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Hepatitis B Virus Infection Is a Risk Factor for Periprosthetic Joint Infection Among Males After Total Knee Arthroplasty

A Taiwanese Nationwide Population-Based Study

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Abstract: Periprosthetic joint infection (PJI) is a grave complication that can affect patients undergoing total knee arthroplasty (TKA). In this study, we aim to determine whether hepatitis B virus (HBV) infection is a risk factor for PJIs.

All patients (1184 males, 3435 females) undergoing primary TKA in Taiwan from 2001 to 2010 were recruited for analysis.

The incidence of PJI was 523 among the males with HBV infection and 110 among the males without HBV (per 10,000 person-years, $P < 0.001$). The males with HBV infection had a 4.32-fold risk of PJI compared with the males without HBV. HBV infection and diabetes were the risk factors for PJI among males. The incidence of PJI was 58.8 among the females with HBV infection and 75.2 among the females without HBV (per 10,000 person-years, $P = 0.67$). The risk of PJI was higher for the males with HBV infection than for the males without 0.5 to 1 year after TKA (hazard ratio [HR] = 18.7, 95% confidence interval (CI) = 1.90–184) and >1 year after TKA (HR = 4.80, 95% CI = 1.57–14.7).

HBV infection is a risk factor for PJI after TKA among males.

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Abbreviations: CI = confidence interval, CKD = chronic kidney disease, DM = diabetes mellitus, HBV = hepatitis B virus, HCV = hepatitis C virus, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, 9th revision, Clinical Modification, LHID = Longitudinal Health Insurance Database, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institute, PJI = periprosthetic joint infection, TKA = total knee arthroplasty.

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INTRODUCTION

Total knee arthroplasty (TKA) is a well-established modality with a high satisfaction rate for treating various knee disorders.[1,2] Despite the undisputed general success of this procedure, periprosthetic joint infection (PJI) is a grave complication that can affect patients undergoing TKA. In addition to its major adverse effects on the quality of life, PJI can also result in a higher incidence of mortality. Thus, it is crucial to recognize the predisposing factors for PJI and possible precautions that may be taken.[3]

Liver cirrhosis has been associated with a higher complication rate after TKA. Among cirrhotic patients, hepatitis B virus (HBV) infection is an independent predictor of PJI.[4] However, the correlation between HBV infection and PJI is not clear at present. Unless associated with cirrhosis, HBV has not been recognized as a risk factor for PJI.

In our study, we aimed to investigate whether HBV infection itself is a risk factor for PJI.

METHODS

Data Source

The Taiwanese government reorganized the 13 previous social health insurance institutions and created a general health insurance project, the Taiwan National Health Insurance program (Taiwan NHI), which has covered almost all Taiwanese citizens since 1995. The National Health Research Institute (NHRI) utilized all of the claims data from the Taiwan NHI to establish a nationwide population-based database called the National Health Insurance Research Database (NHIRD).

In our study, we constructed the study cohort using the Longitudinal Health Insurance Database (LHID), which is a subset of the NHIRD. The LHID comprises the registry data for beneficiaries, inpatient and outpatient files, the registry for drug prescriptions, and other medical services. The medical illness histories of the subjects of interest were collected from inpatient and outpatient files. The *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) system is used as the disease-coding system in NHIRD. The NHRI removed the original identification numbers to safeguard the privacy of all individuals and provided a scrambled and anonymous identification number to link the claim data to each insured citizen before releasing the data for researchers. This study was approved by the Institutional Review Board of China Medical University in central Taiwan (CMUH104-REC2–115).

TABLE 1. Demographic Data of the Study Cohort

	Female			Male		
	HBV (−)	HBV (+)		HBV (−)	HBV (+)	
Variable	N = 3354	N = 81	*P*	N = 1141	N = 43	*P*
Age, y	69.6 ± 7.6	67.7 ± 7.8	0.03	71.7 ± 8.1	68.3 (8.6)	0.01
Morbidities						
DM	836 (24.9%)	21 (25.9%)	0.84	280 (24.5%)	11 (25.6%)	0.88
Cirrhosis	65 (1.9%)	8 (9.9%)	<0.001	26 (2.3%)	9 (20.9%)	<0.001
CKD	132 (3.9%)	3 (3.7%)	0.92	72 (6.3%)	4 (9.3%)	0.43
HCV	95 (2.8%)	17 (21.0%)	<0.001	26 (2.3%)	5 (11.6%)	<0.001

*t test for comparisons between subjects with and without hepatitis virus B infection. CKD = chronic kidney disease, DM = diabetes mellitus, HBV = hepatitis B virus infection, HCV = hepatitis C virus infection.

