CLINICAL ARTICLE

Effect of Cholecystectomy on the Occurrence of Knee Osteoarthritis

Ling-yuan Zeng, MD[1], Shu-yan Yang, MD[2], Zhi-qiang Zhang, MD[1], Tao Wang[1], Yu-ze Wang, PhD, Xiao-chun Wei, PhD[1]

Department of [1]Orthopaedic Surgery and [2]Blood Transfusion, The Second Hospital of Shanxi Medical University, Taiyuan, China

Objective: To evaluate the effect of cholecystectomy on the occurrence of knee osteoarthritis (KOA).

Methods: The present study was a case-control study with a retrospective, cross-sectional, and longitudinal study design. The clinical data for knee osteoarthritis in the Second Hospital of Shanxi Medical University from January 2016 to September 2018 was analyzed. Clinical data, including gender, age, height, weight, smoking, alcohol abuse, prior medical history, and previous surgical history, were recorded. A logistic regression model was used for the univariate and multivariate analysis.

Results: A total of 1659 patients with KOA (KOA group) and 1195 limb fracture patients (control group) were included in this study. Among the 1659 patients with KOA, 388 patients were male and 1271 were female, while among the 1195 patients in the control group, 638 patients were male and 557 patients were female. The period between cholecystectomy and knee osteoarthritis onset ranged from 0.5 years to 17 years; the average interval time was 8.73 ± 2.11 years. The age at disease onset was significantly older when compared to the control group, while the body mass index in the KOA group was significantly higher when compared to the control group ($P < 0.05$). There were 97 patients undergoing cholecystectomy in the KOA group and there were 15 patients undergoing cholecystectomy in the control group. The proportion of cholecystectomy in the two groups was statistically significant. After the univariate analysis, there was a statistically significant difference in distribution between the two groups ($P < 0.05$). The multivariate logistic regression analysis revealed that there was a significant difference in the distribution of these two groups ($P < 0.05$), indicating that cholecystectomy is associated with the occurrence of KOA.

Conclusion: There is a close relationship between cholecystectomy and KOA. However, the specific mechanism remains unknown and should be further researched.

Key words: Cholecystectomy; Disease occurrence; KOA; Osteoporosis; Subchondral trabeculae

Introduction

Osteoarthritis (OA) is mainly the result of a series of lesions on the articular synovium, cartilage, and subchondral bone, leading to the structural malformation and functional dysfunction of diseased joints[1]. With the aggravation of population aging in China, the incidence of OA increases year by year. Among the population aged 55–64 years old, the knee joint is a common site of osteoarthritis, and the incidence of knee osteoarthritis (KOA) can reach up to 49%[2]. This disease is affected by the living environment, living habits, age, gender, and other factors[3]. As people become older, bone density decreases, and as the subchondral trabeculae becomes thinner and harder, their ability to withstand stress decreases[4]. Therefore, osteoporosis leads to a higher incidence of KOA[5]. Importantly, some patients without strong risk factors present with particularly aggressive KOA. Such cases mandate the investigation of other possible factors, such as cholecystectomy.

Laparoscopic cholecystectomy (LC) has been widely used for the treatment of benign gallbladder diseases, such as cholecystitis and gall bladder calculi[6]. Reports of discomfort symptoms after cholecystectomy are also increasing[7]. The

Address for correspondence Xiao-chun Wei, PhD, Department of Orthopaedic Surgery, The Second Hospital of Shanxi Medical University, 382 Wuyi Road, Xinghualing District, Taiyuan, Shanxi Province, China 030001 Tel: +86 03513365105; Fax: +86 03513365105; Email: xiaochunw15@163.com

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major adverse reactions include indigestion and osteoporosis caused by poor vitamin D absorption.

Cholecystectomy disrupts a patient's digestive function. The surgery destroys the patient's gallbladder structure, impacting the patient's bile ducts, and placing pressure on the biliary tract. The operation also destroys the environment of the intestinal flora, and the changes to the intestinal microecological environment weaken a patient's immune ability. Cholecystectomy involves removal of the gallbladder. Bile is only minimally secreted, and the digestive system and the intestines and stomach no longer function as normal. Digestive disorders affect the absorption of vitamin D, leading to vitamin D deficiency, which, in turn, promotes osteoporosis.

