Does diabetes mellitus increase the occurrence of early thrombosis in deep vein following unicompartmental arthroplasty of the knee: a retrospective cohort study

Xu-Feng Jiao

Xuanwu Hospital

Zheng Li

Xuanwu Hospital

Shuai An

Xuanwu Hospital

Jiang Huang

Xuanwu Hospital

Ming-Li Feng

Xuanwu Hospital

Jia-Xing Zheng

Xuanwu Hospital

Guanglei Cao (✉ gregary111@163.com)

Xuanwu Hospital <https://orcid.org/0000-0002-8456-9522>

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Abstract

Introduction

Many patients with knee osteoarthritis also suffer from diabetes mellitus and the possibility of deep venous thrombosis (DVT) is increased following unicompartmental knee arthroplasty (UKA). Therefore, we evaluated whether DVT occurrence increased 3 days following operation in diabetic patients undergoing UKA.

Materials and methods

The incidence of deep venous thrombosis between non-diabetic and diabetic patients who underwent UKA in our hospital from August 2018 to January 2020 was compared, and the effect of glycosylated hemoglobin levels on DVT was evaluated.

Results

Of the 84 patients, 25 (29.8%) had diabetes and 59 (70.2%) did not. Within 3 days after operation, DVT occurred in 12 cases (48.0%) in the diabetic group and 8 cases (13.6%) ($p < 0.001$) in the control group. In logistic regression analysis, the results demonstrated that the risk of deep venous thrombosis in diabetic group was 5.53 times higher compared with non-diabetic group. For every 1 unit increase of glycosylated hemoglobin, the incidence of DVT increased 2.88 times (95% CI: 1.097–7.559, $p = 0.032$). There was no significant difference in age, sex, body mass index, hypertension, mode of anesthesia, operation time, intraoperative blood loss, tourniquet pressure and time between the two groups.

Conclusion

The incidence of DVT in diabetic patients within 3 days after UKA is significantly higher than that in non-diabetic patients. The higher the concentration of glycosylated hemoglobin, the greater the risk of DVT.

Introduction

As a burden around the world, venous thromboembolism (VTE) consists of pulmonary embolism (PE) and deep vein thrombosis (DVT), and it is also one of the serious complications following joint replacement operations. The occurrence of DVT is related to many aspects, such as gender, age, anesthetic mode, body mass index (BMI), heart disease, diabetes mellitus, active cancer and so on[1].

The global population is entering an aging stage, followed by an increasing proportion of patients with diabetes in joint replacement surgery. Researchers have confirmed that there are abnormalities in the coagulation system[2], hemostatic system[3] and fibrinolysis[4] when the patients suffer from diabetes. Similarly, previous studies have shown that diabetes mellitus is related to multiple defects in fibrinolysis and coagulation system, resulting in the procoagulant and thrombotic susceptibility, so diabetes could significantly increase the risk of DVT[5-6].

Orthopedic surgery, especially joint replacement, remarkably increases the risk of hospital-acquired DVT, even up to 40% to 60%[7-8]. In previous studies, diabetes mellitus was shown to increase the postoperative DVT risk in those with total knee arthroplasty (TKA)[9]. However, compared with TKA, unicompartmental knee arthroplasty (UKA), which is characterized by less trauma, short operation time and rapid postoperative recovery[10-11], has become the first choice of many doctors for end stage unicompartmental knee osteoarthritis[12]. To our knowledge the effect of DM on postoperative VTE hasn't been studied in UKA. Therefore, we conducted a retrospective cohort study to verify whether diabetes mellitus increased the risk of postoperative DVT in patients with UKA. The hypothesis was that DM increases the postoperative DVT risk in UKA patients.

Material And Methods

In this retrospective cohort study, the patients with confirmed diagnosis of unilateral or bilateral osteoarthritis in knees who underwent UKA from August 2018 to January 2020 in our hospital were enrolled. Patients were excluded if they had infectious, gouty or rheumatoid arthritis, DVT revealed by ultrasonography before surgery, previous history of DVT or vascular surgery in lower extremities, or one-stage bilateral UKA. Patients with coronary heart disease, arrhythmia, chronic heart failure, tumor history, long-term prophylactic use of anticoagulants such as aspirin, or severe postoperative complications were also excluded. The patients were assigned to diabetes group and non-diabetes group, respectively.

