Title:

Diabetes Mellitus and Gender have a Negative Impact on the Outcome of Hip Fracture Surgery – a Pilot Study

Running Title:

Hio Fracture Mortality and Diabetes

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Adam Galbraith performed data collection, database organisation, assisted data analysis, constructed and authored the main manuscript.

Clara Sanz-Nogués executed data analysis and interpretation, created the resultant tables, figures and contributed to the associated narrative, reviewed and edited drafts of the manuscript.

Sharon Glynn contributed to data analysis and interpretation, performed survival analysis, reviewed and edited drafts of the manuscript.

Cynthia Coleman co-conceived the concept of this study, wrote and obtained ethical permission to conduct the investigation, secured collaborations to execute the investigation, contributed to database organisation and data interpretation, reviewed and edited drafts of the manuscript.

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Abstract

Diabetes mellitus (DM) is associated with an elevated risk of post-operative complications. The impact it has on patients living with DM following hip fracture surgery (HFS) is not completely understood, and may represent a predictor of increased mortality. This study investigates the impact of DM, gender, American Society of Anaesthesiologists (ASA) grade and fracture location, on outcome of HFS in Ireland. The Hospital Inpatient Enquiry (HIPE) database records all fragility hip fractures within Galway University Hospital. Retrospective data collection was performed over a three-year period. Data collected included patient age, gender, date of HFS, anatomical fracture location, type of operation, ASA grade, DM status and mortality. A database of 650 individuals was created including 461 females and 189 males, with an average group age of 80.2±9.3 years. Results showed a significantly higher incidence of hip fractures in males with DM (19.57%) than females with DM (12.36%) (χ^2 test, $p = 0.020$). Cox regression survival analysis indicated that DM status and ASA grade were the two main independent predictors of patient survival following HFS. Nevertheless, when examining the combined impact of gender and DM status on survival after HFS, results showed that survival post HFS differed significantly with gender and presence of DM (log-rank test, $p < 0.001$), with males with DM performing worse than females with DM (p=0.021) or males without DM (p=0.001). This gender and disease-associated outcome should prompt early multi-disciplinary team approach to the management of hip fractures in patients with DM.

Keywords:

Hip Fracture Surgery, Diabetes Mellitus, Mortality, ASA grade, Diabetic Osteopathy

Introduction

In line with improvements in global well-being and healthcare delivery, a vast growth in the proportion of the population aged 65 years and over has occurred and is expected to double by 2060 [1]. The 2018 European Ageing Report projects that the old-age dependency ratio will increase significantly from 25% in 2010 to 51.2% in 2070 [2]. In keeping with this growth in the elderly populations, an equivalent increase in the incidence of hip fractures is expected [2, 3]. The absolute number of all fragility fracture admissions increased by 30% between the years of 2002 to 2014 in Europe [2]. In Ireland, the Health Service Executive (HSE) has identified hip fractures as "one of the most serious illness pertaining to long-term hospital admission" [4]. The Irish Hip Fracture Database (IHFD) reported over 3,000 hip fractures annually in a total population of 4.7 million people since it was established nationally in 2015 [5].

A better understanding of factors impacting upon hip fracture surgery (HFS) outcomes is becoming apparent, following the introduction of hip fracture care pathways and collaborative review of national data. The blue book standards outlined by the British Orthopaedic Association (BOA) have been referenced globally [6]. Their adoption in Ireland, in the form of the Irish Hip Fracture Standards (IHFS) has led to a transformation in the delivery of hip fracture care. However, internationally the reported one-year mortality following hip fractures remains persistently high ranging from 8.4% to 34% [7-9]. Hip fracture patients represent a high-risk surgical group, yet the individual influence of any single comorbidity remains unclear [7, 10, 11].

The impact of diabetes mellitus (DM) in HFS is unclear [12-14]. The global prevalence of DM among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014 with the WHO projecting that DM will be the seventh leading cause of death in 2030 [15]. DM has been

reported an independent risk factor for fragility fractures, with research reporting an incidence of hip fracture in DM patients up to 70% higher than patients without DM [16]. DM is associated with higher level of osteoporosis and osteopenia, increased osteoblast apoptosis and osteoclast mediated bone resorption resulting in poorer bone healing and regenerative capacity following injury [17-20]. The impact of DM on HFS rehabilitation and long-term post-operative outcomes remains unclear, as individuals living with DM are reported to be at an increased risk of post-operative complications and mortality following HFS [12, 13], while others studies have reported no significant difference between patients living with and without DM regarding HFS [21].