Osteoporosis (OP) is a systemic disease characterized by bone loss and bone microstructural degradation, resulting in brittle bones and increased risk of fracture. OP and OA are closely correlated to bone and cartilage metabolism, and the aging process of the body. These are generally considered two completely different diseases. In the 1990s, scholars have proposed that there is a close relationship between these two diseases. Osteoporosis is an important risk factor of knee osteoarthritis[8]. Various studies have shown that OA is associated with higher bone mineral density (BMD), which can reduce the risk of OA progression[9]. Therefore, the relationship between OA and BMD is complex, and bone metabolism plays a very important role in the pathophysiology of both.

It remains unknown whether cholecystectomy is associated with the incidence of KOA. Therefore, a consecutive cohort of patients in China who presented with KOA was retrospectively studied. The aim of the present study was: (i) to evaluate the association between cholecystectomy and KOA; (ii) to analyze the clinical characteristics of patients with KOA; and (iii) to investigate whether cholecystectomy is a risk factor for the disease.

Materials and Methods

Research Data

The present study was a case-control study with a retrospective, cross-sectional and longitudinal study design. The present study was approved by the Ethics Committee of the Second Hospital of Shanxi Medical University.

Data were collected from the medical record system of the Second Hospital of Shanxi Medical University, in accordance with the laws of the People's Republic of China on electronic medical records management and the medical record writing basic specifications developed by Shanxi Communication Company. Queries regarding the patient can be raised by entering their personal information (age, gender, and family address), including associated diseases and the general condition of the patient. The system can also be used to access clinical laboratory information for patients, such as blood and urine test reports and video imaging reports. Due to personnel and funding constraints, patients selected for the KOA group and the control group were all patients admitted to the Department of Orthopedics of the Second Hospital of Shanxi Medical University from January 2016 to September 2018.

Inclusion and Exclusion Criteria

Inclusion criteria: (i) participants diagnosed with OA according to the guidelines of OA issued by the Rheumatology Branch of the Chinese Medical Association[10]; (ii) patients who had undergone cholecystectomy; (iii) patients who had a Kellgren–Lawrence classification[11] of III and IV; and (iv) in the control group, patients diagnosed with a limb fracture based on radiography.

Exclusion criteria: (i) patients with severe osteoporosis; (ii) patients with immune system disease; (iii) patients with severe infection; (iv) patients with liver and kidney dysfunction; (v) patients with coagulation dysfunction; (vi) patients with malignant tumors; (vii) patients with light knee pain symptoms from the very beginning to the time of surgery; (viii) and patients whose registration data was incomplete.

Patients

A total of 1659 patients with KOA fit the diagnostic criteria. Patients whose registration data was incomplete were contacted by telephone or postal questionnaire to obtain additional data.

In the longitudinal study, patients with disease progression were collected. With reference to the diagnostic criteria for KOA[12], and on the premise of excluding KOA, 1023 patients with physical fractures caused by trauma were admitted to the trauma ward group in the Department of Orthopedics of the Second Hospital of Shanxi Medical University during this period.

Data Collection

The clinical data of these patients were observed and recorded, which included age, height, weight, smoking history, alcohol abuse history, and history of hypertension, diabetes, hyperlipidemia, coronary heart disease, cerebrovascular disease, hyperlipidemia, peripheral blood vessels, hysterectomy, thyroidectomy, and cholecystectomy.

Collection Criteria of Related Variables

(i). Hypertension was defined as having a systolic blood pressure higher than 140 mmHg or a diastolic blood pressure higher than 90 mmHg (1 mmHg = 0.133 kpa, measured at least three times).

(ii). Dyslipidemia was defined as having total cholesterol (TC) of >5.2 mmol/L or triglyceride (TG) of >1.7 mmol/L.

(iii). Diabetes was defined as having diabetes symptoms + fasting blood glucose of ≥7.0 mmol/L or random blood glucose of ≥11.1 mmol/L, and a 2-h blood glucose of ≥11.1 mmol/L in the oral glucose tolerance test (measured at least two times).

