Risk of revision of a total hip replacement in patients with diabetes mellitus

A POPULATION-BASED FOLLOW UP STUDY

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We have evaluated the extent to which diabetes affects the revision rate following total hip replacement (THR). Through the Danish Hip Arthroplasty Registry we identified all patients undergoing a primary THR (n = 57,575) between 1 January 1996 and 31 December 2005, of whom 3278 had diabetes. The presence of diabetes among these patients was identified through the Danish National Registry of Patients and the Danish National Drug Prescription Database. We estimated the relative risk for revision and the 95% confidence intervals for patients with diabetes compared to those without, adjusting for the confounding factors.

Diabetes is associated with an increased risk of revision due to deep infection (relative risk = 1.45 (95% confidence interval 1.00 to 2.09), particularly in those with type 2 diabetes (relative risk = 1.49 (95% confidence interval 1.02 to 2.18)), those with diabetes for less than five years prior to THR (relative risk = 1.69 (95% confidence interval 1.24 to 2.32)), those with complications due to diabetes (relative risk = 2.11 (95% confidence interval 1.41 to 3.17)), and those with cardiovascular comorbidities prior to surgery (relative risk = 2.35 (95% confidence interval 1.39 to 3.98)).

Patients and surgeons should be aware of the relatively elevated risk of revision due to deep infection following THR in diabetes particularly in those with insufficient control of their glucose level.

Given the ageing population and the continued increase in demand for total hip replacement (THR), the number of these procedures carried out in Denmark is expected to increase by 210% between 2002 and 2020.1 Diabetes mellitus is one of the world’s major public health problems, with a prevalence of 8% in 2007.2 The number of people with diagnosed diabetes is projected to triple by the year 2050.3 As a consequence it is likely that in the future an increasing proportion of patients having a THR will be diabetic.

Because diabetes is associated with a number of micro- and macrovascular complications,4,6 and might have an impact on bone remodelling,7,8 THR in diabetic patients may have serious medical sequelae. Current information on the post-operative complications among diabetic patients with joint replacements is limited. The risk of deep joint infection, and post-operative infection in general, as well as dislocation of a THR, has been reported to be similar or higher in patients with diabetes than in the non-diabetic.9,13 There have been no investigations into the revision rate following arthroplasty, defined as exchange or removal of an implant, in these patients even though deep infection would probably lead to revision. Experimental animal and clinical studies indicate a comparable revision rate of dental implants in diabetic and non-diabetic patients, providing that the metabolic status of diabetic subjects is controlled.7,8

We hypothesised that diabetes is associated with an increased risk for revision after primary THR, particularly when deep infection is involved. We therefore conducted a cohort study in Denmark to evaluate the extent diabetes affects the revision rate due to aseptic loosening, deep infection and dislocation following THR.

Patients and Methods

We used population-based medical databases to identify patients with THRs. The Danish national health system provides free access to tax-supported medical care for all Danish residents, and partially reimburses the costs of most prescription drugs. Since 1968, all Danish citizens have been assigned a unique ten-digit personal identification number at birth, encoding their gender and date of birth. This identifier is part of all Danish electronic medical databases, permitting unambiguous record linkage between them.14
We used the Danish Hip Arthroplasty Registry\textsuperscript{15} to identify all patients who underwent a primary THR surgery in Denmark during between 1 January 1996 and 31 December 2005. All 45 orthopaedic departments in Denmark reported to the registry during this period, using a standardised form.

We used the Danish National Registry of Patients and the Danish National Drug Prescription Database to identify the presence of diabetes among those patients who had undergone THR. Diabetes was considered present if patients were hospitalised with diagnoses of type 1 or type 2 diabetes at least one year before their operation. The national registry of patients has collected data on all hospital admissions since 1977 and, since 1995, on all hospital specialist outpatient visits, including the dates of admission and discharge, and up to 20 discharge diagnoses coded according to the International Classification of Diseases (Eighth edition until the end of 1993, Tenth edition thereafter). The ICD-8 codes for diabetes were 249 and 250, and ICD-10 codes were E10, E11, E14, G63.2, H36.0 and N08.3. In Denmark the proportion of patients identified using ICD codes who are correctly diagnosed with diabetes was previously reported to be 97\% (95\% confidence interval (CI) 89 to 100).\textsuperscript{16,17}