Any prophylactic anticoagulation treatment was not given before surgery. The anesthesiologist chose general anesthesia or intraspinal anesthesia according to the patients' condition. A tourniquet was used during the operation and the pressure was usually set as 100mmHg above the systolic pressure, which continued from the beginning of the operation until the prosthesis was fixed with bone cement. The operations were performed with medial parapatellar approach incision, cemented Oxford phase II (two pegs; MP instrument; Biomet UK LTD, Waterton Industrial Estate, Bridgend CF31 3XS, UK), and cocktail injection (tranexamic acid 60ml, parecoxib sodium 40mg, epinephrine 0.15ml, ropivacaine hydrochloride 20ml:200mg, oxycodone 10ml:1mg, injected into joint capsule, synovium, subperiosteum, and subcutaneous tissues).

No drainage was used after operation. Exercises of ankle flexion and quadriceps muscle contraction were encouraged as early as possible, and ambulation with complete weight with the aid of crutches should be conducted four hours after operation. The lower limb pneumatic blood circulation pump was used on the night of the operation. On the third day after operation, all patients were given standard low molecular weight heparin (LMWH; 0.2ml: 2,000 AxaIU, Enoxaparin Sodium Injection) to prevent thrombosis, and deep vein color Duplex sonography of lower extremities was performed again. According to the results of ultrasound, DVT was diagnosed and categorized into distal type and proximal type, and then double doses of heparin were given.

The blood glucose was controlled by long-acting insulin before going to sleep and short-acting insulin before meals. Fasting and postprandial blood glucose concentrations of 5~7mmol/L and 8~10 mmol/L

respectively were acceptable.

The statistical results included the body mass index (BMI), age, sex, surgery side, and concomitant disease, recorded glycosylated hemoglobin value, the pressure and duration of applying tourniquet during operation, and blood loss in the operation.

t-test was used to compare continuous variables, and Pearson Chi-square test was used to compare counting variables. Statistical packages R (The R Foundation; <http://www.r-project.org>; version 3.4.3) and Empower (R) (www.empowerstats.com, X&Y solutions, inc. Boston, Massachusetts) were used for analysis. If p value <0.05, the results were considered to be significantly different.

Results

In our study there were 121 patients, and they all underwent UKA from August 2018 to January 2020 in our hospital. Among them, 37 patients were excluded according to the exclusion criteria, including 26 with history of coronary cardiac disease, 4 with arrhythmia, 5 with DVT confirmed by preoperative ultrasound, 1 with breast cancer and colon cancer.

A total of 84 patients were finally included, including 21 males and 63 females, among which 25 had diabetes mellitus. No significant difference was observed in BMI, mean age, sex, tension or the duration of applying tourniquet, and intraoperative blood loss between the two groups ($p > 0.05$). In diabetes group, the glycosylated hemoglobin was remarkably increased compared with the group without diabetes (6.4 ± 0.6 vs. 5.8 ± 0.8 , $p = 0.004$). The basic information of the study population is shown in Table 1.

On the third day after operation, 20 patients were diagnosed as peripheral DVT by using color Doppler ultrasound examination, among which 12 had diabetes mellitus. Significant difference was found between diabetes and non-diabetes groups ($p < 0.001$). Among those with DVT, 14 were affected in the ipsilateral leg, 4 in the contralateral leg, and 2 in bilateral legs. No proximal DVT was found. After BMI, sex, age, hypertension, and some other confounding factors were adjusted, multivariate logistic regression model showed that diabetes mellitus ($OR = 5.527$) and glycosylated hemoglobin ($OR = 2.880$) were risk factors of DVT after UKA. The risk for DVT in those who had diabetes was 5.527 times higher than that in patients without diabetes. In addition, the risk of developing DVT increased 2.88 fold for every unit increase in glycosylated hemoglobin (Table 2).

Discussion

VTE is a serious complication of joint arthroplasty. The risk of symptomatic PE was the highest in the first week after surgery, 81% of which occurred within three days post operation[13-14]. Therefore, it is very important to prevent the occurrence of VTE in the early stage after joint replacement surgery.

In this retrospective cohort study, the occurrence of DVT in early stage post UKA was closely associated with diabetes, and was proportional to glycosylated hemoglobin levels.

VTE is caused by multiple factors and associated with the relationship between VTE-related risk factors and acquired or hereditary thrombosis, including BMI and increasing age, hospital care for an acute disease, major surgery, congestive heart failure, arrhythmia, active cancer and dyskinesia[15-16]. However, whether diabetes is associated with the incidence of thromboembolism remains controversial.