Study Population

This study aimed to elucidate the effect of HBV infection on the risk of PJI among patients undergoing TKAs. We performed a retrospective population-based study by establishing a TKA cohort that included all patients undergoing primary TKAs from 2001 to 2010. We identified individuals who had HBV infection before the primary TKA using the *ICD-9-CM* codes V02.61, 070.20, 070.22, 070.30, and 070.32. All of the recruited subjects were followed from the date of operation to the onset of PJI (*ICD-9*: 996.6), withdrawal from insurance, or December 31, 2011. Most orthopedic surgeons in Taiwan used the criteria defined by Tsukayama et al[5] for the diagnosis and treatment of PJI after TKA from 2001 to 2010. PJI was diagnosed when multiple intraoperative cultures showed growth of the same organism, when there was clinically apparent pus in the knee joint, or both.

The medical comorbidities analyzed included diabetes mellitus (DM, *ICD-9-CM* 250), chronic kidney disease (CKD, *ICD-9-CM* 585), liver cirrhosis (*ICD-9-CM* 571), and hepatitis C virus infection (HCV, *ICD-9-CM* V02.62, 070.41, 070.44, 070.51, and 070.54).

Statistical Analysis

Because of the significant interaction between sex and HBV infection status (P for interaction = 0.02), we examined all results without merging the 2 sexe together.

We describe the study cohorts using means ± standard deviations for continuous variables (age, time interval) and number and percentage for sex and comorbidities. We assessed the significance of between-group differences using Student t test for continuous variables and the χ^2 test for categorical variables.

The incidence density of PJI for each study population was calculated by dividing the total number of PJI events by the sum of follow-up years (per 10,000 person-years). The PJI cumulative incidence curve was constructed using the Kaplan-Meier method, and the log-rank test was used to assess the significance of the difference between the curves. The comparisons of PJI risks between different populations were described as hazard ratios (HRs) and 95% confidence intervals (CIs) using single-variable and multivariable Cox proportional hazard models.

All the statistical analyses were performed with the SAS 9.4 software (SAS Institute, Cary, NC), and the cumulative incidence curve was drawn with the R software (R Foundation for Statistical Computing, Vienna, Austria). All tests were 2-sided, and a P value of <0.05 was considered statistically significant.

C-CL, a professional epidemiologist who is included in our author list, performed all the statistical analyses.

RESULTS

Between January 2001 and December 2012, 1184 males and 3435 females underwent primary TKAs (Table 1). The individuals with HBV infection were younger than those without HBV among both sexes ($P = 0.03$ for males, $P = 0.01$ for females). Both the male and female patients with HBV infection were more likely to have liver cirrhosis and HCV infection than those without HBV infection (all of the pertinent P values <0.05).

The incidence of PJI was 523 among the males with HBV infection and 110 among the males without HBV (per 10,000 person-years; Table 2). The cumulative incidence curves showed that the males with HBV infection had a higher risk of PJIs than the males without HBV ($P < 0.001$; Figure 1). After adjustment for age and all comorbidities, the males with HBV infection had a 4.32-fold risk of PJI compared with the males without HBV (HR = 4.32, 95% CI: 1.85–10.09).

The incidence of PJI was 58.8 among the females with HBV infection and 75.2 among the females without HBV (per 10,000 person-years; (Table 2). The difference in PJI incidence by HBV infection status was not apparent among the female patients who underwent TKAs ($P = 0.67$; Figure 2).

