Risk factors for venous thromboembolism in patients with diabetes undergoing joint arthroplasty

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Research article

Keywords: Diabetes, Total knee arthroplasty, Total hip arthroplasty, Venous thromboembolism, Deep venous thrombosis

Posted Date: June 5th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-33207/v1

Version of Record: A version of this preprint was published at BMC Musculoskeletal Disorders on July 6th, 2021. See the published version at https://doi.org/10.1186/s12891-021-04453-9.

Abstract

Background: Venous thromboembolism (VTE) is a significant complication after joint arthroplasty. Diabetes is related to a few changes in coagulation and fibrinolysis that may lead to thrombophilia. We aim to investigate the incidence of and risk factors for VTEs in patients with diabetes undergoing total hip (THA) or total knee anthroplasty (TKA) in a single centre in China.

Methods: Patients with diabetes who underwent THA or TKA from January 2016 to December 2018 (n=400) at Beijing Jishuitan Hospital were recruited in this study. Lower limb venous Doppler ultrasound was performed before and after surgery to confirm deep venous thrombosis (DVT). Computer tomography pulmonary angiography was done to confirm pulmonary embolism (PE) for those with new postoperative DVT and typical symptoms of PE. A multivariate logistic regression model was conducted to examine factors associated with the development of postoperative VTE.

Results: The overall incidence of postoperative VTE in patients with diabetes after THA or TKA was 46.8% (187 of 400). Female patients and patients undergoing TKA had higher incidence of postoperative VTE. Patients who developed postoperative VTE were older, and had higher levels of preoperative D-Dimer level and Caprini score. Increased VTE risks were associated with high level of preoperative D-Dimer (OR=2.11, 95%CI=1.35-3.30) and TKA (OR=2.29, 95%CI=1.29-4.01). Postoperative initiation of concomitant mechanical prophylaxis and low molecular weight heparin (LMWH) was protective for postoperative DVT (OR=0.56, 95%CI=0.37-0.86).

Conclusions: VTE is common in patients with diabetes undergoing joint arthroplasty. Patients undergoing TKA or with a high level of preoperative D-Dimer are at a considerable risk of developing postoperative VTE. There may be a protective role of postoperative initiation of concomitant mechanical prophylaxis and LMWH for VTE.

Background

The aging population and rising incidence of arthritis have caused an increasing number of people undergoing joint arthroplasty, such as total hip arthroplasty (THA) or total knee arthroplasty (TKA). Over the last several decades, the global prevalence of diabetes has also increased significantly [1]. In China, there are currently more than 110 million people with diabetes and about 20% of people aged over 60 years old have diabetes[1]. Therefore, the number of people with diabetes selecting to undergo joint arthroplasty is proportionally increasing[2,3]. In 2008 a study from the U.S. including 751,340 THA or TKA patients revealed that 8.55% of patients have the comorbidity of diabetes and the risk of postoperative complications increased significantly for patients with diabetes[4].

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism, is a common and potentially significant postoperative complication of arthroplasty surgery and leads to an increase of mortality and morbidity, as well as an increase of the cost of care[5]. The incidence of VTE following orthopedic surgery is highly variable due to heterogeneities of the studied populations, different treatment strategies and diagnostic measures, with published rates ranging from 1-2% to 60% [6-8]. Evidence shows that diabetes is related to a few changes in coagulation and fibrinolysis that may lead to thrombophilia[9]. A longitudinal study investigating relationship between risk factors of coronary heart disease and VTE reported that diabetes and obesity both significantly increased the risk of incident VTE independently of age, race and sex[10]. Those with diabetes at baseline had a 1.7-fold greater risk for VTE than those with normal fasting glucose levels[10]. Additionally, patients with diabetes who subsequently developed VTE had a 74% increase in the risk of recurrent DVT and 40% increased risk of long-term major bleeding[11].