Diabetes was also considered present if patients had received at least one prescription for insulin or an oral antidiabetic drug at least one year before THR. The National Prescription Database, maintained by the Danish Medicine Agency, has kept information on all drugs purchased at pharmacies without a prescription, as well as all prescription drugs dispensed since 1 January 1995, including the type of diabetic drug prescribed according to the Anatomical Therapeutic Chemical classification system\textsuperscript{18} (A10A and A10B) and the prescription fill dates. Hospital dispensaries do not report to the Database.\textsuperscript{19}

Confounding factors. We obtained data from the Danish Hip Registry on age (10 to 49 years, 50 to 59, 60 to 69, 70 to 79 and > 80), gender, primary diagnosis of the hip disorder (primary arthrosis, avascular necrosis, paediatric diseases, rheumatoid arthritis and other hip diseases), hospital type (university hospital and other), fixation technique (cemented, uncemented and hybrid implants), duration of surgery (< 60, 61 to 120, 121 to 180, 181 to 240 and > 240 minutes) and the year of surgery (three periods: 1996 to 1998, 1999 to 2001 and 2002 to 2005).

We considered the prescription of several classes of drug that may be related to the treatment of diabetes as possible confounders if prescribed during the year preceding THR, and also to the revision rate for THR.\textsuperscript{20} These included low-dose or high-dose aspirin (200 mg to 500 mg), non-steroidal anti-inflammatory drugs (NSAIDs), statins, platelet inhibitors, topical and systemic corticosteroids, bisphosphonates and antidepressants. Relevant data were obtained from the drug prescription database.

In order to adjust for confounding by comorbidity, we extracted information on the disease categories used in calculating the Charlson Comorbidity Index score\textsuperscript{21} from the Danish National Registry of Patients. For each THR patient we identified all the diagnoses for primary and secondary discharge for all hospital admissions and outpatient visits from 1 January, 1977 to the date of primary THR. The Charlson Comorbidity Index includes 19 major disease categories.\textsuperscript{22} As not all diagnoses included in this index are necessarily confounding factors in the association between diabetes and risk for revision following primary THR, we defined a new variable to serve as a measure of comorbidity prior to surgery. We classified diabetic and non-diabetic patients according to three levels of comorbidity, defined as: none, where there had been no admissions prior to the time of surgery; cardiovascular comorbidities, including one of the following five major disease categories: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease or renal disease prior to the time of surgery; and other comorbidities, embracing one of the other 12 major disease categories included in the Charlson Comorbidity Index.\textsuperscript{23} Diabetes, which is usually part of this index, was not included in the new comorbidity variable, as it represented the exposure variable in our study. In addition, we extracted information from the Registry of Patients regarding prior hospital diagnoses of obesity, which may be a confounding factor both associated with diabetes and predisposing to revision of a THR.\textsuperscript{24}

In order to adjust for socioeconomic status, we included data on gross income in bandings of < $20 000, $20 000 to $30 000, $30 000 to $50 000 and > $50 000; educational status according to whether the patient had received vocational training/basic school, upper secondary school, one to two years of higher education, three to four years of higher education, more than four years of higher education and other; and civil status: married, widowed, divorced or single; all of which have been available since 1980 from the Integrated Database for Labour Market Research. Socioeconomic status was measured at the beginning of the year of surgery for each patient. In addition, we used the Danish Civil Registration System to identify each patient’s county of residence, which may be associated with the treatment of diabetes and thresholds for willingness to perform/undergo revision surgery for both surgeons and patients. The Danish Civil Registration System, which is a national database of residents, has kept records for the entire Danish population on vital status and residence since 1968.

Outcome. The outcome measure, obtained from the hip registry, was the time to the first revision, which was defined as a new open operation involving partial or total removal or exchange of components after an initial THR. The primary outcome measure was time to any revision, and secondary outcome measures were time to revision due to aseptic loosening, dislocation of the prosthesis and deep infection. Superficial infection or wound infections were not included as outcomes.

Statistical analyses. The period of follow-up for all patients started on the date of primary THR and ended on the date...
of the first revision, death, emigration, or the 31st of December 2005, whichever came first. Information on deaths and emigration was obtained from the Danish Civil Registration System.\textsuperscript{14} We computed revision rates as the number of revisions in THR patients with diabetes divided by the number of person-years at risk within the same group of patients, per 1000 person-years. Similarly, revision rates were calculated for patients with a THR who did not have diabetes, according to the four outcomes of interest. We used Poisson regression analyses to compare the revision rate following primary THR among patients with diabetes with that among patients without. We estimated the rate ratio as a measure of relative risk and 95% CI for patients with diabetes compared to patients without, both crudely and adjusted for potentially confounding factors. The same analyses were repeated for events within two years of surgery as the short-term risk. We performed several sensitivity analyses stratified according to several definitions of diabetic patients (diabetics identified only in the registry of patients, diabetics identified only in the drug prescription database, and those identified in both databases), the duration of diabetes prior to primary THR (< five years, five to ten years and > ten years), the presence of complications due to diabetes involving the eye, kidney, peripheral nerves, myocardial infarction, stroke or peripheral arterial diseases identified in the registry of patients and those without these complications, and according to presence of cardiovascular and non-cardiovascular comorbidities prior to the primary THR.