Fuller suggested that diabetic patients had higher levels of VII and X factor, fibrinogen and platelet adhesion, but lower fibrinolytic activity and whole blood platelet count[2]. In addition, in patients with diabetes, the sensitivity of platelets to spontaneous aggregation increased, and the fibrinogen survival rate and platelet survival rate were shortened. When exposed to pro-aggregation agents, the platelets can produce more substances like prostaglandins in those with diabetes. These platelets release more arachidonic acid from membrane phospholipids, which are further converted into large amounts of thromboxane A and prostaglandins, making platelets more likely to aggregate[3]. The spontaneous fibrinolytic activity in those with diabetes was lower compared with non-diabetic patients[4]. These findings suggest a potentially important association between thrombosis trends and vascular disease in diabetes. Some clinical observation studies also supported these views. Petrauskienė's study found that after adjusting for age, the VTE risk in the patients with diabetes was more than twice of that in non-diabetic people[6]. After further adjustment for race and gender, Tsai suggested that the risk of VTE at baseline in diabetic patients was 1.70 times higher compared with those who had normal fasting blood glucose (95% CI, 1.20-2.40)[17]. Retrospective analysis and prospective evaluation of renal transplants also showed that diabetes was remarkably related to VTE[5, 18-19]. Previous retrospective research of 358 subjects showed that DVT incidence within 14 days after TKA in patients who had diabetes mellitus was 2.7 times higher compared with those without diabetes mellitus[9]. This is consistent with our results. Compared with TKA, the surgery time of UKA is shorter, and the interval between the end of operation and the beginning of ambulation is shorter. Thus, the duration of applying tourniquet, the amount of blood loss during surgery and immobilization of the affected limb have less influence on the results. In addition, we found that because the less trauma and shorter recovery cycle of UKA, the incidence of DVT in our study(23.8%) was much lower than that of TKA (55.3%)[9].

However, some authors have put forward the opposite opinion. Jones compared 60 diabetic patients admitted for heart disease, stroke or abdominal surgery with 60 matched controls, and it was found that diabetes had no relationship with the increased risk for VTE. The authors believed that the underlying illness affected the arterial wall or target organ and caused DVT, not the effect of diabetes[20]. However, high-risk diseases that cause DVT had been ruled out in our study, and the results showed that there was a high correlation between DVT and diabetes. In another 5-year follow-up research, Asplund compared 53 diabetes patients with stroke and 53 normal patients who had matched sex, age and were diagnosed as cerebrovascular disorders. The occurrence of fatal PE in those with diabetes was 7%, which was lower compared with the normal subjects (21%)[21]. In the field of joint replacement—after analyzing 197 patients who underwent the preliminary total hip arthroplasty or revision surgery without routine chemoprophylaxis, Wong found that only 15 patients (8%) had DVT, and the occurrence of DVT was not associated with diabetes[22]. But among these 197 samples, there were only 29 in the diabetic group. A large quantitative gap between the two groups may bias the results.

Glycosylated hemoglobin is a form of hemoglobin that reflects the average plasma glucose concentration over a period and is recommended for blood glucose control in those who had diabetes. In our research, it was found that for every 1 unit increase in glycosylated hemoglobin, the risk of DVT increased by 2.88 times (95%CI, 1.097-7.559). However, the relationship between glycosylated hemoglobin and macrovascular disease is not clear[23]. In contrast, Adams analyzed the outcomes of 4,0491 patients undergoing total knee arthroplasty from 2001 to 2009. When comparing 7,567 (18.7%) diabetic patients with normal subjects, there was no relationship between DVT or PE risk and controlled diabetes (HbA1c< 7%) (OR, 0.84; 95%CI 0.60 - 1.17)[24].

In this study, no significant difference was found in hypertension, surgery time and intra-operative blood loss, although these factors may cause hemodynamic changes that increase the risk of DVT. The effect of tourniquet on DVT after joint replacement is controversial. A case-control trial showed that applying tourniquet could reduce perioperative blood loss without increasing the risk of DVT[25]. Similar results have been presented in a meta-analysis which included 11 controlled randomized trials containing 541 patients[26]. However, a study involving 200 patients demonstrated that DVT occurrence after TKA in those who released tourniquet in an early phase was significantly lower compared with those who released in a later phase. Additionally, releasing tourniquet in an early phase could reduce DVT incidence and would not increase the occurrence of complications[27]. Another randomized controlled trial involving 109 patients showed that no difference was found in the occurrence of proximal DVT between those who applied tourniquet and those who did not after TKA. However, the risk of distal DVT in those who applied tourniquet group was remarkably higher compared with those who did not use tourniquet[28]. In this study, the tourniquet was used from the beginning of the operation until the implant was fixed with bone cement. No significant difference was found in the pressure and duration of applying tourniquet between diabetic and non-diabetic groups. Furthermore, there was no limb edema, pain or limitation of movement in the two groups. All cases of DVT were asymptomatic distal DVT, indicating that the patients may benefit from early postoperative functional exercise.