Although guidelines recommend routine VTE prophylaxis after arthroplasty surgery[12], the appropriate strategy for preventing VTE in high-risk arthroplasty surgery has been debated over several decades. The importance of VTE prophylaxis is more apparent for patients with diabetes undergoing THA or TKA. VTE treatment presents risks including heparin-induced thrombocytopenia and bleeding complications by itself. There are various risk assessment models (RAMs) for VTE in Western countries to stratify patients based on risk factors and help to deliver individualized VTE prophylaxis[13-15] , but there is no clear data about VTE in Chinese patients with diabetes following THA or TKA. The aim of our study was to present the incidence of DVT among people with diabetes following THA or TKA and investigate its associated risk factors in current clinical practice. Such information is important for prediction of postoperative DVT and can be incorporated into the choice of appropriate thromboprophylaxis in this high-risk population.

Methods

Data sources

Patients who underwent THA or TKA at Beijing Jishuitan Hospital were enrolled in this study (n=415). From January 2016 to December 2018, 720 patients with diabetes had undergone THA or TKA at the Department of orthopedics of Beijing Jishuitan Hospital. Patients who had THA or TKA due to infection, fracture, or arthrofibrosis; patients who had history of malignancy or had received preoperative VTE prophylaxis; patients who had been diagonsed with VTE before surgery; patients without VTE-related images and tests of pre-operative D-Dimer were excluded from the study. The demographic and clinical information was obtained from electronic medical records.

Definition of VTE and diabetes

Lower limb venous Doppler ultrasound was performed before and after surgery for screening of deep venous thrombosis (DVT). Computer tomography pulmonary angiography (CTPA) was done to confirm pulmonary embolism (PE) for those with new postoperative DVT and typical symptoms of PE. A VTE event was determined to have occurred if either a DVT or PE as defined previously occurred.

Patients were considered to have prevalent diabetes when this was documented in medical records or taking antiglycaemic agents for previously diagnosed diabetes.

Other demographic and clinical measures

The clinical status was evaluated when patients were admitted. Detailed anthropometric measurements were collected by trained nurses, adhering to standardized techniques. Standing height was measured to an accuracy of 0.1cm and weight to an accuracy of 0.1 kilogram (kg). The body mass index (BMI) was calculated as weight in kilogram divided by the square of the height in meters. Blood pressure was measured twice on the right arm with an electronic sphygmomanometer (HEM-907; Omron Healthcare Company, Kyoto, Japan), in the sitting position, and was rounded to the nearest 1 mmHg. The average readings were used. Venous blood samples were obtained by nurses after an overnight fasting for 8-10h. Fasting levels of blood glucose were measured using an autoanalyzer (Hitachi 7600-110E/ Hitachi 7180E; Hitachi, Tokyo, Japan). Fasting levels of D-Dimer were measured by immunoturbidimetric assay using an automatic coagulation analyzer (Sysmex CS-5100, Sysmex Corporation, Japan).

Information about postoperative prophylaxis regimens were collected from electronic medical records. Mechanical prophylaxis was defined as either elastic stockings or foot pump.

Statistical analysis

Data analysis was carried out using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Data were presented as median (25th, 75th Quartile), mean ± SD or n (%). Continuous variables were compared using either student's t test or Mann- Whitney U test. Categorical variables were compared using χ^2 test or Fisher's exact test. Age (≥ 65 years versus < 65 years), gender (female versus male), smoking (smoking versus no smoking), preoperative comorbidities (hypertension, cerebrovascular disease and varicose veins of lower extremity versus none) , BMI (≥ 28 kg/m^2 versus < 28 kg/m^2), SBP (≥ 140mmHg versus < 140mmHg), DBP (≥ 90mmHg versus < 90mmHg), operative procedures (TKA versus THA), preoperative fasting blood glucose (≥ 7mmol/L versus < 7mmol/L), preoperative D-Dimer (> 0.55 mg/L FEU versus ≤ 0.55 mg/L FEU) and postoperative prophylaxis regimens (mechanical prophylaxis versus concomitant mechanical prophylaxis and low molecular weight heparin (LMWH)) were treated as independent variables, which were previously shown to be risk factors for VTE. A multivariable logistic regression analysis was performed to determine the independent risk factors for VTE. All analyses were two-tailed and $P<0.05$ was considered to be statistically significant.

