

Universal haemoglobin A1c screening reveals high prevalence of dysglycaemia in patients undergoing total knee arthroplasty

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ABSTRACT

Introduction: Diabetes mellitus is an established modifiable risk factor for periprosthetic joint infection (PJI). Haemoglobin A1c (HbA1c) is a glycaemic marker that correlates with diabetic complications and PJI. As diabetes and prediabetes are frequently asymptomatic, and there is increasing evidence to suggest a correlation between dysglycaemia and osteoarthritis, it is reasonable to provide HbA1c screening before total knee arthroplasty (TKA). The aim of the present study was to determine the prevalence of dysglycaemia in patients who underwent TKA and investigate whether HbA1c screening and optimisation of glycaemic control before TKA affects the incidence of PJI after TKA.

Methods: Patients who underwent primary TKA before and after routine HbA1c screening was introduced in our unit were reviewed. Prediabetes and diabetes were defined according to the American Diabetes Association. Patients with HbA1c $\geq 7.5\%$ were referred to an endocrinologist for optimisation of glycaemic control before TKA. The incidence PJI, defined according to the Musculoskeletal Infection Society criteria, was recorded.

Results: A total of 729 patients (934 knees) had HbA1c screening before TKA. Of them, 17 (2.3%) and 184 (25.2%) patients had known prediabetes and diabetes, respectively, and 265 (36.4%) and

12 (1.6%) had undiagnosed prediabetes and diabetes, respectively. The incidence of PJI was significantly lower in all patients who received HbA1c screening compared with those who did not (0.2% vs 1.02%, $P=0.027$).

Conclusion: Screening for HbA1c before TKA provides a cost-effective opportunity to identify undiagnosed dysglycaemia. Patients identified as having dysglycaemia receive modified treatment, significantly reducing the rate of PJI when compared with historical controls.

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New knowledge added by this study

- There is a high prevalence of undiagnosed diabetes and prediabetes in patients undergoing total knee arthroplasty (TKA) in Hong Kong.
- Universal haemoglobin A1c (HbA1c) screening before TKA can identify patients with undiagnosed dysglycaemia.

Implications for clinical practice or policy

- HbA1c screening should be considered for all patients before TKA.

Introduction

Worldwide, the prevalence of diabetes mellitus and the number of total knee arthroplasty (TKA) surgeries performed is increasing; therefore, the number of patients with dysglycaemia undergoing TKA is expected to rise.¹⁻³ The proportion of patients undergoing TKA who have diabetes mellitus was reported to be 20.6% in the US in 2018.⁴ Diabetes

mellitus is associated with various adverse outcomes after total joint arthroplasty, including periprosthetic joint infection (PJI).⁵⁻¹⁰ Although the occurrence of PJI is rare, it is a devastating complication after total joint arthroplasty, resulting in significant morbidity and even mortality. The economic burden to manage PJI after total joint arthroplasty is projected to be over US\$1.62 million by 2020.¹¹ Despite advances in

total joint arthroplasty, the risk of PJI remains and likely cannot be eliminated. Therefore, enhancing preoperative screening and optimisation of various risk factors for PJI is of the utmost importance.

Glycated haemoglobin A1c (HbA1c) is a readily accessible glycaemic control marker and, according to the American Diabetes Association, HbA1c is also a predictor for diabetes-related complications.¹² Previous studies have found that preoperative HbA1c >7.5% or 8% is associated with an increased risk of PJI and wound complications after TKA.¹³⁻¹⁵ Therefore, optimising HbA1c levels to below these suggested thresholds might be a feasible strategy to reduce PJI. Moreover, patients with prediabetes and diabetes are frequently asymptomatic in the early stages and up to 50% of patients present with complications at the time of diagnosis.¹⁶ Diabetes mellitus is also associated with the development of osteoarthritis.^{17,18} Preoperative assessment for TKA provides an ideal opportunity for diabetes screening.

In our centre, we introduced universal HbA1c screening 2 to 3 months before surgery for all patients undergoing TKA, regardless of their diabetic status, in March 2017. Patients with HbA1c level $\geq 7.5\%$ are referred to an endocrinologist for optimisation of glycaemic control before proceeding to TKA surgery.