All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, North Carolina). The study was approved by the National Board of Health and the Danish Data Protection Agency.

**Results**

We identified 57 575 patients with a primary THR from the Hip Registry during the study period. Of these, 3278 (5.7%) had diabetes. Compared to the patients without diabetes, those with diabetes were older, had more comorbid conditions, were more likely to have a lower gross income, be less well educated and to live alone. The use of medication potentially related to revision THR was more frequent among diabetic patients than among non-diabetics.

The prevalence of diabetes among THR patients decreased from 4.3% between 1996 and 1998 to 5.3% between 1999 and 2001, and to 7.2% between 2002 and 2005. Among those with diabetes, 358 (11%) had been diagnosed with type 1 diabetes and 2920 (89%) with type 2. The condition had been present for less than five years in 2051 (62.6%), for five to ten years in 1050 (32.0%), and for more than ten years in 177 (5.4%).

During the maximum period of follow-up of 11 years, 883 (27%) diabetic THR patients were followed for up to two years, 1359 (41.5%) for two to five years, and 1036 (31.6%) for five or more years. Among those patients without diabetes, 10 436 (19.2%) were followed for up to two years, 20 125 (37.1%) for two to five years, and 23 736 (43.7%) for five or more years. During the period of follow-up, 39 (1.2%) THR patients with diabetes and 398 (0.7%) without either died or emigrated.

**Primary outcome.** The overall revision rate for any cause was 12.0 per 1000 person-years among diabetic THR patients, compared to 8.9 per 1000 person-years among those without diabetes, which corresponds to an adjusted relative risk of 1.13 (95% CI 0.96 to 1.33). The corresponding short-term risk estimate for events within two years of surgery was 1.11 (95% CI 0.94 to 1.32). We found no substantial difference in the risk of revision for any cause among THR patients with type 1 diabetes (relative risk = 0.95, 95% CI 0.60 to 1.52) or type 2 diabetes (relative risk = 1.15, 95% CI 0.97 to 1.37) compared to non-diabetic THR patients. If all causes of death or emigration were assumed to be associated with any revision, the resultant worst-case scenario would be that 5.9% (156 plus 39 of 3278) diabetic THR patients and 5.1% (2356 plus 398 of 54 297) THR patients without diabetes sustained any revision. The time to any revision was 2.1 years (median 1.2) for patients with diabetes and 2.8 years (median 1.7) for those without.

**Secondary. Aseptic loosening.** Revision due to aseptic loosening occurred in 1.3% of diabetic patients (revision rate = 3.2 per 1000 person-years) and in 1.5% of those without diabetes (revision rate = 3.1 per 1000 person-years). This corresponded to an adjusted relative risk of revision of 1.02 (95% CI 0.74 to 1.39) for diabetic patients compared to non-diabetic patients. The corresponding short-term risk estimate was 0.97 (95% CI 0.69 to 1.37). The relative risk for revision due to aseptic loosening was similar for type 1 diabetes (relative risk = 1.03, 95% CI 0.47 to 2.28) and type 2 diabetes (relative risk = 1.01, 95% CI 0.72 to 1.42), compared to patients without diabetes.

**Dislocation.** Among diabetic patients with a THR, 1.7% underwent revision because of dislocation of the prosthesis (revision rate = 4.2 per 1000 person-years), compared to 1.5% of non-diabetic patients (revision rate = 3.1 per 1000 person-years), corresponding to an adjusted relative risk of 1.05 (95% CI 0.80 to 1.39). The corresponding short-term risk estimate was 1.09 (95% CI 0.81 to 1.45). The relative risk for revision due to dislocation was 1.09 (95% CI 0.52 to 2.30) and 1.05 (95% CI 0.78 to 1.40) for patients with type 1 diabetes and type 2 diabetes, respectively, compared to non-diabetic patients.

