

# Knee Arthropathy and Bilateral Total Knee Arthroplasty Ratio in Hemophilia A Patients

## Hemofili A Hastalarındaki Diz Artropatisi ve Bilateral Total Diz Artroplastisi Oranı

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### Abstract

Objective	This epidemiological study was conducted in the joint haematology-orthopaedics clinic of a university hospital. The aim was to analyze the data in terms of age and radiology of patients with moderate or severe haemophilia A and knee involvement. ( <i>Sakarya Med J</i> 2019, 9(3):506-512).
Materials and Methods	This was a cross sectional and descriptive retrospective study of 49 patients with knee problems out of 130 haemophilia A and musculoskeletal problems. Kellgren-Lawrence (KL) classification was used for radiological assessments of osteoarthritis degree.
Results	KL degree was 3 or 4 for most patients (27/41, 65.85%) in the group. There was statistically a meaningful correlation between KL degree and patients' age (Spearman's: $rs = 0.512$ , $p = 0.001$ ). There were 7 patients with KL degree 4 at the age of 50 or younger (14.29%). 25 patients in 49 (51.02%) had total knee arthroplasty (TKA) and 10 (40%) of those was bilateral. Mean age for bilateral TKA (56.35) was higher than unilateral (49.87). There was a statistically meaningful correlation between patient age and the patients with TKA (Spearman's: $rs = 0.338$ , $p = 0.017$ ). There were 2 revision surgeries out of 35 TKA (5.71%). Most of the patients had prophylactic factor treatment (43, 87.75%).
Conclusion	Our study signifies the high ratio of bilateral knee replacements in hemophilia A patients and how early age they progressed to KL stage 4 comparing to normal population. These results show the importance of patient care in this group of patients, close follow-up and prophylactic treatment. They should be managed in experienced unites by an experience team to decrease the risks and complications.
Keywords	Hemophilia A; Total knee arthroplasty; Bilateral

### Öz

Amaç	Hemofili hastalarında epidemiyolojik olarak yapılan çalışmamızda, bir üniversite hastanesinin hematoloji-ortopedi ortak kayıtları kullanıldı. Bu çalışmanın amacı, orta ve ileri derecede hemofili A' s'ı olan hastalarda, diz problemlerini, cerrahi tedavi sıklığını yaş ve radyolojik açıdan değerlendirmektir. ( <i>Sakarya Tıp Dergisi</i> 2019, 9(3):506-512)
Gereç ve Yöntemler	Tanımlayıcı-kesitsel bir retrospektif çalışma olup, iskelet-kas sistemi problemleri olan 130 hemofili A hastasından diz problemleri olan 49'u bu çalışmaya dahil edildi. Kellgren-Lawrence (KL) sınıflaması, osteoartritlerin radyolojik değerlendirilmesinde kullanıldı. Elektronik datalardan elden edilen bilgiler, sonuçları analiz etmek ve istatistiksel değerlendirmeler için kullanıldı.
Bulgular	Diz diz grafişi çekilmiş hastaların çoğunluğunda (27/41, %65,85), KL derecesi 3 veya 4 idi. KL derecesi ile hastaların yaşları arasında istatistiksel olarak anlamlı bir korelasyon mevcut idi (Spearman's : $rs = 0,512$ , $p (2-tailed) = 0,001$ ). Ayrıca, KL derecesi 4 olan 50 yaş ve altında 7 hasta (%14,29) vardı. 49 diz problemi olan hastanın 25'inde (%51.02) total diz artroplastisi (TDA) yapıldı ve bunların da 10 tanesi (%40) bilateral idi. Bilateral TDA için ortalama yaş (56.35), unilateral TDA dan (49.87) daha yüksekti. Hastaların yaşı ile TDA olmaları arasında istatistiksel olarak anlamlı bir korelasyon vardı (Spearman's: $rs = 0,338$ , $p = 0,017$ ). 35 TDA yapılan hastada 2 revizyon tespit edildi (%5.71). Çalışmaya dahil edilen hastaların çoğu (43/49, %87.75), profilaktik faktör tedavisi almaktaydı.
Sonuç	Çalışmamız, hemofili A hastalarındaki yüksek bilateral TDA oranını ve normal popülasyona göre bu grubunun ne kadar erken yaşta KL 4 safhasına ilerlediklerini vurgulamaktadır. Bu sonuçlar bize, bu grup hastalardaki tedavi yaklaşımının, yakın takibin ve profilaksinin önemini göstermektedir. Bu hastalardaki risk ve komplikasyonları azaltmak için; tedavileri, tecrübeli merkezlerde ve özelleşmiş bir grup tarafından yapılmalıdır.
Anahtar Kelimeler	Hemofili A; Total Diz Artroplastisi; Bilateral