The aim of the present study was to determine the prevalence of prediabetes and diabetes in patients who underwent TKA and investigate whether the introduction of universal HbA1c screening and optimisation of glycaemic control affected the rate of PJI after TKA.

Methods

All patients who underwent primary TKA at Queen Mary Hospital, Hong Kong, from December 2014 to May 2019 were reviewed. Patients were diagnosed as prediabetes or diabetes according to the American Diabetes Association definitions, wherein a HbA1c level of 5.7% to 6.4% is defined as prediabetes, and a HbA1c level $\geq 6.5\%$ is defined as diabetes.¹⁰ Patients were classified as undiagnosed prediabetes or diabetes if there was no previous diagnosis or diabetic status in the patient's medical record. Patients with HbA1c level $\geq 7.5\%$ were referred to an endocrinologist for optimisation of glycaemic control before proceeding to TKA.

Patients who underwent primary TKA from December 2014 to February 2017 did not receive universal HbA1c screening. These patients were included in the study as historical controls, to compare the PJI rate with patients who received HbA1c screening before undergoing TKA from March 2017 to May 2019. These 27-month periods immediately prior to and after the initiation of HbA1c screening were chosen to match as closely as possible the duration, comparable indications,

血紅蛋白A1c篩查顯示全膝關節置換術患者的血糖異常高發

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引言：糖尿病是關節假體周圍感染（PJI）的既定可改變危險因子。血紅蛋白A1c是與糖尿病併發症和PJI相關的血糖標記。由於糖尿病和糖尿病前期通常無症狀，並且越來越多證據表明血糖異常與骨關節炎相關，因此在全膝關節置換術（TKA）前進行血紅蛋白A1c篩查是合理的。本研究旨在確定接受TKA的患者的血糖異常現患率，並檢視TKA前接受血紅蛋白A1c篩查和優化血糖控制是否影響TKA後的PJI現患率。

方法：對在本院進行常規血紅蛋白A1c篩查前後接受原發性TKA的患者進行回顧，並根據美國糖尿病協會界定糖尿病前期和糖尿病。在接受TKA前將血紅蛋白A1c $\geq 7.5\%$ 或以上患者轉介至內分泌專科優化血糖控制。根據美國肌肉骨骼感染學會標準記錄PJI現患率。

結果：729名患者（膝934例）在TKA前接受血紅蛋白A1c篩查，17名（2.3%）和184名（25.2%）患者分別患有糖尿病前期和糖尿病，265名（36.4%）和12名（1.6%）患者未被診斷為糖尿病前期和糖尿病。與未接受血紅蛋白A1c篩查的患者相比，接受血紅蛋白A1c篩查患者的PJI現患率均顯著較低（0.2%比1.02%， $P=0.027$ ）。

結論：在TKA前進行血紅蛋白A1c篩查是經濟且有效鑑定未診斷血糖異常的方法。與歷史對照組相比，被確定患有血糖異常的患者接受改良治療可顯著降低PJI現患率。

perioperative management, surgical technique, and wound care protocol for better comparisons.

All patients received one dose of prophylactic antibiotic on the induction of anaesthesia and no further doses of antibiotics postoperatively. All PJIs were defined according to the Workgroup of the Musculoskeletal Infection Society diagnostic criteria.¹⁹

The primary outcome of this study was the prevalence of undiagnosed prediabetes and diabetes in patients undergoing TKA, identified by universal HbA1c screening. The secondary outcome was the difference in the PJI rate between patients undergoing TKA who received HbA1c screening and historical control patients undergoing TKA who did not receive HbA1c screening.

Fisher's exact test was used for statistical analysis of categorical variables, and Student's *t* test was used for continuous variables. We used SPSS (Windows version 26.0; IBM Corp, Armonk [NY], US) for all analyses. A *P* value <0.05 was considered statistically significant.