Results

The detailed approach for participants' selection is shown in Figure 1. A total of 400 patients with diabetes who underwent THA or TKA between January 2012 and December 2018 (n=400) at Beijing Jishuitan Hospital were included in this study, 24.3% of whom were males. The mean age of these patients was 64.9 years. The overall incidence of postoperative VTE among patients with diabetes was

46.8% (183 of 400). Among 153 VTE patients, none of them had PE. The incidence of VTE in patients who received THA was 32.3% (30 of 97), while the incidence of VTE after TKA was 51.1% (157 of 307).

Demographic and clinical characteristics of patients by VTE status are presented in Table 1. There were more females who developed VTE among this population. The mean surgery age of patients who developed VTE was significantly older than those without VTE (66.0 versus 64.1 years, P=0.012). Furthermore, the preoperative D-Dimer in VTE patients was higher than in those without VTE (0.46 versus 0.40 mg/L FEU, P=0.007). There was no difference in terms of prevalence of smoking, hypertension, cerebrovascular disease or varicose veins, BMI, SBP, DBP, preoperative fasting glucose and Caprini score between patients with and without VTE. Among this population, 55.5% of patients were given mechanical prophylaxis after THA or TKA for venous thromboembolism prophylaxis, while 45.5% of patients were given concomitant mechanical prophylaxis and LMWH. VTE incidence in patients who were given concomitant mechanical prophylaxis and LMWH after THA or TKA was significantly lower than in those who were given mechanical prophylaxis alone.

Table 3 summarises the results of the multivariable logistic regression analysis for postoperative VTE. We found that TKA was associated with 2.3-fold higher risk of VTE as compared to THA. Preoperative D-Dimer >0.55 (mg/L FEU) was associated with 2.1-fold higher risk of VTE as compared to preoperative D-Dimer ≤ 0.55 (mg/L FEU). Mechanical prophylaxis and LMWH combined reduced the risk of VTE by 44% as compared with mechanical prophylaxis alone.

Discussion

The overall incidence of postoperative DVT was 46.8% in patients with diabetes undergoing THA or TKA in this single center study and no PEs were confirmed. Patients with diabetes undergoing joint arthroplasty remain at high risk for developing postoperative VTE. Since guidelines for VTE prophylaxis were published, thromboprophylaxis with multiple strategies were routinely applied on most patients after arthroplasty surgery. This study is one of very few studies that investigate the incidence of and risk factors for VTE among patients with diabetes following joint arthroplasty under the real-world clinical practice, which may help to guide orthopaedic surgeons in their choice of VTE prophylaxis. We found that the VTE incidence for those undergoing TKA was 51.1%, which was higher than those undergoing THA. TKA was associated with 2.3-fold higher risk of postoperative VTE as compared with THA. This is consistent with other studies[16,17]. It is possibly due to more extensive damage to soft-tissue and bone during TKA, which leads to the local release of tissue factors, thus initiating the coagulation cascade and also destruction of vascular anatomy[18].

D-dimer is a degradation product of cross-linked fibrin, and therefore a biomarker of coagulation activation and fibrinolysis. Plasma D-dimer level is often measured in order to screen VTE. A low D-dimer level may be useful for excluding acute thrombosis in clinical settings. However, there is a paucity of studies with respect to D-dimer as a risk factor for incident VTE. Our study suggests that high level of preoperative D-Dimer was an independent risk factor for postoperative VTE. Using a sample of the general US population, Cushman et al. found that higher baseline D-dimer level was correlated with increased risk of subsequent VTE[19]. Another two case-control studies showed that patients with a history of VTE were more likely to have elevated D-dimer level than controls[20,21]. A potential explanation proposed for the association between D-dimer and VTE is that D-dimer may be a marker for other factors associated with the pathophysiology of VTE. Evidence indicates that D-dimer is higher in the presence of genetic risk factors (eg. prothrombin 20210A, factor V Leiden, or elevated factor VIII:c) for VTE[22]. However, these genetic mutations are rare in Asian populations[23]. In addition, some possible risk factors for VTE such as age, smoking and inflammatory status are also reported to be associated with higher D-dimer[24-26]. Therefore, measurement of baseline D-dimer may provide comprehensive clinical information than assessment of some specific thrombosis risk factors, such as genes or obesity.