The aim of this study was to evaluate the impact of DM on HFS outcomes, with particular interest regarding any associations between the presence of DM, gender, anatomical fracture location, type of fixation, American Society of Anaesthesiologists (ASA) grade and early post-operative mortality rates following HFS.

Methodology

This was a Level 3 retrospective cohort study. All patients admitted to Galway University Hospital with fragility hip fractures were recorded in the hospital in-patient enquiry (HIPE) database and included in the study. Data was collected retrospectively from 1st January 2014 to 31st December 2016 in adherence with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines [22]. In line with the criteria utilised by the National Hip Fracture Database and IHFD, all patients over 60 years old with hip fractures (intracapsular, intertrochanteric and subtrochanteric) other than periprosthetic fractures were included, regardless of cause [5]. A total of 650 patients were included in the analysis. Data collected included patient age, gender, DM status, anatomical neck of femur fracture location, date of primary HFS, type of fixation, ASA grade and patient mortality [23]. ASA grade is

recorded by the IHFD as a surrogate marker for co-morbidities. Registry measured endpoints were followed and therefore additional specific patient co-morbidities have not been recorded [5]. Time to surgery was under 48 hours for 75% of the patients, as per the IHFD annual reports [5]. Diabetic status was confirmed by a consultant endocrinologist and cross-referencing with the hospital laboratory system provided identification of patients' HbA1c level.

Participants' mortality was checked up to the 1st November 2017. The electronic patient demographic system (PAS system) was used to identify deceased patients. A patient database linked the computerised PAS system to the HIPE database. HIPE is an Irish national database of coded discharge summaries from acute public hospitals. Ireland has used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) for both diagnosis and procedure coding from 1990 to 2005 and ICD-10-CM thereafter [24]. Following discharge from hospital, the hospital administrators update the PAS data when they are made aware of a patient's death. In addition, an online public database of death notifications (RIP.ie) was utilised to cross-check all notifications. Other countries link inpatient admissions with national births/deaths registries via a unique identifier, allowing for real-time accuracy. Lacking such a system in Ireland, mortality rates are likely underestimated.

Cross-referencing with the hospital radiology system was also performed to confirm the anatomical fracture location and definitive surgical intervention performed. Ethical approval for this study was granted by the Galway University Hospitals Research Ethics Committee (CA1783).

Statistical Analysis

Statistical analyses were performed using the Minitab17 software package for Windows. Survival curves and cox regression analysis was performed using Stata/SE 14 statistical software (Stata Corp) as previously described [25]. All statistical tests were 2-sided, and an association was considered statistically significant with *p*-values less than 0.05. A Student's *t*-test was used to analyse differences in mean age and follow-up time between the DM and non-DM groups. Pearson's Chi Squared (χ^2) analysis was used to determine the association between explanatory variables such as DM status, gender, fracture location, type of operation and ASA grade. Survival was calculated for the period from the date of primary HFS to the date of last completed search for death entries (1st November 2017) for the 650 case patients with hip fracture. The Kaplan-Meier method and the log-rank test were used for univariable survival analysis. Multivariable cox regression survival analysis was used to calculate an adjusted hazard ratio (HR). The following covariates were included in the analysis: age at diagnosis (as a continuous variable), gender (male *vs*. female), DM (yes *vs*. no), fracture location (subtrochanteric vs. intracapsular vs. intertrochanteric), and ASA grade (2 *vs*. 3 *vs*. 4). A statistical test for interaction was performed in Stata to determine the association between gender and DM with survival after primary HFS.

Results

Demographics:

A database of 650 individuals was collated including 461 (70.9%) females and 189 (29.1%) males, with an average patient age of 80.2±9.3 years ranging between 60 and 101 years. Those categorized as living with DM (n=79, n=15 missing data) had an average HbA1c of 52.76±18.97 mmol/mol ranging from 26 to 128 mmol/mol. There were no statistically significant differences among the age of participants living with DM (79.9±8.4 years) and

those living without DM (80.3±9.5 years) (2-sided *t*-test, $p = 0.739$) or male (79.4±9.6 years) vs female (80.6±9.2 years) (2-sided *t*-test, $p=0.137$). When looking at the percentage of females and males with hip fractures that had DM, there were significantly more males with DM (19.57%) than females with DM (12.36%) (χ^2 test; $p=0.020$) (Table 1). DM was not found to affect the anatomical location of neck of femur fractures, with a similar distribution of fracture location among individuals with DM and without DM (χ^2 test; $p=0.864$). Furthermore, the type of fixation did not significantly differ among individuals living with DM and those without DM (χ^2 test; $p=0.434$) (Table 1).