Results

A total of 1566 patients (2017 knees) who underwent primary TKA were included for analysis. Of them,

TABLE 1. Demographics of patients who received HbA1c screening and optimisation of glycaemic control before undergoing TKA, and patients who underwent TKA without screening*

	TKA after HbA1c screening and optimisation of glycaemic control (n=729)	TKA without HbA1c screening (n=837)	P value
No. of knees†	934	1083	
Age (years)	68 ± 12 (23-91)	69 ± 8 (42-93)	0.45
Male sex	178 (24%)	218 (26%)	0.66
Known diabetes	184 (25%)	226 (27%)	0.52
Body mass index (kg/m ²)	28.4 ± 4.7 (17.2-45.6)	27.1 ± 4.5 (17.0-44.0)	0.0001
Diagnosis for TKA	(n=934)	(n=1083)	
Primary osteoarthritis	887 (95%)	1050 (97%)	0.81
Rheumatoid arthritis	22 (2.3%)	19 (1.7%)	0.38
Other diagnosis	25 (2.7%)	14 (1.3%)	0.08

Abbreviations: HbA1c = haemoglobin A1c; TKA = total knee arthroplasty

* Data are shown as mean ± standard deviation (range) or No. (%), unless otherwise specified

† Some patients underwent TKA of both knees

729 patients (934 knees) received HbA1c screening before TKA surgery and 837 patients (1083 knees) did not. The baseline demographics for both groups of patients, including age, sex, body mass index (BMI), the prevalence of known diabetes and diagnosis for TKA are shown in Table 1. The BMI of patients who received HbA1c screening was significantly higher than that of patients who did not (28.4±4.7 vs 27.1±4.5, P=0.0001). Other baseline characteristics were not significantly different between the two groups.

Of the patients who received HbA1c screening, 17 (2.3%) patients were referred to an endocrinologist for optimisation of glycaemic control before TKA and all 17 were seen within 4 months. All 17 of these patients had TKA performed 3 to 18 months after HbA1c level was controlled to <7.5%.

Concerning the results for universal HbA1c screening, the overall prevalence of diabetes and prediabetes was 26.9% and 38.7%, respectively. Patients with a known diagnosis of diabetes and prediabetes consisted of 25.2% and 2.3%, respectively, while undiagnosed diabetes and prediabetes consisted of 1.6% and 36.4% as shown in Table 2. Therefore, a total of 38% of patients scheduled for primary TKA have undiagnosed dysglycaemia that were only detected with HbA1c screening. Mean (±standard deviation) HbA1c levels for patients with undiagnosed diabetes, undiagnosed prediabetes, known diabetes, known prediabetes, and those without diabetes were 6.7%±0.15 (range, 6.5-7%), 5.9%±0.20 (range, 5.7-6.4%), 6.6%±0.62 (range, 4.6-8.6%), 6.1%±0.45 (range, 5.4-6.4%), and 5.4%±0.19 (range, 4.8-5.6%), respectively, as shown in Table 2.

The PJI rate for patients who received HbA1c screening before undergoing TKA was significantly

TABLE 2. Prevalence of diabetes status and HbA1c% of patients who had universal HbA1c screening before total knee arthroplasty (n=729)

Diabetes status	Prevalence, No. of patients (%)	HbA1c%, mean ± SD (range)
Diabetes	196 (26.9%)	
Known	184 (25.2%)	6.6 ± 0.62 (4.6-8.6)
Undiagnosed	12 (1.6%)	6.7 ± 0.15 (6.5-7.0)
Prediabetes	282 (38.7%)	
Known	17 (2.3%)	6.1 ± 0.45 (5.4-6.4)
Undiagnosed	265 (36.4%)	5.9 ± 0.20 (5.7-6.4)
Non-diabetes	251 (34.4%)	5.4 ± 0.19 (4.8-5.6)

Abbreviations: HbA1c = haemoglobin A1c; SD = standard deviation

lower than that for the historical control group (0.2% vs 1.0%; P=0.027) [Table 3]. Further comparisons found that the PJI rate for patients with dysglycaemia was not significantly higher than that for patients without dysglycaemia in the HbA1c screening group (0.33% vs 0%; P>0.05). The rate of PJI was not significantly different between patients with and without diabetes in the historical control group (1.03% vs 1.02%; P>0.05).