Given that thromboprophylaxis has become the standard of care for patients undergoing THA or TKA, early mobilization combined with mechanical compressive device is highly recommended and has been the primary method of VTE prophylaxis in our center since 2012. In our study, all patients used mechanical prophylaxis for VTE after surgery and less than half of patients used LMWH. Concomitant use of mechanical prophylaxis and LMWH decreased the risk of VTE by 43% as compared with mechanical prophylaxis alone. A meta analysis including 14 trials showed that LMWH decreased asymptomatic DVT by 50% (combined risk ratio [RR], 0.50; 95% CI, 0.43-0.59) for major orthopedic surgery without significant increase in bleeding rates, which is similar with our result[12]. However, it is necessary to measure the bleeding risk versus thrombotic risk before commencing pharmacological prophylaxis especially for situations where the patients' personal bleeding risks are high.

There are various risk assessment models (RAMs) for VTE in Western countries, among which Caprini RAM is often applied to orthopedics inpatients. THA or TKA would give a score of 5 if assessed using the Caprini RAM. This places all patients in the high-risk category. In our study, no significant difference was found about Caprini score between patients with and without VTE. Therefore, Caprini RAM is highly sensitive but poorly specific for patients undergoing THA or TKA, which might not facilitate managing diverse patients with personalized VTE prophylatic strategies. Further studies need to be carried out to develop a specific VTE risk assessment model that serves this high risk population.

This study has several limitations. First, this study was carried out in only one large center, which limits its external validity in other population. Second, VTE in our study is defined as all venous thromboembolism including calf vein thrombosis, proximal vein thrombosis and PE. Whether calf vein thrombosis requires anticoagulant therapy is currently a debated issue due to its uncertain clinical significance. However, some investigators reported that therapeutic anticoagulation was associated with a significant reduction in the risk of extension to proximal DVT or PE among patients with calf DVTs[27,28]. Current American College of Chest Physicians guidelines recommends therapertic anticoagulation for calf vein thrombosis under the presence of the risk factors, such as active cancer, history of VTE or inpatient status[12]. As patients enrolled in our study could all be classified at high risk of developing VTE based on Caprini RAM, it might be reasonable to include calf vein thrombosis in the analysis. Lastly, lack of investigation of other risk factors such as anesthesia type, perioperative red blood cell transfusion and plasma homocysteine was also a limitation of this study.

Conclusions

VTE is common in patients with diabetes following joint arthroplasty. Patients undergoing TKA or with a high level of preoperative D-Dimer are at an increasing risk of VTE. There may be a protective role of postoperative initiation of concomitant mechanical prophylaxis and low molecular weight heparin for VTE.

Abbreviations

VTE: Venous thromboembolism; DVT: Deep venous thrombosis; PE: Pulmonary embolism; THA: Total hip anthroplasty; TKA: Total knee anthroplasty; RAM: Risk assessment models; LMWH: Low molecular weight heparin

Declarations

Acknowledgments

We are grateful to the research participants for their participation in this study. We are also grateful for the research team who contributed to the data collection and laboratory measurement.

Funding

This study was supported by Beijing Municipal Science & Technology Commission (No. Z161100000116091).

Availability of data and materials

The data and materials in the study are available on reasonable request.