Pearson's χ^2 analysis revealed no association between fracture location and gender: male intracapsular (59.8%), intertrochanteric (31.2%), subtrochanteric (9.0%) compared with female intracapsular (56.6%), intertrochanteric (34.1%), subtrochanteric (9.33%) (χ^2 test; $p=0.750$) (Table 2). We identified an association with increasing ASA grade in patients living with DM (ASA ≥ 3, 72.63%, n = 61) compared with non-DM patients (ASA ≥ 3, n=247) ($p=0.001$) (Table 1). Pearson's χ^2 analysis identified a significant association between ASA grade and gender: male ASA ≥ 3, 65.1%(n=110) compared with females 48.41% (n=198) (Table 2).

Survival Analysis:

The effect of age, gender, DM status, anatomical fracture location and ASA grade on predicting patient survival was examined using the Kaplan-Meier method (Figure S-1) and univariate and multivariable cox regression survival analysis (Table 3). The Kaplan-Meier analysis and univariate cox regression analysis showed that only the presence of DM (log-rank test, $p=0.002$,) and ASA grade (log-rank test, $p=<0.01$) were statistically significant predictors of patient survival, which remained significant in the multivariable cox regression analysis after adjusting for age at diagnosis. Other factors such as gender and fracture

location were not found to be statistically significant. In the multivariable cox regression analysis adjusting for age at diagnosis, gender became significantly associated with patient outcome (p=0.035). Nevertheless, in a combined multivariable cox regression survival analysis only DM status and ASA grade were shown to be good independent predictors of patient outcome.

We then examined the combined impact of gender and DM status on patient outcome after HFS as shown in Figure S-2. These results demonstrate that patient survival differed significantly depending on gender and DM status (log-rank test, p<0.001). Univariate cox regression survival analysis showed no significant differences between males and females without DM (HR 1.09, 95% CI 0.70-1.70, *p=0.706*) or females without DM versus females with DM (HR 1.36, 95% CI 0.75-2.45, p=0.314). Interestingly, there was a significant difference between males without DM versus males with DM (HR 2.72, 95% CI 1.46-5.06, p=0.002), and females with DM versus males with DM (HR 2.32, 95% CI 1.11-4.85, p=0.025), which remained significant in the multivariable cox regression analysis after adjusting for age at diagnosis, and in the combined multivariable cox regression analysis (Table 4). A test for statistical interaction between gender and DM status on patients' survival showed a near significant interaction (p=0.092), corroborating these findings.

Discussion:

Patients with hip fractures represent a high-risk surgical group. However, the individual influence of any single comorbidity remains unclear [7, 10, 11]. Furthermore, Franklin et al, when investigating patient characteristics and pre-operative co-morbidities between European and American patients undergoing elective surgery found significant differences between the two groups with respect to pre-operative characteristics and co-morbidities [26]. Evidence has shown that patients living with DM are at increased risk of sustaining fragility fractures, however the overall impact of DM patients undergoing HFS is unknown [12, 13, 27]. Gulcelik et

al, reported a significant increase in the probability of one year survival following HFS in patients living without DM (87.3%) compared to patients living with DM (68.0%) [14]. Our research is the first to describe the association of DM and mortality following HFS in an Irish population. The demographic represented in this study is similar in characteristics to data published by hip fracture databases nationally and internationally with respect to gender, ASA grade and hip fracture location [5, 28]. We have identified a significant increase in mortality of individuals living with DM undergoing HFS with a particular gender effect on patient's outcome. Furthermore, we have identified an association between hip fracture patients living with DM and higher ASA grade which may be a contributing factor to the increased post-operative mortality observed. This research brings into focus the need for early multi-disciplinary team management in patients requiring HFS and those who are living with co-morbid DM.

DM and overall mortality of patients living with DM following HFS

This study has demonstrated that patients with DM had a significantly greater post-operative mortality following HFS when compared to patients without DM. Two previously published studies have reported that the presence of DM does not negatively impact survival following HFS [12, 13]. Norris et al, reported that patients living with DM had an increased inpatient length of stay and were more likely to develop post-operative complications including pressure sores and cardiovascular issues, however the one-year post-operative mortality between patients living with DM and non-DM patients was not affected [12]. Ekstrom et al have similarly reported that although individuals living with DM may have increased post-operative pain and risk of overall post-operative complications, the presence of DM did not impact upon the long-term rehabilitative capacity of this patient cohort [12, 13, 21]. Although the research presented here has not examined the impact of DM specifically on post-operative

rehabilitation, it does indicate a negative impact of patients living with DM on long-term survival and overall mortality. The increase in overall mortality identified here is likely multifactorial, and may be explicable due to differing ASA grade and overall incidence of DM in our cohort when compared to Norris and Ekstrom [12, 13].