Discussion

The main finding of the present study is that a substantial proportion (38.0%) of patients undergoing primary TKA had undiagnosed prediabetes or diabetes. This finding is consistent with an earlier study in the US, which reported 33.6% of patients had undiagnosed dysglycaemia before total hip or knee arthroplasty.²⁰ Universal HbA1c screening allows

TABLE 3. Rate of periprosthetic joint infection in patients who underwent total knee arthroplasty with or without universal HbA1c screening before surgery

	TKA after HbA1c screening and optimisation of glycaemic control (n=934)	TKA without HbA1c screening (n=1083)	P value
Total	0.21% (2/934)	1.02% (11/1083)	0.027
Prediabetes/diabetes	0.33% (2/604)	1.02% (3/294)	
Non-diabetes	0% (0/330)	1.01% (8/789)	
P value (prediabetes/diabetes vs non-diabetes)	0.540	1.000	

Abbreviations: HbA1c = haemoglobin A1c; TKA = total knee arthroplasty

for earlier diagnosis of prediabetes and diabetes and timely intervention. Because diabetes mellitus is an established risk factor for PJI,⁵⁻⁹ identifying patients with prediabetes and diabetes allows better preoperative communication and risk expectation with the patient before surgery. Moreover, initiating medical treatment to optimise blood glucose control may reduce postoperative hyperglycaemia, of clinical significance, which is an independent risk factor for wound complications and PJI.²¹⁻²³

Undiagnosed prediabetes was found in 36.4% of our TKA patients. These patients might have remained undiagnosed for a long period, as most were asymptomatic. Nathan et al²⁴ reviewed the natural history of prediabetes and found that 25% of patients with prediabetes progress to diabetes over the subsequent 3 to 5 years. Therefore, early detection and treatment of prediabetes is important to prevent the development of diabetes and its complications. Early lifestyle changes and medical treatment for prediabetes reduce the chance of progressing to diabetes.^{25,26}

In the present study, the PJI rate for patients who received HbA1c screening before undergoing TKA was significantly lower than that for the historical control group (0.2% vs 1.0%; $P=0.027$). However, only 17 (2.3%) of the screened patients required endocrinologist referral; therefore, the observed reduction in PJI is likely the result of multiple factors. Antibiotic-loaded cement can reduce PJI after total joint arthroplasty^{27,28}; therefore, we routinely use antibiotic-loaded cement for patients with dysglycaemia, who are considered at higher risk of PJI. Further measures are used to prevent postoperative hyperglycaemia in patients with dysglycaemia, such as closer monitoring of glucose level, choice of intravenous fluid, and providing a diabetic diet during their in-patient stay. In addition to screening for dysglycaemia and direct optimisation of glycaemic control, employing a more preventive perioperative care might have contributed to the observed lower rate of PJI in all patients who received HbA1c screening.

Patients with diabetes and prediabetes are

at increased risk of transient hyperglycaemia and increase glycaemic variability.^{29,30} Acute glucose fluctuation increases oxidative stress at the cellular level increasing diabetic microvascular and macrovascular complications.^{29,31,32} Moreover, a recent retrospective review using point-of-care glucose measurement showed that higher postoperative glucose variability after total joint arthroplasty is associated with adverse outcomes, including surgical site infection and PJI.³³ Therefore, identifying patients with prediabetes and diabetes before surgery allows closer postoperative surveillance and glycaemic control, which might improve the patients' clinical outcomes.

Universal HbA1c screening for diabetes among patients undergoing primary TKA fulfils many of the criteria for effective screening set out by Wilson and Jungner³⁴ in 1968, including being an important and prevalent health issue, having an acceptable screening test and treatment, and having a recognised early asymptomatic stage. Quan et al³ reviewed the complete census of public health records in Hong Kong and reported that the overall incidences of diabetes and prediabetes in 2014 were 10.29% and 8.9%, respectively. In the present study, we found that the prevalences of diabetes and prediabetes in Hong Kong patients undergoing TKA were 26.9% and 38.7% respectively, which are much higher than in the general local population. This is explained by the linkage between diabetes and osteoarthritis, together with the relatively older age of patients undergoing TKA.^{17,18} Moreover, the mean BMI in both patient groups is above the cut-off value for obesity in the Hong Kong Chinese population,³⁵ and these patients are therefore considered at high risk for developing type 2 diabetes and cardiovascular disease by the World Health Organization.³⁶ Thus, preoperative assessment for TKA provides an ideal occasion for opportunistic screening for diabetes.