(iv). Smokers were those who smoked at least 100 cigarettes (five packs) in their entire life[13]

(v). Binge drinking was defined as heavy drinking, with a daily alcohol intake of 80 grams or more for over 5 years. Ethanol content (g) = alcohol consumption (mL) × ethanol concentration (%) × 0.8[14].

Statistical Analysis

The SPSS 22.0 software program (IBM, Chicago, USA) was used to conduct the statistical analysis. Continuous variables were expressed as mean ± standard deviation, including history of smoking, alcohol abuse, hypertension, diabetes, coronary heart disease, cerebrovascular disease, peripheral blood vessels, hysterectomy. thyroidectomy, and cholecystectomy. Discontinuous variables were expressed in percentage (%), including age, height, and weight. For two comparisons, each value was compared by *t*-test when each datum conformed to the normal distribution, while non-normally distributed continuous data were compared using non-parametric tests. Counting data were analyzed by χ^2-test. The correlation analysis of cholecystectomy and the occurrence and KOA was performed through univariate and multivariate logistic regression analysis, and the correlation factors of age, gender, body mass index (BMI), hyperlipidemia, smoking history, alcohol abuse history, hypertension, diabetes, cerebrovascular disease, hysterectomy, and thyroidectomy were adjusted. $P < 0.05$ was considered statistically significant.

Results

Patient Characteristics

A total of 1659 patients with KOA (KOA group) and 1195 limb fracture patients (control group) were included in this study. As shown in Table 1, among the 1659 patients with KOA, 388 patients were male and 1271 were female, while among the 1195 patients in the control group, 638 patients were male and 557 patients were female. The period between cholecystectomy and knee OA onset ranged from 0.5 years to 17 years; the average interval time was 8.73 ± 2.11 years. The age at disease onset was significantly older when compared to the control group, while the BMI in the KOA group was significantly higher, when compared to the control group ($P < 0.05$). Furthermore, there was a significant difference in previous medical history (hypertension, diabetes, and cerebrovascular disease) between these two groups ($P < 0.05$). The risk factors (smoking, alcohol abuse, and hyperlipidemia) for KOA were significantly different between the KOA group and the control group ($P < 0.05$). However, there was no significant difference in peripheral vascular disease between these two groups ($P > 0.05$). Furthermore, surgical history (thysterectomy, thyroidectomy, and cholecystectomy) was significantly different between the KOA group and the control group ($P < 0.05$).

Cholecystectomy and Knee Osteoarthritis (KOA)

Univariable Logistic Regression

The univariate regression analysis showed that age (OR: 1.046, $P < 0.001$), gender (OR: 3.752, $P < 0.001$), BMI (OR: 1.191, $P < 0.001$), smoking (OR: 0.258, $P < 0.001$), alcohol abuse (OR: 0.200, $P < 0.001$), hyperlipidemia (OR: 0.002, $P < 0.001$), hypertension (OR: 3.566, $P < 0.001$), diabetes (OR:1.534, $P < 0.001$), cerebrovascular disease (OR: 1.432, $P < 0.001$), hysterectomy (OR: 759982675.2, $P < 0.001$), thyroidectomy (OR: 759982675.2, $P < 0.001$), and cholecystectomy (OR:9.214, $P < 0.001$) were correlated with KOA ($P < 0.05$) (Table 2).

Multiple Logistic Regression

In addition, the relationship between cholecystectomy and the occurrence of KOA was analyzed by logistic multiple regression analysis. In the analysis of the two models (cholecystectomy group and without cholecystectomy group), risk factors, such as age, gender, BMI, smoking, alcohol abuse, hyperlipidemia, hypertension, diabetes, cerebrovascular disease, hysterectomy, and thyroidectomy, were adjusted. The

TABLE 1 Baseline data of patients in the case group and the control group of knee osteoarthritis (KOA)