Authors' contributions

WD, LLH, QY and WT designed the study. DYH, QL, JC, LL, QYZ, and WL were involved in data collection. WD and LLH analyzed the data and wrote the first draft of the manuscript. QY, DYH, QL, JC, LL, QYZ, WL and WT reviewed/edited the manuscript. QL, JC, LL, QYZ, and WL were involved in laboratory analyses and quality control. All authors contributed to the interpretation of the results and revision of the manuscript for important intellectual content and approved the final version of the manuscript. WT is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval and consent to participate

Informed consent was obtained from all individual participants included in the study. The study was approved by the ethics committees of Beijing Jishuitan Hospital

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Demographic and clinical characteristics of patients with diabetes undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA)

	Total	VTE (+)	VTE (-)	Z value/t value/χ2 value	P value
Gender (M/F)	97/303	34/153	63/150	7.040	0.010
Age (years)	64.9±7.7	66.0±6.7	64.1±8.3	-2.513	0.012
Smoke, % (n)	16.5 (66)	13.9 (26)	18.8 (40)	1.718	0.225
Alcohol drink, % (n)	11.5 (46)	11.2 (21)	11.7 (25)	0.025	1.000
Hypertension, % (n)	64.8 (259)	64.7 (121)	64.8 (138)	0.000	1.000
Cerebrovascular disease, % (n)	14.0 (56)	15.0 (28)	13.1 (28)	0.276	0.665
BMI (kg/m^2)	26.9±3.4	27.1±3.5	26.7±3.4	-1.225	0.221
SBP (mmHg)	144 (131, 157)	144 (133, 157)	143 (130, 157)	-1.001	0.317
DBP (mmHg)	80 (73, 88)	80 (72, 88)	80 (73, 88)	-0.351	0.725
Preoperative fasting glucose (mmol/L)	7.7±2.2	7.8±2.3	7.7±2.1	0.104	0.917
Preoperative D-Dimer (mg/L FEU)	0.43 (0.27, 0.83)	0.46 (0.28, 1.14)	0.40 (0.27, 0.66)	-2.696	0.007
Varicose veins, % (n)	8.3 (33)	8.0 (15)	8.5 (18)	0.024	1.000
Operative procedures					
THA, % (n)	23.3 (93)	32.3 (30)	67.7 (63)	10.222	0.001
TKA, % (n)	76.8 (307)	51.1 (157)	48.9 (150)		
Caprini score	7.2±0.7	7.2±0.8	7.1±0.8	-0.827	0.409

Table 2 Postoperative prophylaxis regimens of patients with diabetes undergoing total joint arthroplasty

	Total	VTE (+)	VTE (-)	Z value/t value/ χ2 value	P value
Mechanical prophylaxis, % (n)	55.5 (222)	29.5 (118)	26.0 (104)	8.216	0.005
Mechanical prophylaxis + Low molecular weight heparin, % (n)	44.5 (178)	17.3 (69)	27.2 (109)		

Table 3 Adjusted odds ratios and 95% CI between risk factors and VTE status

Risk factors	OR	95% CI	P value
Age (≥ 65 years versus < 65 years)	0.904	0.585 – 1.399	0.652
Gender (female versus male)	1.541	0.862-2.755	0.144
Smoking (yes versus no)	1.234	0.633-2.405	0.537
Varicose veins (yes versus no)	0.769	0.367-1.729	0.565
Hypertension (yes versus no)	0.828	0.518-1.326	0.432
Cerebrovascular disease (yes versus no)	1.136	0.616-2.094	0.683
BMI (≥ 28 kg/m^2 versus < 28 kg/m^2)	0.834	0.536-1.300	0.423
SBP (≥ 140mmHg versus < 140mmHg)	1.143	0.720-1.812	0.571
DBP (≥ 90mmHg versus < 90mmHg)	0.976	0.561-1.699	0.932
Operative procedures (TKA versus THA)	2.285	1.287-4.058	0.005
Preoperative fasting glucose (≥ 7mmol/L versus < 7mmol/L)	1.211	0.794-1.847	0.374
Preoperative D-Dimer (> 0.55 mg/L FEU versus ≤ 0.55 mg/L FEU)	2.109	1.348-3.300	0.001
Postoperative prophylaxis regimens (mechanical prophylaxis versus mechanical prophylaxis and LMWH)	0.559	0.365-0.855	0.007