## INTRODUCTION

Hemophilia, which is an x-linked deficiency of factor VII and IX is the commonest bleeding disorders.<sup>1-3</sup> One of the most common complications is musculoskeletal bleeding and especially in moderate and severe forms, it leads to intraarticular bleeding (haemarthrosis).<sup>4</sup> Hemophilia is classified according to the amount of factor deficiency.<sup>5</sup> If the factor concentration is between 1 and 5%, it is considered as moderate and if below 1%, named as severe.<sup>4,5</sup> Haemarthrosis can develop as spontaneous or trauma-related and the presence of blood in the joint may provoke syn-ovial tissue reaction, this may eventually lead to cartilage damage and the progression of the damage can cause hemophilic arthropathy.<sup>1,6</sup>

Plane x-rays may show subchondral irregularities, joint space loss and osteophytes.<sup>1,7</sup> For diagnosis, in addition to patient history and clinical examination, ultrasound scan is useful to show hypertrophic synovitis and fluid inside the joint. However, magnetic resonance (MR) scan is a gold standard to assess the soft tissue.<sup>8</sup> Early diagnosis and prevention of haemarthrosis with prophylactic treatment in the bleeding disorders is the most important stage of the disease.<sup>4,9</sup> Modification of life style, physical therapy and medical treatment are useful, and radiosynovectomy in chronic synovitis and intraarticular injections are the other available treatment options.<sup>10-12</sup> When these measurements are not enough, next option is surgical treatment, which includes open or arthroscopic synovectomy, releasing soft tissue for contracture, arthroplasty and joint fusion.<sup>1,4</sup>

The main indication for total knee arthroplasty (TKA) in hemophilic patients is a disabling pain. However, functional mobility loss and developing knee deformity in the absence of pain could be also indication for TKA.<sup>13</sup> In surgical approach, there are high risks of bleeding and infections therefore in such patients, factor replacement treatment is recommended.<sup>8</sup>

The aim of the current study is to analyze the patients profile with age and radiological assessments in moderate and severe hemophilia A patients who had knee involvement and presented to our joint unit of hematology and orthopaedics departments.

## MATERIALS and METHODS

The study was conducted in a specialized joint clinic of hematology and orthopaedics at a university hospital in the UK. The study included moderate or severe hemophilia A patients with knee involvement. The study was a cross sectional and descriptive retrospective observational one and part of an epidemiological study including the data of the patients who attended the Manchester University Hospitals NHS Trust between 2007 and 2019.

There were 140 patients with above criteria and 10 patients were excluded due to insufficient data in the system. Fortynine patients with knee problems were detected in the remaining 130.

In the unit, all the patients were assessed by both hematology and orthopaedic teams and the assessment included clinical examination, radiological evaluation and regular followups. All the data including clinic letters, operation notes, referrals were recorded in the electronic database and these were used in our study.

Kellgren and Lawrence (KL) osteoarthritis (OA) scale was used in the radiological assessment of hemophilic arthropathy. KL classification system was described on plane AP x-rays. 0 degree means a normal knee whilst 4 degree means advanced OA with joint deformity<sup>14</sup> (table 1).

The patients' data were anonymized, transferred to an Excel sheet and this file was used for descriptive and statistical analysis. Social Science Statistics<sup>15</sup> online programme was used for statistics and for nonparametric data, Spearman's correlation test was used for the correlation of age, TKA and KL degrees.

Degree	Description
0: Normal	
1: Questionable	Doubtful narrowing of joint space and possible osteophytic lipping
2: Mild	Definite osteophytes and possible narrowing of joint space
3: Moderate	Moderate multiple osteophytes, definite narrowing of joint space, some sclerosis, and possible deformity of bone ends
4: Severe	Large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends



There was no conflict of interest and the authors did not receive any funding for this study.

It was conducted according to Helsinki Declaration and ethical approval was obtained.

### RESULTS

Forty-nine patients with knee problems out of 130 who had moderate and severe hemophilia A were included to the study. Twentyfive patients had bilateral knee problems.

In this group of patients, most of the patients had advanced OA (table 2). 26 knee in 16 patients had end stage, KL 4, OA disease (table 2, figure 1).