Project	KOA group (n = 1659)	Control group (n = 1195)	x^2/*t*-values	*P*-values
Age	67.3 ± 7.6	60.8 ± 16.4	−12.650*	<0.001
Male	388 (23.4%)	638 (53.4%)	271.539*	<0.001
Body mass index	26.5 ± 4.1	24.1 ± 3.8	−14.231*	0.002
Smoking	287 (24.0%)	125 (7.5%)	152.774*	<0.001
Alcohol abuse	189 (15.8%)	60 (3.6%)	129.816*	<0.001
Hypertension	828 (49.9%)	261 (21.8%)	231.939*	<0.001
Diabetes	198 (11.9%)	97 (8.1%)	10.924*	0.001
Hyperlipemia	969 (83.1%)	13 (0.8%)	2046.200*	<0.001
Cerebrovascular disease	111 (6.7%)	57 (4.8%)	4.627*	0.031
Peripheral vascular Disease	24 (1.4%)	9 (0.8%)	2.923	0.087
Hysterectomy	87 (5.2%)	5 (0.4%)	64.638*	<0.001
Thyroidectomy	19 (1.1%)	4 (0.3%)	13.778*	<0.001
Cholecystectomy	97 (5.8%)	15 (1.3%)	52.545*	<0.001

* $P < 0.05$ when compared to the control group.

TABLE 2 Univariate regression analysis of the risk of cholecystectomy and knee osteoarthritis

Factors	Univariate regression analysis OR (95% CI)	*P*-values
Gender	3.752 (3.195–4.406)*	<0.001
Age	1.046 (1.039–1.053)*	<0.001
Body mass index	1.191 (1.160–1.222)*	<0.001
Smoking	0.258 (0.206–0.323)*	<0.001
History of alcoholism	0.200 (0.148–0.270)*	<0.001
Hypertension	3.566 (3.015–4.216)*	<0.001
Diabetes	1.534 (1.189–1.980)*	0.001
Hyperlipemia	0.002 (0.001–0.003)*	<0.001
Cerebrovascular disease	1.432 (1.031–1.988)*	0.032
Peripheral vascular disease	1.934 (0.896–4.177)	0.093
Hysterectomy	759982675.2 (0.000 - ∞)*	<0.001
Thyroidectomy	1177129535 (0.000 - ∞)*	<0.001
Cholecystectomy	9.214 (4.463–19.023)*	<0.001

* $P < 0.05$ in the univariate regression analysis of the risk of cholecystectomy and knee osteoarthritis.

analysis results revealed that cholecystectomy was significantly correlated with the occurrence of KOA (0.079 [0.008–0.795], $P = 0.031$, Fig. 1).

Discussion

The outcomes of the present study revealed that among the 1659 patients with KOA, the proportion of cholecystectomy cases in the cholecystectomy group and the control group was statistically significant. Furthermore, there was a statistically significant difference in the distribution between these two groups. The multivariate logistic regression analysis revealed that there was a significant difference in the distribution of these two groups, indicating that cholecystectomy is associated with the occurrence of KOA. Therefore, there is a significant association between cholecystectomy and KOA.

For KOA, which clinically manifests as bone hyperplasia, cystic change or hardening of cartilage and subchondral bone, synovial hyperemia and edema, joint capsule contracture, and relaxation or ligament contracture, the muscle will also gradually present with weakness, and the joint edge and subchondral bone with be non-renewable, as characterized by the chronic inflammation of the joints[15]. The pathogenesis of KOA remains unclear. KOA is affected by age, gender, weight, genetics, living environment, working environment, and other factors[3]. However, degenerative changes of the articular cartilage often occur with aging[16]. In the process of aging, bone density gradually decreases, and the subchondral trabecular bone progressively becomes thinner and harder, resulting in low bone mass, the destruction of bone tissues and bone microstructure, and reduced bone strength, leading to increased risk of OA in osteoporosis patients[17,18].