Among the male patients, HBV infection (OR = 4.32, 95% CI: 1.85–10.09) and DM (OR = 2.21, 95% CI: 1.34–3.64) were associated with a higher risk of PJI. However, there was no identifiable risk factor for PJI among the females. It is worth noting that the presence or absence of cirrhosis and HCV infection did not influence the incidence of PJI among either sex (Table 2).

The incidences of PJI within 28 days after primary TKA were not significantly different between subjects with and without HBV infection among both sexes. The risk of PJI was higher among the males with HBV infection than among the males without HBV 0.5–1 year after TKA (HR = 18.7, 95% CI = 1.90–184) and >1 year after TKA (HR = 4.80, 95% CI = 1.57–14.7; Table 3).

DISCUSSION

In our study, we showed that HBV infection and DM were risk factors for PJI among males undergoing TKA. There were no identifiable risk factors for PJI among female patients. Both cirrhosis and HCV infection were not identified as risk factors for PJI among both sex groups in our model. Compared with the

TABLE 2. The Incidence of Periprosthetic Joint Infection and the Multivariate Cox Proportional Hazards Regression Analysis

	Female				Male			
Variable	**Event**	**PYs**	**Rate**	**HR**	**Event**	**PYs**	**Rate**	**HR**
HBV								
No	123	16,356	75.2	Ref	58	5292	110	Ref
Yes	2	340	58.8	0.68 (0.17–2.81)	7	134	523	4.32 (1.85–10.09)
Age, y								
<65	37	4631	79.9	Ref	13	1258	103	Ref
65–74	59	8520	69.3	0.85 (0.56–1.28)	32	2421	132	1.32 (0.68–2.57)
≥75	29	3546	81.8	0.95 (0.58–1.55)	20	1747	114	1.06 (0.51–2.17)
DM								
No	87	12,737	68.3	Ref	39	4240	92.0	Ref
Yes	38	3959	96.0	1.35 (0.92–1.98)	26	1186	219	2.21 (1.34–3.64)
Cirrhosis								
No	121	16,378	73.9	Ref	62	5272	116	Ref
Yes	4	318	126	1.50 (0.53–4.25)	3	154	195	1.07 (0.32–3.61)
CKD								
No	117	16,110	72.6	Ref	59	5137	115	Ref
Yes	8	586	136	1.70 (0.83–3.49)	6	289	207	1.44 (0.62–3.38)
HCV								
No	120	16,220	74.0	Ref	63	5310	119	Ref
Yes	5	476	105	1.24 (0.49–3.19)	2	116	172	1.06 (0.25–4.45)

Model adjusted for age, DM, liver cirrhosis, CKD, and HCV. CKD = chronic kidney disease, DM = diabetes mellitus, HBV = hepatitis B virus infection, HCV = hepatitis C virus, HR = hazard ratio (95% confidence interval between the parentheses), PYs = person-years, Rate = incidence rate, per 10,000 person-years

males without HBV infection, the males with HBV infection had an 18.7-times higher risk of PJI 0.5∼1 year after TKA and a 4.80-times greater risk >1 year after TKA. These results have not been reported previously.

The literature regarding HBV infection and total joint surgery is scarce. Shih et al reported 51 cirrhotic patients undergoing 60 TKAs and matched these patients with subjects without cirrhosis for comparison. The authors reported that TKAs were associated with more blood loss, longer hospital stay, more complications, and higher mortality rate among cirrhotic patients compared with controls. Hepatic decompensation and variceal bleeding were independent predictors of complications. Infection was the most prevalent complication, with a prevalence rate of 21%, and age, thrombocytopenia, and HBV infection were the predictors.[4] In this study, HBV infection was highlighted as the risk factor for infection among cirrhotic patients undergoing TKAs. In our study, we demonstrated that HBV itself is a risk factor for PJI. The impact of cirrhosis on the incidence of PJI was not apparent in our model. The relatively small number of cirrhotic patients undergoing TKA surgeries in our study may have limited our ability to perform a pertinent analysis.