KL Scale	Number of patients(%)	Number of knees with OA(%)
1	8 (16.33%)	10 (13.51%)
2	6 (12.25%)	7 (9.46%)
3	11 (22.45%)	15 (20.27%)
4	16 (32.65%)	26 (35.14%)
Patients with no pre-operative x-ray	8 (16.33%)	16 (21.62%)
in Total	49 patients (100%)	74 (100%)

Statistically, there was a meaningful correlation between

Figure 1: Kellgren-Lawrence (KL) scale 4 in a hemophilia A patient on AP x-ray.

KL scale and patients' age (Spearman's correlation:  $r_s = 0.517$ ,  $p$  (2-tailed) = 0.001). On the other hand, there were 7 patients with KL scale 4 at the age of 50 or younger. Although 9 patients had KL scale 4, they did not have or need TKA by the time this study was completed.

25 patients out of 49 (51.02%) had TKA (figure 2, table 3) and 10 of them had bilateral TKA (40%). In total, 35 TKA were performed. 8 patients out of 25 (32%) who had bilateral knee problems did not have any TKA so far.

Hemophilia A		Mean age	%
Gender	All male	46.23 (22-75)	100%
Number of patients with knee involvement	49	46.23 (22-75)	100%
Number of patients with bilateral knee involvement	25	48.80 (24-75)	51.02 %
Number of patients with TKA	25	52.44 (26-75)	51.02 %
Number of patients with one side TKA	15	49.87 (26-58)	30.61 %
Number of patients with bilateral TKA	10	56.35 (32-75)	20.40 %



Figure 2: Postoperative total knee arthroplasty (TKA), AP view of the same hemophilia A patient

All the patients included to the study were male and the mean age of the patients with bilateral TKA was higher than the ones with unilateral TKA (table 3).

Statistically, there was a meaningful correlation between patients' age and TKA surgery (Spearman's correlation:  $r_s = 0.517$ ,  $p$  (2-tailed) = 0.001).

In total, there were 2 revision surgeries of the patients who had TKA (5.71%, in 35 patients). One of two revisions was due to infection but for the other case, there was no documentation on reason of revision. Most of the patients who had knee involvement (43, 87.75%) had prophylactic factor replacement. Only 2 patient diagnosed with moderate hemophilia A and the rest had severe disease (47, 95.9%).

## DISCUSSION

In the current study, we assessed the patients with hemophilia A and knee involvement who presented to our joint clinic between hematology and orthopaedic departments at a university hospital. The data was evaluated in terms of age, OA degree and TKA surgery. The results suggested high ratio of bilateral TKA in this group.

Hemophilia A patients are generally male as in our study

and musculoskeletal complications and bleeding are very common. According to Napolitano and colleagues, the most commonly affected joint is the knee and this is followed by elbow, ankle, shoulder and wrist with decreasing order.<sup>9</sup> High transfusion rate in this group of patients increases the risk of HCV, HIV.<sup>16</sup> Also, these risks can be increased due to immunosuppression in this group of patients.<sup>17</sup>

For assessment of knee arthritis and TKA indications, plane x-rays are sufficient mostly.<sup>1,7</sup> KL classification system is most commonly used clinical diagnostic tool for diagnosis of OA and interobserver correlation for knee is quite high.<sup>18</sup> KL degree 4 is the end stage of the disease<sup>19</sup> and described as established loss of joint space, cartilage deformation, osteophytes and sclerosis.<sup>18</sup> Those patients are generally candidate for TKA and in our study, there were 7 patients with KL 4 at the age of 50 or below (%14.3). In normal population, it is rare to have KL stage 4 OA below 60 years old.<sup>20</sup> Interestingly, there were 7 patients with 9 knees in our study with KL stage 4 who did not require or have TKA by the time of completion of this study. It is not easy to comment on their reasons as we do not have further details in our database, however, it could be due to the fact that they may withstand the pain more than normal population due to their long standing problems or they may be fed up with so many interventions. On the other hand, they might possibly require TKA in the future. This may show the importance of earlier diagnosis and close follow up.

Treatment approach for knee involvement starts with radiosynovectomy and arthroscopic debridement and progresses to TKA.<sup>21</sup> According to Napolitano et al., radioactive and chemical nonsurgical synovectomies are more commonly used in developing countries, where the required clotting factor replacement concentrates are not available.<sup>9</sup> In a study from the Italian Hemophilia Centre, Tagariello and colleagues showed that the patients with hemophilia A had a three-fold higher risk of undergoing

joint arthroplasty when compared to hemophilia B.<sup>22</sup> Outcome scores showed improvement after TKA in hemophilia patients.<sup>23</sup> In the current study, knee problems in hemophilia A patients were very common and 25 patients had TKA for their 35 knees.

