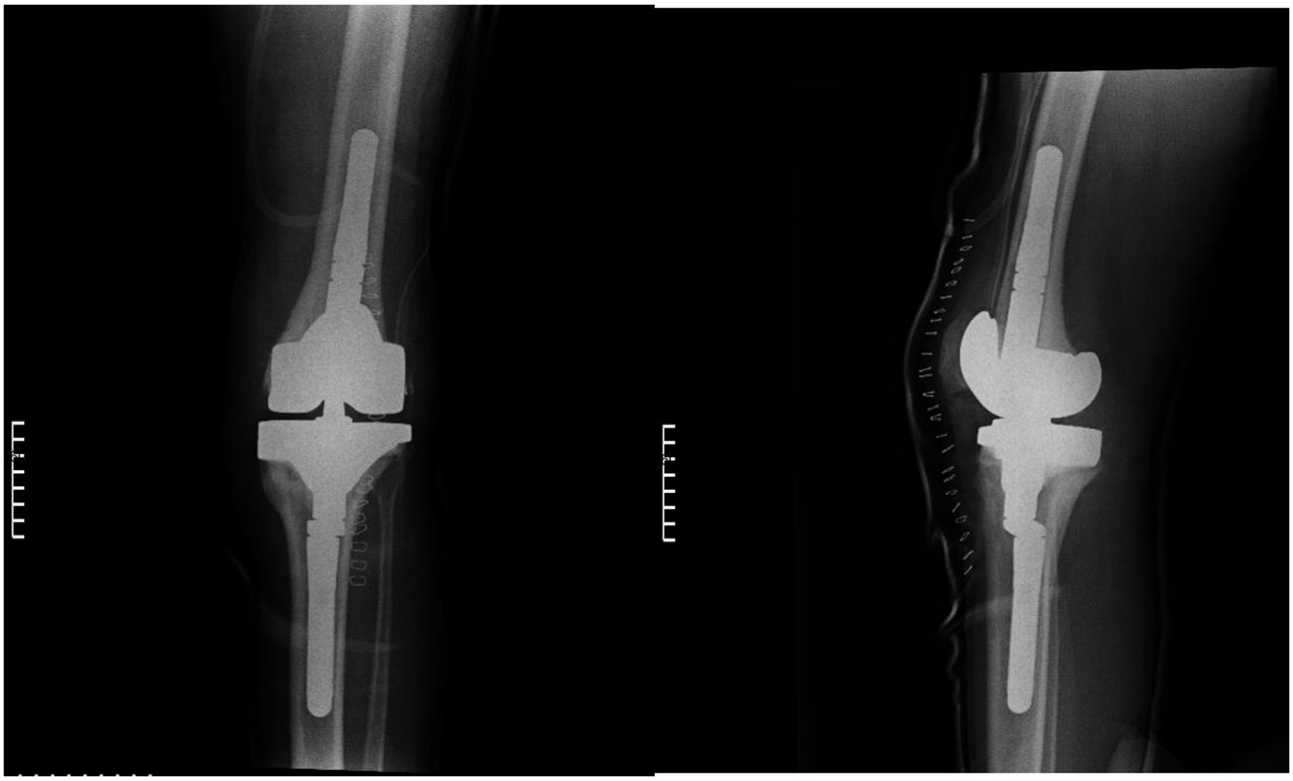

Figure 2. Representative postoperative anteroposterior and lateral view of total knee arthroplasty demonstrating satisfactory knee alignment. Scale bar, 63 mm.

and haemophilic knee arthropathy, the pathogenesis of these diseases has substantial differences. In haemophilic knee arthropathy, recurrent intra-articular bleeding and subsequent intra-articular deposition of haemosiderin and iron lead to upregulation of pro-inflammatory cytokines, synovial hypertrophy and articular cartilage destruction (31). TKA in haemophilic patients has resulted in a good prosthetic survival rate. However, as haemophilic arthropathy is more severe than primary osteoarthritis, accompanied by more extensive joint destruction, the results of TKA in haemophilic patients are generally poorer in comparison to patients without bleeding disorders (30,32). Despite the clear role of TKA in the improvement of quality of life and satisfaction in patients with haemophilic knee arthropathy, post-operative knee scores are slightly inferior to those in patients with primary knee osteoarthritis (33,34). Generally, patients with haemophilia tend to have less demands to improve daily living activities as they have become used to their status, which is partly due to multi-joint involvement and their gradual adaptation to their musculoskeletal issues since childhood (35).

The age at which a patient with haemophilia will suffer from end-stage arthritis with a need for TKA depends on the severity of the haemophilia and any previous prevention of recurrent intra-articular bleeding. Westberg *et al* (36) assessed 107 patients with haemophilic arthropathy who underwent TKA and found a mean age of 41 years. In a study by Chiang *et al* (37), the mean

age was 34.2 years. In a similar study by Viliani *et al* (28), the mean age of the patients was 37 years (range, 22-55), while in a retrospective study by Schick *et al* (27), the mean age of the TKA patients was 44 years (range, 23-68) (27). TKA in younger populations without bleeding disorders has been correlated with inferior prosthetic survival rates when compared with those in corresponding elderly patients (38-40). For 108 TKAs performed in patients <55 years, the reported survival rate was 87% at the 18-year follow-up (33), respectively in patients who have over 65 years of age the survival rates reach 97% (41). In a study that included 32 robot-assisted TKAs, Kim *et al* (42) suggested that the restoration of a neutral mechanical axis in younger haemophilic patients may ensure better long-term outcomes. In the present study, the mean age of the patients at the time of surgery was 52.1 years, which was slightly higher than the age of the patients in other studies. This can be attributed to better medical services and higher patient compliance in treatment, leading to less frequent intra-articular bleeding.

The present study has several limitations. The small sample size and the absence of a control group are major disadvantages that may be attributed to the rarity of these cases. Additionally, the outcomes of the three groups of patients could not be compared. Most literature on TKA in haemophilic patients, however, reports a small series of cases, with modest results and significant complications (31,43). The follow-up in the present study is rather short, but the study is ongoing and aims to perform a further evaluation of these patients in the following years.

In conclusion, the present study indicated a significant improvement in quality of life and clinical outcomes after TKA in patients with advanced haemophilic arthropathy. Good functional outcomes and improved health-related quality of life can be achieved after TKA, after the application of specialized perioperative and rehabilitation protocols tailored to this subpopulation of patients. Despite the surgical challenges of TKA in this subgroup of patients, the results from this study are encouraging. Haemophilic patients should be informed about the increased risks of TKA for severe haemophilic arthropathy and the inferior clinical outcome in comparison to that experienced by non-haemophilic patients. More high-quality studies are needed to fully elucidate the value of TKA in these patients.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KZ wrote the original manuscript, reviewed, edited and investigated. AK and GCT were responsible for conceptualization and reviewing. DK and SDC performed data collection during patient examination preoperatively and postoperatively. OK was responsible for designing and reviewing the study, and ensuring that all the aspects of the study were appropriately performed. AV performed the statistical analysis and data curation. ZK, KA and GCT confirm the authenticity of all the raw data. All authors have read and approved the manuscript.

Ethics approval and consent to participate

All the participants provided informed written consent. Ethics approval was provided by the local Institutional Review Board of Laiko General Hospital (Athens, Greece; 702/1128).

Patient consent for publication

Written consent for publication was obtained from all patients.

Competing interests

The authors declare that they have no competing interests.

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