**Deep infection.** Among diabetic patients, 1% had a revision because of deep infection (revision rate = 2.6 per 1000 person-years), compared to 0.7% of the non-diabetic (revision rate = 1.4 per 1000 person-years). This corresponded to an adjusted relative risk of 1.43 (95% CI 1.00 to 2.05). Within two years of surgery, the relative risk for revision due to infection was 1.49 (95% CI 1.02 to 2.19) for diabetic patients compared to the non-diabetic. The relative risk for revision due to deep infection was 1.01 (95% CI 0.33 to
3.12) in patients with type 1 diabetes and 1.49 (95% CI 1.02 to 2.18) in those with type 2 diabetes, compared to non-diabetic patients. If all causes of death or emigration were assumed to be associated with revision due to deep infection, the worst-case scenario would be that 2.2% (34 plus 39 of 3278) of diabetic and 1.4% (367 plus 398 of 54297) of those without diabetes had a revision owing to deep infection. The time to revision owing to deep infection was 1.7 years (median 0.7) for patients with diabetes and 1.8 years (median 1.1 years) for those without.

**Sensitivity analyses. Definition of diabetes.** We found no substantial difference in risk estimates if diabetic patients were identified from the Danish National Registry of Patients or the drug prescription database (corresponding to our primary definition of diabetes), or if the risk estimate was based on cases in which diabetes was present only in the former, only in the latter, or in both.

**Duration of diabetes.** The risk for revision was dependent on the duration of diabetes prior to THR. Patients with diabetes for less than five years prior to THR had an increased risk of revision for any cause, because of dislocation and because of deep infection, compared to non-diabetic patients (adjusted relative risk = 1.19 (95% CI 1.03 to 1.38), 1.26 (95% CI 0.98 to 1.62) and 1.69 (95% CI 1.24 to 2.32), respectively. In contrast, for both primary and secondary outcomes, risk estimates were similar for THR patients who had diabetes for five to ten years and for more than ten years prior to THR, compared to non-diabetic THR patients.

**Presence of complications due to diabetes.** Diabetic patients with complications had an elevated adjusted relative risk for revision due to any cause of 1.36 (95% CI 1.12 to 1.66) compared to the non-diabetic. This seems to be driven by the high risk of revision owing to dislocation and deep infection in diabetic patients with complications, compared to non-diabetic patients (adjusted relative risk = 1.49 (95% CI 1.07 to 2.07) and 2.11 (95% CI 1.41 to 3.17), respectively). Diabetic patients without complications had a risk of adverse outcomes similar to that of the non-diabetic.

**Presence of cardiovascular comorbidities.** Diabetic patients with cardiovascular comorbidities prior to primary surgery had an increased risk for revision due to any cause (adjusted relative risk = 1.46 (95% CI 1.12 to 1.90), with a particularly high risk for revision due to deep infection (adjusted relative risk = 2.35 (95% CI 1.39 to 3.98)), compared to non-diabetic patients.

**Discussion**

In this nationwide population-based cohort study of 57,575 primary patients with THR, including 3278 with diabetes, we found that diabetes was associated with an increased risk for revision due to deep infection.

**Methodological considerations.** Our study’s strengths include its population-based prospective design and complete follow-up. It also has a large study population because of the availability of nationwide population-based medical databases, with documented overall high data validity.17,25 The comprehensive assessment of comorbidity and other confounding factors was based on data collected routinely from administrative registries independently of the objective of our study. Several limitations of the study must be recognised. Orthopaedic surgeons may be less likely to operate on patients with diabetes or those with less well-regulated diabetes for both a primary THR or a revision, thereby introducing the problem of confounding by indication. We cannot exclude the possibility of selection bias in THR and registration between diabetic and non-diabetic patients, which may have influenced our results. However, we performed sensitivity analyses in relation to the different methods of identifying diabetic patients in order to clarify potential selection bias and allow comparison with studies based on different data sources.

The use of medical databases to identify diabetic patients could be associated with coding errors and misclassification. Thus we may have missed some diabetic patients or included some who did not have diabetes, thereby introducing information bias. However, relying on several databases to identify diabetic patients reduced that risk. Although we have no reason to believe that misclassification of the diagnosis of diabetes is related to later rates of revision, the remaining truncation of data may bias our estimates. The magnitude of misclassification of diabetic patients treated only with diet is unknown, but is unlikely to be associated with revision.

Another issue concerns misclassification of revisions. Some may have been registered as a primary THR in the Danish registry, and vice versa; if so, the misclassification of revision is presumably not related to the diabetic status at primary THR. The completeness of registration of revisions in the Hip Registry is about 90%.25 In the light of the prospective registration of data in the Hip Registry, it is unlikely that missing registration of revisions occurred systematically as a function of diabetic status.