Blood HbA1c level is a useful marker in monitoring glucose control and correlates with diabetic complications.^{12,37} Multiple studies have shown that high preoperative HbA1c is associated with PJI and wound complications after TKA, with

proposed HbA1c thresholds from 7.5% to 8%.¹³⁻¹⁵ Other glycaemic markers, such as preoperative fasting glucose, fructosamine, postoperative hyperglycaemia, and glucose variability, are also associated with an increased risk of adverse clinical outcomes, including PJI.^{21-23,31,38} Future studies are needed to clarify the role of each marker, and the use of continuous glucose monitoring devices can reveal the postoperative glucose profile in patients with and without diabetes mellitus after TKA.

The rate of PJI after total joint arthroplasty is 0.5% to 2%, and PJI remains the leading cause of revision arthroplasty, comprising up to 25% of all TKA failures.³⁹⁻⁴² Preventing PJI will have a substantial impact on clinical outcomes and the economic burden on our healthcare system. The cost of a single HbA1c test in local laboratories ranges from HK\$290 to HK\$480. We found that 38% of patients scheduled for primary TKA had undiagnosed dysglycaemia. Therefore, the cost to identify each case of undiagnosed dysglycaemia would be HK\$870 to HK\$1440, and these patients can receive appropriate and timely treatment. In contrast, treating a single PJI would cost HK\$530 000 to HK\$830 000.⁴³ Using 7.5% as the HbA1c threshold for referral, we found that only 2.3% of the screening population required assessment and optimisation of glycaemic control by an endocrinologist. Hence, our HbA1c screening and optimisation of glycaemic control did not result in excessive use of medical services.

To the best of our knowledge, this is the first study to compare the PJI rate of patients who underwent TKA with or without preoperative universal HbA1c screening. Our findings from a Hong Kong Chinese population add to the body of evidence supporting universal HbA1c screening for patients undergoing TKA. Although few patients in the present study required endocrinologist assessment, identifying undiagnosed dysglycaemia allows early and appropriate intervention. Knowing the diabetic status of patients undergoing TKA also alters the perioperative treatment of these patients, including the use of antibiotic-loaded cement, the choice of intravenous fluid, and postoperative glucose monitoring. Because primary TKA is an elective surgery, the risk factors for adverse outcomes should be thoroughly assessed and optimised, to improve patient safety and maximise the benefit of the surgery.

There are several limitations to this study. This was a retrospective study involving Hong Kong Chinese patients undergoing TKA at a single institution. Genetic and social differences affect the prevalence of diabetes,⁴⁴ and the perioperative care for dysglycaemic patients varies between different institutions; therefore caution is advised when generalising the results to other populations. Other

medical co-morbidities that affect the risk of PJI were not controlled for, such as rheumatological diseases, obesity, malnutrition, preoperative anaemia, history of steroid administration, and malignancy.^{7,45,46} In the present study, diagnosis and identification of PJI was based on analysis of medical records in the public healthcare system. Patients treated elsewhere, such as in the private healthcare sector, were not included in this study. Similarly, patients in the historical control that had dysglycaemia diagnosed and managed by private practitioners would be labelled as non-diabetes. Moreover, diabetes and prediabetes were defined using only HbA1c, and fasting blood glucose and oral glucose tolerance tests were not performed, potentially leading to an underestimation of dysglycaemia. Finally, although all TKA procedures and perioperative care routines were performed consistently by the same surgical team, advances in surgical technique and perioperative patient care may have created bias when historical data are used as controls. Future prospective, comparative studies with larger sample sizes and multivariate analyses are required to clarify the role of universal diabetes screening and optimisation of the risks of PJI after total joint arthroplasty.

Conclusion

Universal HbA1c screening for patients before undergoing TKA provides a valuable opportunity to identify undiagnosed dysglycaemia. Patients identified as having dysglycaemia receive modified treatments, including preoperative optimisation of glycaemic control, resulted in a significantly lower rate of PJI when compared with historical controls.

Author contributions

All authors contributed to the concept of the study, analysis or interpretation of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Declaration

The results of this study were presented in part as a free paper on adult joint reconstruction at the Hong Kong Orthopaedic Association Annual Congress in 2019.

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Ethics approval

This study was approved by the University of Hong Kong/Hospital Authority Hong Kong West Cluster Institutional

Review Board (Ref UW 20-157). The need for informed consent from the patients was waived by Institutional Review Board, owing to the retrospective nature of the study.

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