The system proposed by Tsukayama et al[6] is widely used to classify PJIs. A type I infection describes a patient with at least 1 set of positive intraoperative cultures and requires the use of intravenous antibiotics only. A type II infection is an early infection within 4 weeks after surgery. Treatment comprises irrigation and debridement, and retention of the prosthesis is possible in this scenario. A type III infection is a late (>4 weeks after TKA) acute hematogenous infection with a symptom duration of <4 weeks. Irrigation and debridement may be tried, but prosthesis removal and 2-stage exchange arthroplasty may be necessary. A type IV infection is a late (>4 weeks after TKA), chronic infection with symptoms persisting for >4 weeks. Prosthesis removal with possible 2-stage exchange arthroplasty is mandatory for eradication.

Using the Tsukayama classification, we showed that males with HBV infection have a significantly higher risk of PJIs than males without HBV 6∼12 months and 12 months after primary TKAs. This finding indicates that males with HBV infection have a higher risk of Tsukayama type III and IV PJIs than males without HBV. It is prudent to suggest that if a PJI develops in a male with HBV infection, debridement and prosthesis retention is often unreliable, and strenuous exchange arthroplasties may be unavoidable.

The mechanisms of higher risk for chronic PJI among males with HBV infection are not clear at present. We propose that HBV may release some unknown factors that can facilitate and sustain biofilm assembly, which is a critical component of chronic PJI. We hypothesize that the different sex hormone profiles of males and females may have different effects on HBV-associated biofilm properties. Our hypothesis is not without grounds. Estradiol has been reported to regulate the planktonic growth, coaggregation, polysaccharide production, and biofilm formation of the *Prevotella* group of bacteria.[7] Human follicular fluid, which is rich in estradiol and progesterone, has been reported to foster the biofilm of several bacterial species, including *Lactobacillus*, *Propionibacterium*, and *Streptococcus* group microbes.[8] The effects of sex hormones on the pathogenesis of PJIs merit further investigation.

There are limitations to our study. First, we cannot exclude the possibility that the patients became infected with HBV after their TKAs. However, adults without compromised immunity

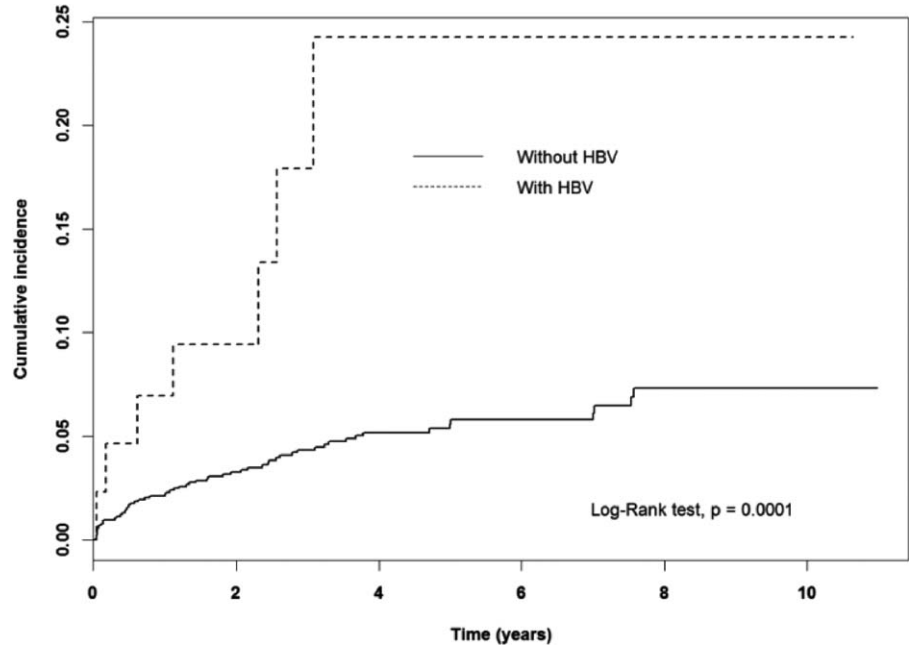

FIGURE 1. The incidence of periprosthetic joint infections (PJIs) among male patients. The dashed line indicates the population of subjects with hepatitis B virus (HBV) infection, and the solid line indicates the population of individuals without HBV infection. The log-rank test was used to assess the significance of the difference between the curves.

rarely become carriers after HBV exposure, and dedicated screening in Taiwan reduces the risk of transfusion-related HBV exposure. Second, we could not identify the duration of HBV infection among the HBV carriers in our model. The duration of HBV exposure may have dose-dependent effects on the risk of PJI. Third, the limited number of cirrhotic patients in our cohort may have underpowered pertinent statistical analyses.