Although misclassification of confounding factors, including comorbidity diagnoses included in the Charlson Comorbidity Index, is unlikely to be associated with diabetes, any lack of specificity of routinely recorded data may have reduced our ability to remove confounding completely. Although information on major diagnoses extracted from the Danish National Registry of Patients enabled us to adjust for most comorbidities, and thereby to reduce their confounding effect, we lacked information on their severity. This could have introduced residual confounding and thereby diminished our ability to identify associations.

One of the main disadvantages of studies based on medical databases is the lack of data on potential confounding factors such as lifestyle and body mass index (BMI). We were able to control for obesity, which could partly remove BMI-related confounding, but if the prevalence of a high BMI is related to both diabetes and the probability of undergoing both primary and revision THR,26 our estimates could be biased. For smoking, we used comorbidities.
such as cancer, heart disease and chronic obstructive pulmonary disease as surrogate measures, and thereby controlled for smoking-related confounding, at least in part. Laboratory and microbiological data were not available in our dataset.

Main findings compared to other studies. Our findings support the limited available data on the association between diabetes and the risk of revision following arthroplasty. The increased risk of revision due to deep infection in diabetic patients with a THR agrees with the case-control study of Lai et al.11 of 52 infected and 52 non-infected primary hip or knee arthroplasties. Bolognesi et al.9 observed no association between diabetes and surgical infection or dislocation following THR. However, the definition of infection and dislocation used in the study is unclear. Another study10 including 95,000 patients with shoulder, hip or knee replacements found a higher risk of post-operative complications in diabetic than in non-diabetic patients (odds ratio = 1.06, 95% CI 1.02 to 1.12). Although the study had a large sample size, it only examined one outcome defined very broadly, as post-operative complications including infections, non-healing or disruption of surgical wounds, and vascular complications. It did not look at revision of implants as an outcome, thereby reducing the possibility of comparison with our study. The revision rate due to deep infection in our study agrees with the results of two previous knee studies,12,13 but differs from the 5.5% reported by Yang et al.27 The studies had a small sample size, and it is unclear whether deep infection included only revision or also infections treated non-surgically. Yet it is unclear whether the risk of revision due to deep infection differs between total hip and knee replacements, thereby reducing the possibility of comparison.

The association between diabetes and the risk of common infections is well recognised, because of peripheral sensory neuropathy, impairment of the innate immune system and the polymorphonuclear neutrophils and peripheral arterial disease.28,29 Any form of injury, including surgery in THR, results in insulin resistance and hyperglycaemia. Post-operative hyperglycaemia has previously been linked to an increased risk of surgical site infection in cardiothoracic surgery.30 Notably, our study found that the risk of infection is related to the presence of cardiovascular comorbidities prior to THR, and to the presence of diabetes-related complications, as well as the duration of diabetes of less than five years prior to surgery, which is probably a result of poorly controlled diabetes and levels of glucose. These diseases may be associated with variations in the levels of glucose, owing to initial difficulties in determining adequate doses of medication shortly after diagnosis. Several studies in diabetic cardiothoracic and critically ill patients have observed that improved glucose control in the peri-operative period is associated with a reduction in infections.30-32 The extent of reduction in the rise of infection when diabetic patients have sustained permanent organ damage is unknown.

Our finding of no association between diabetes and the risk of revision due to aseptic loosening supports and extends the limited experimental data available.7,8,33 The results may be explained by the similar osteo-integration process around the implant in both diabetic and non-diabetic patients.

We found that diabetes was not associated with the risk of revision due to aseptic loosening and dislocation in THR patients. Nevertheless, both patients and surgeons should be aware of the relatively elevated risk of revision for deep infection following THR in diabetics, particularly in patients who have had diabetes for less than five years, those with cardiovascular comorbidities prior to surgery, and those with diabetes-related complications, all related to insufficient control of glucose levels. Further research is warranted in order to clarify the mechanisms for the association, focusing on metabolic control of the glucose level prior to surgery, as well as research on the type of infection following surgery.

Supplementary material

Tables showing i) the characteristics of patients with a total hip replacement (THR) with and without diabetes between 1995 and 2005, ii) the risk of revision following THR in patients with diabetes compared to patients without, iii) the risk of revision following THR in patients with diabetes compared to those without, according to the presence of diabetes complications and iv) the risk of revision following THR in patients with diabetes compared to those without, according to the presence of cardiovascular comorbidities prior to surgery, are available with the online version of this article on our website at www.wjbs.org.uk.

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References