ASA grade and overall mortality of patients living with DM following HFS

The ASA classification first described in 1941 is a highly effective grading system which identifies patient risk of post-operative morbidity and mortality. It forms an integral component of the WHO pre-operative checklist (Haynes, 2009), a check-list that following implementation has shown an overall reduction in post-operative mortality at one year by up to 50% [29]. The ASA classification continues as a widely utilised and effective assessment tool, recently updated by the American Society of Anaesthesiologists in 2014 [30-32]. The ASA classification is a subjective assessment performed by anaesthesiologists in which patients are assigned as grade one to five based upon increasing risk of post-operative morbidity [32]. The system also carries a subclassification "E" which is added to a patients' baseline grade in the event that their surgery is emergency, in the setting of HFS by virtue of their pathology hip fracture patients are immediately assigned to this subclassification. ASA grade is recorded by the IFHD as a surrogate marker for co-morbidities and previous research has indicated its importance in the setting of HFS [5, 33, 34].

As previously discussed, all hip fracture patients represent a high-risk surgical patient cohort in which, up to 70% of patients are classified as ASA grade ≥ 3 [35]. Overall in, this study (n=650), almost 53% of hip fracture patients had ASA grade ≥ 3. Nevertheless, we found that a higher percentage of patients with DM had ASA grade ≥ 3 (72.62%) compared to those without DM (49.79%), which could be explained by the higher presence of co-morbidities in DM patients.

In this investigation, we identified that presence of DM and higher ASA grade were both independent predictors of patient mortality after primary HFS (p=0.025 and p<0.001 respectively). Similarly, Hu et al, conducted a systematic review and meta-analysis assessing the pre-operative predictors of mortality following HFS in which they also identified higher ASA grade and the presence of DM as strong predictors of overall mortality [10].

The use of the validated assessments of patient frailty, such as the Frailty Index (FI), may represent a more encompassing assessment tool for predicting adverse outcomes and mortality following HFS [27, 36]. The FI assesses patient health based on accumulation of disease, including the presence or absence of DM. The incidence of a greater number of patient co-morbidities indicates increased frailty [36]. When assessing patient frailty with respect to fracture risk, Li et al, identified that patients living with DM were significantly frailer than those living without DM, with a significant relationship between the FI and the risk of incident fragility fracture, "a hazard ratio (HR) of 1.02 (95% CI 1.01-1.03) and 1.19 (95% CI 1.10-1.33) for per-0.01 and per-0.10 FI increase, respectively (p=0.018)" [37].

Further research is required to understand this association. In addition, research has shown that increased FI is associated with increased overall mortality[37, 38]. Improved management of DM as a disease entity has the potential to improve both FI and post-operative outcomes for this high-risk group [38].

Gender and overall mortality of patients living with DM following HFS

Several studies have identified an association between male gender and increased mortality following HFS, the aetiology of which is not fully understood [39]. Endo et al, established that overall ASA grade was higher in males and the incidence of post-operatively complications were more common in men [40]. In this study we also found that ASA grade was higher in males (57.4% ASA grade 3 and 7.69% ASA grade 4) than in females (44.99% ASA grade 3

and 2.93% ASA grade 4) (χ^2 test; p=0.001).When we look at the combined impact of gender and DM status on patient outcome after HFS, our results showed that males with DM performed poorer than males without DM (p=0.001) and females with DM (p=0.025). Multiple studies have shown that overall, irrespective of DM status that male patients may have up to a 10% overall increase in one-year mortality following HFS than their female counterparts [41-43]. Multiple factors may be responsible for this difference. Diagnosis of osteoporosis is an important preventative measure which has been shown to reduce the incidence of hip fractures when treated appropriately. It has been suggested that osteoporosis may be underdiagnosed in the male population. Diagnosis of osteoporosis currently relies upon bone mineral density (BMD) based on a non-gender specific reference value. Cawthon et al, argue that specific gender reference values of BMD should be created. As a result, more men would be diagnosed with osteoporosis, despite having an overall higher BMD reference value of their counterpart females [44]. Gregg et al suggest that the presence of DM contributes to a substantial reduction in overall life expectancy of both sexes, but the impact is greater in females [45]. The development of DM-related cardiovascular disease may represent a significant aetiological factor, where the risk is as high as a six-fold increase in females compared with a two to three-fold increase in males [46]. It is postulated that these gender difference may in part be due to physiological differences between males and females and the impact of diabetic nephropathy upon oestrogen regulation [47].