There were several limitations in our study. First, venography is the generally accepted standard in diagnosing DVT but the invasive and expensive characteristics limited its application. Thus, color Doppler ultrasound, an economical and convenient method, is often used in clinical screening. A study on the diagnosis of DVT after TKA showed that when venography is used as a baseline reference, the specificity and sensitivity of ultrasound in diagnosing DVT were 63% and 87%, respectively[29]. But for proximal DVT, doppler ultrasonography can provide good sensitivity (86%) and specificity (100%), and can be a reliable diagnostic tool[30]. The two groups in our study received the same ultrasound examination, so the interference of ultrasound errors to the results can be ignored. Second, we do not distinguish between the types of diabetes, and different types of diabetes may have different effects on DVT. Third, different anesthetic methods exert different influence on hemodynamics, thus affecting the occurrence of postoperative DVT[31]. In this study, all patients received general or intraspinal anesthesia, and no significant difference was observed between them ($p=0.940$). Additionally, the incidence of DVT was the highest in the 1st week following operation[32]. However, patients who underwent UKA can be discharged from hospital about five days after operation due to the minimal trauma and rapid recovery, so color

Doppler ultrasound data could only be collected three days after operation. Due to stringent enrollment criteria, only 84 patients were included in our study, the sample size was small, which may also lead to deviation in the results.

Conclusions

According to our study, The risk of developing DVT in the early stage after UKA was significantly increased in the patients with diabetes mellitus. Additionally, a higher level of glycosylated hemoglobin was related to a higher risk of DVT. It is hoped that a large-scale prospective population-based study in the future, including a detailed description of diabetes typing and glucose tolerance, which will help to further clarify the relationship between diabetes and DVT.

Declarations

Ethics approval and consent to participate This clinical study is a retrospective study. It only collects clinical data of patients, does not interfere with the patient's treatment plan, and does not bring risks to the patient's physiology. The researchers will make every effort to protect the information provided by the patients from disclosing personal privacy. This study has obtained the consent of all participants.

Consent for publication: All authors have approved the version submitted for publication.

Availability of data and materials: The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Tables

Table 1 Clinical features and population distribution

	Diabetes mellitus	Non- Diabetes mellitus	P-value
N	25	59	
Age	70.0 $\pm$ 7.6	69.0 $\pm$ 8.1	0.584
BMI(kg/m ²)	27.1 $\pm$ 3.2	27.0 $\pm$ 2.9	0.873
Gender			0.491
Male	5	16	
Female	20	43	
Glycosylated hemoglobin	6.4 $\pm$ 0.6	5.8 $\pm$ 0.8	0.004
Hypertension	19	36	0.187
Anesthesia			0.940
General anesthesia	7	17	
Intravertebral anesthesia	18	42	
Duration of surgery (min)	107.5 $\pm$ 15.9	107.7 $\pm$ 20.8	0.960
Duration of tourniquet (min)	69.3 $\pm$ 8.1	67.5 $\pm$ 7.4	0.356
Tension of tourniquet (mmHg)	260.8 $\pm$ 4.0	261.7 $\pm$ 5.6	0.473
Intra-operative blood loss (ml)	52.3 $\pm$ 16.1	48.5 $\pm$ 14.4	0.288
DVT	12	8	<0.001

Data: Mean $\pm$ SD / N

Table 2 Multivariate Logistic regression analysis of influencing factors of DVT

Factor	OR	95% CI	P
Age	1.043	0.944-1.152	0.409
Sex	2.267	0.210-24.453	0.500
BMI (kg/m2)	0.612	0.065-5.790	0.669
Hypertension	0.667	0.146-3.051	0.601
Diabetes mellitus	5.527	1.329-22.99	0.019
Glycosylated hemoglobin	2.880	1.097-7.559	0.032
Tension of tourniquet (mmHg)	1.111	0.976-1.266	0.111
Duration of tourniquet (min)	1.014	0.899-1.144	0.819
Duration of surgery (min)	1.003	0.953-1.056	0.903
Intra-operative blood loss (ml)	0.969	0.925-1.015	0.178