In summary, ours is the first nationwide study to investigate the correlation between HBV infection and PJI after TKA surgery. We showed that males with HBV infection have a higher risk of developing chronic PJIs that necessitate strenuous

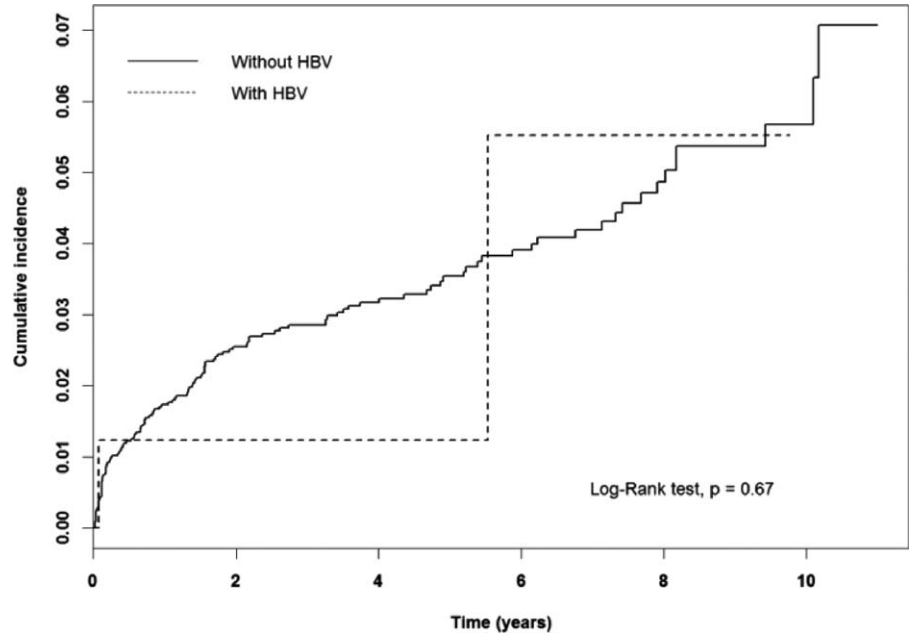

FIGURE 2. The incidences of periprosthetic joint infections (PJIs) among female patients. The dashed line indicates the population of subjects with hepatitis B virus (HBV) infection, and the solid line indicates the population of individuals without HBV infection. The log-rank test was used to assess the significance of the difference between the curves.

TABLE 3. The Incidence of Periprosthetic Joint Infection and the Multivariate Cox Proportional Hazard Regression Analysis According to the Status of HBV infection, sex, and follow-up duration

	Female					Male				
	HBV (−)		HBV (+)			HBV (−)		HBV (+)		
Duration	case	rate	case	Rate	HR	case	rate	case	rate	HR
<1 mo	13	468	1	1488	2.27 (0.27–19.42)	8	848	1	2829	4.20 (0.50–35.4)
1–6 mo	28	203	0	0	—	11	236	1	581	1.64 (0.19–14.2)
0.5–1 y	17	104	0	0	—	5	91.3	1	504	18.7 (1.90–184)
>1 y	65	49.8	1	38.4	0.66 (0.09–4.90)	34	81.3	4	429	4.80 (1.57–14.7)

Model adjusted for age, DM, liver cirrhosis, CKD, and HCV. CKD = chronic kidney disease, DM = diabetes mellitus, HBV = hepatitis B virus infection, HCV = hepatitis C virus infection, HR = hazard ratio (95% confidence interval between the parentheses), PYs = person-years, Rate- = incidence rate per 10000 person-years.

exchange arthroplasties after TKAs compared with males without HBV infection. The risk of PJI should be discussed with male HBV carriers before TKA surgeries.

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