The mean age for TKA in normal population is generally much higher and a study by Kurtz et al. showed the percentage of patients <65 years of age is as low as 30.5% (range 19.7–43.6%) in international survey of primary and revision total knee replacement.<sup>24</sup> Similarly, another study from Canada with 5606 TKA cases showed a mean age of 68.<sup>25</sup> This figure was as low as 52 in our case series of TKA with hemophilia patients and only 8.2 % (4 patients) were above 65 years old. In the patients with hemophilia, the mean age is generally younger for TKA. For example, the mean age was even less than ours in a series of 57 patients, as young as 43.<sup>26</sup>

High ratio of bilateral TKA in the current study group is not unreasonable, given that hemophilic arthropathy of both knees is often involved, bilateral TKA is always unavoidable in the end stage.<sup>27</sup> Bilateral TKA could be performed as simultaneous or staged. In young patients without comorbidities other than the causal disease, simultaneous bilateral TKA could be considered.<sup>28</sup> We had only one simultaneous bilateral TKA at age of 51 and the rest were staged bilateral TKAs.

It was stated that life time factor replacement treatment is an ideal treatment for hemophilia patients.<sup>18</sup> Prophylaxis that can convert severe hemophilia into a moderate condition is important in preventing long-term complications.<sup>5-7,28</sup> In addition to factor replacement treatment, satisfactory results have been reported with intraarticular traxenamic acid injection during TKA surgery to control bleeding.<sup>18</sup> In this group of patients with low incidence and high cost of treatment, the diagnosis and treatment approach showed a wide variety of difference between developed and developing countries.<sup>29</sup> Common use of prophylaxis in developed countries provides more ideal patient care for haemophilia.<sup>29</sup>

In our unit, regular prophylactic factor replacement ratio was very high (87.8%), however, despite these standards of care, for pain relief and functional life style, many patients are still needed TKA.

Meanwhile, due to high infection risk in hemophilia patients, prior to surgery for example dental procedure, antibiotics were strongly recommended to decrease the infection risk.<sup>16</sup> In developed countries, HCV, HIV type viral infection rate decreased with modern factor replacement technology but inhibitor formation to the factor is currently an important problem.<sup>30</sup> As well, VTE risk is higher comparing to primer OA patients, which is around 3.2% and therefore, this requires or advised to have VTE prophylaxis.<sup>16</sup>

Although TKA is very good option for OA in hemophilia patients however, complication rate is also high and infection risk is as high as 7%.<sup>8</sup> The outcome of TKA in these patients is worse comparing to normal population and revision rate is also high.<sup>31</sup> We had 2 revision surgeries in our case series (%5.7, 35 TKA). Revision rate was 8.8% in a series of 34 TKA with haemophilia,<sup>32</sup> 8.7 % in 23 TKA<sup>33</sup> and 5.6% in the mean followup of 6 years among 54 prostheses in another case series.<sup>20</sup> Eventually, to deal with problems in this patient group and for their care, there is a need for a strong communication between hematology and orthopaedics department and probably, a specialized center is required.<sup>34</sup> When considering the complication risks, costs and difficulties in patients' care, the procedures such as TKA requires experienced team or unit on bleeding disorders.<sup>34</sup>

Higher mean age of the patients, who had bilateral TKA in hemophilia A, comparing to unilateral TKA and still having many patients with bilateral knee symptoms or problems as well as many patients with high KL scale and without TKA means that these groups of patients may possibly require further TKA in the future. This signify

the importance of factor replacement treatment and keeping these patients under close follow-up but this may not mean they will definitely avoid TKA as we had high level of prophylactic factor replacement treatment and regular follow up in our centre. This means that this group of patients are to be informed about these conclusion during their consultation.

### **Limitations**

This was a retrospective study of existing patient records. Although the case number was limited in this study, in the literature, this figure on hemophilia patients with orthopaedic problems was also limited.

### **Strengths**

This study was based on records from a regional centre for hemophiliac patients, with well-established documentation.

In conclusion, our study signifies the high ratio of bilateral knee replacements in hemophilia A patients and how early age they progressed to KL stage 4 comparing to normal population. This indicates that the patients with knee problems who did not have the operation yet may require TKA in the future. These results show the importance of patient care in this group of patients, close followup and prophylactic treatment. They should be managed in experienced unites by an experienced team to decrease the risks and complications.

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