Figures

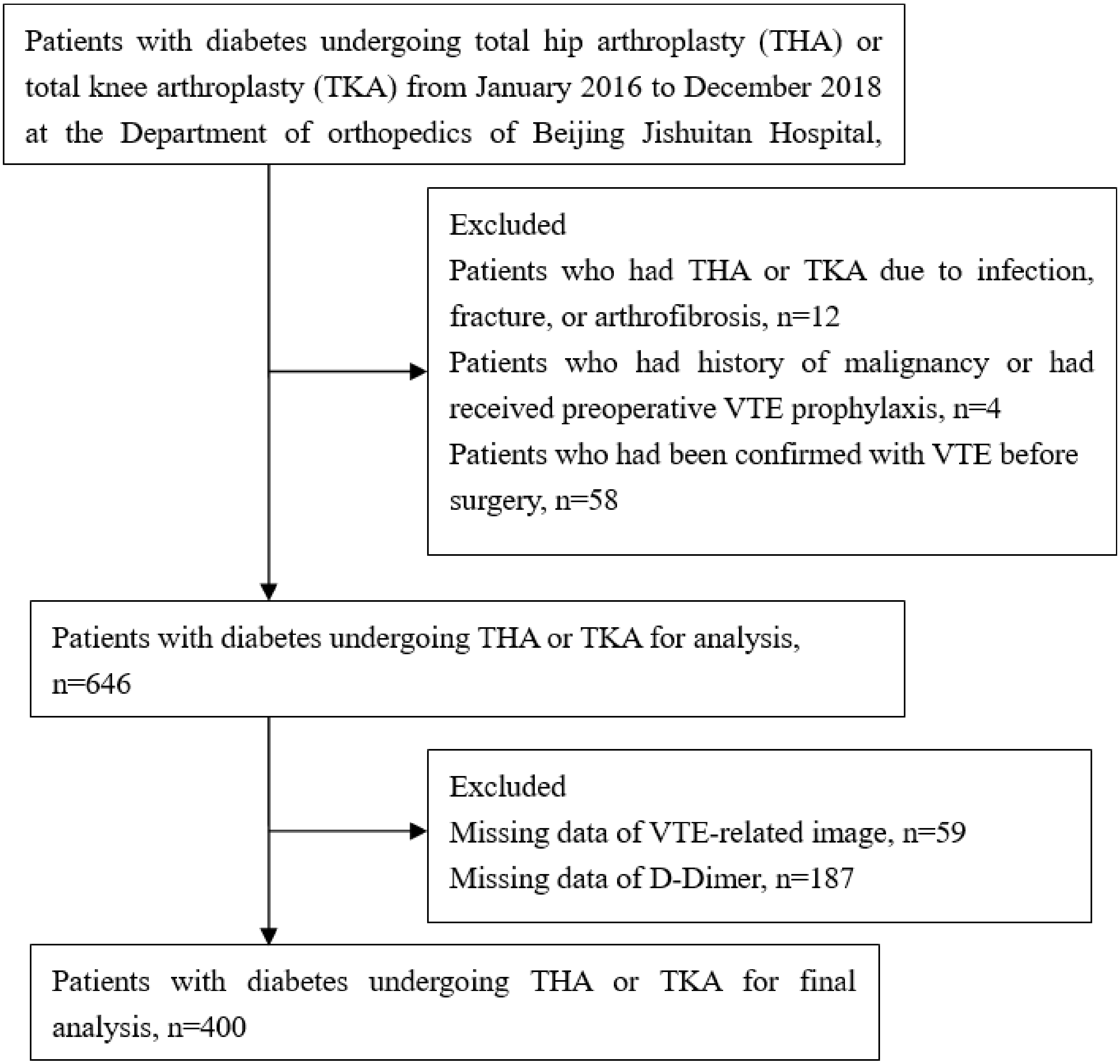

Figure 1

Detailed approach for the selection of participants