Carl Langenbuch successfully carried out the first cholecystectomy in 1882[19]. The procedure has since been carried out worldwide. Subsequently, with the continuous progression of LC, and due to its advantages, such as less trauma, less blood loss, and fewer complications[20], the application of cholecystectomy has increased. However, with the rising number of surgical cases, more complications have been reported. In the clinical findings, most patients presented with digestive function turbulence, osteoporosis, and other complications after cholecystectomy. Ekiz *et al.* compared the values of 25-hydroxyvitamin D (25-OH-D) and bone mineral density (BMD) in patients with and without cholecystectomy. It was found that the level of 25-OH-D in the

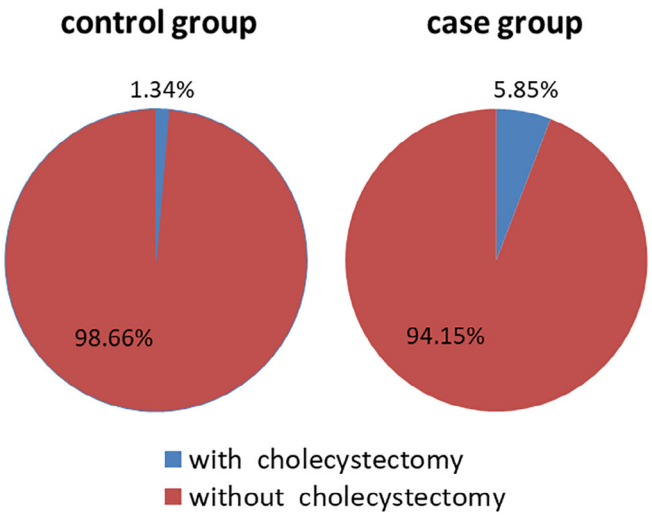

Fig. 1 Relationship between cholecystectomy and knee osteoarthritis. The results revealed that cholecystectomy was significantly correlated with the occurrence of knee osteoarthritis ($P < 0.05$).

cholecystectomy group was significantly lower than that in the control group (12.1 ± 6.2 *vs* 15.6 ± 6.6 ng/mL)[21]. Polat and Beyazal also reported that serum levels of 25-OH-D and bone density were lower in postmenopausal women before cholecystectomy[22].

Osteoporosis is characterized by less bone tissue per unit volume and thinner cortical bones. Osteoporosis can occur in all age groups but is mostly found in elderly men and postmenopausal women. Osteoporosis is diagnosed by low BMD detected by dual energy X-ray absorption assay. Studies have confirmed that OP is not only correlated to diet, living habits, age, and gender, but also closely correlated to cardiovascular disease, hyperlipidemia, and diabetes in the elderly population. However, its exact pathogenesis is not fully understood. Furthermore, the main pathogenesis is the disorder of bone metabolism, which involves genetic factors and very important factors of bone metabolism, such as vitamin D, PTH, phosphate, calcium, sex hormones and cytokines[9]. In addition, the malabsorption of the intestinal tract, changes in hepatointestinal circulation, and decrease in skin synthesis of vitamin D in patients with jaundice all lead to vitamin D deficiency, which, in turn, triggers osteoporosis.

The effect of cholecystectomy on KOA has not been reported. On the above theoretical basis, it can be observed that osteoporosis caused by the vitamin D deficiency described above is an important link between cholecystectomy and KOA. Hence, the absorption of vitamin D after cholecystectomy is affected, leading to osteoporosis. Osteoporosis is an important pathophysiological process of knee arthritis, especially in the elderly and postmenopausal women. In the present study, the age of patients in the KOA group was significantly greater than of patients in the control group. The rate of incidence in females was also significantly increased in the case control. The univariate regression analysis revealed that KOA was the result of multiple factors. Hysterectomy is also an important influencing factor. However, it remains unknown whether this factor and cholecystectomy can synergistically cause KOA. This led the investigators to conduct a large sample and prospective study.

The results of studies that have evaluated the value of LC for KOA are quite positive. This further proves that cholecystectomy is an independent risk factor for the occurrence and progression of KOA.

The present study has several limitations. First, the study design was retrospective in nature, and a relatively small cohort of patients was analyzed with a short follow-up period. Second, because the study population and inclusion criteria differed considerably, the selection of cases did not include patients with early KOA. Hence, this suggests that cholecystectomy has a different impact on disease progression,. Third, there was not enough data covering different time periods, which should be considered in future research.

Conclusion

There is a close relationship between cholecystectomy and KOA. However, the specific mechanism remains unknown and should be further researched.

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