Identifying the aetiological explanation regarding our finding of reduced long-term survival of men living with DM versus their female counterparts following HFS goes beyond the scope of this research and highlights another area in which national databases could extend their data collection profile to include co-morbidities and other previously identified predictors of increased mortality.

Strengths and Limitations

Galway University Hospital has a population census of greater than 300,000 individuals, of which this study cohort included a total of 650 patients, in which there was a higher presence of females with hip fractures (n=461) compared to males (n=189). Nevertheless, this study is representative of a significant percentage of the Irish population improving the application of our findings to the national population.

The principle limitation of this study is its retrospective nature. The study was performed in a single tertiary orthopaedic facility, which may reduce generalisability of the study. However, the clinical protocols followed in this facility are homogenous both nationally and internationally and this dataset is representative of the rest of the nation. In addition, no data was obtained regarding additional comorbidities, modes of treatment or duration of control due to ethical restrictions. It was therefore not possible to delineate whether patients were T1DM or T2DM, but paucity of T1DM cases in this cohort of patients has been reported at 0.12 – 0.18% [48]. In addition, in this study, ASA grade was used as a surrogate marker for co-morbidities, as recorded by the IFHD. There is scope for a prospective study or national hip fracture registry data which should aim to capture all potential confounding factors influencing long-term mortality following HFS such as BMI, cardiovascular disease and lifestyle factors.

The absolute mortality rate is likely to be underestimated. HIPE data has the limitation of recording inpatient mortality only and is not linked with national Cental Statistics Office (CSO) data. Our research utilised publicly available databases to crosscheck and minimise this potential deficiency error, and our mortality trend is consistent with that of a previous research that based upon CSO data [3, 49].

Conclusion

Patents living with DM are at an increased risk of hip fracture [16, 50]. Internationally, improvement measures of hip fracture patients are focused on a myriad of factors including admission time to appropriate orthopaedic units, timely access to surgery and integrated peri- and post-operative multi-disciplinary team input. This study is the first in Ireland to note a deleterious effect of DM and gender on post-operative mortality following HFS and indicates the necessity of an early multi-disciplinary approach for the management of hip fracture patients living with DM. Increased cross specialty awareness is required to appreciate the increased rate of fragility fractures in patients living with DM and the associated increase in post-operative mortality as outlined in this research. Further studies are recommended to consider the systemic physiological impact of DM and gender and its role in the context of the biochemical and biomechanical impact of DM on bone morphology.

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Figure Legends

Figure S-1. Kaplan-Meier survival estimates following primary HFS. A) Kaplan-Meier cumulative survival curves of hip fracture patients by DM status (n = 644). The survival of patients with DM (n = 93) was significantly poorer than the survival of patients without DM (n=551, log-rank test, p=0.002). B) Kaplan-Meier cumulative survival curves of hip fracture patients by gender (n =644). No significant difference in survival was observed between male (n=186) versus female (n =458) hip fracture patients (log-rank test, p=0.089). C) Kaplan-Meier cumulative survival curves of hip fracture patients by fracture location (n=644). No significant difference in survival was observed depending on fracture location (log-rank test, p=0.620). D) Kaplan-Meier cumulative survival curves of hip fracture patients by ASA grade 2, 3 and 4 (n=588). An increase in poor outcome was seen in patients with ASA 2 versus ASA 3 (log-rank test, p<0.001), ASA 3 versus ASA 4 (log-rank test, p=0.001), and ASA 2 versus ASA 4 (log-rank test, p<0.001).

Figure S-2. Impact of gender and diabetes status on patient survival after HFS. Kaplan-Meier cumulative survival curves of hip fracture patients depending on gender and presence of DM (n=644). The survival of patients differed significantly depending on gender and DM status (log-rank test, p<0.001). While there was no significant difference between males and female without DM (p=0.705) or females without DM versus DM (p=0.311), there was a significant difference between males without DM versus DM (p=0.001), and females with DM versus males with DM patients (p=0.021). (Note – within figure M=male; F=female; D=diabetes; ND=no diabetes.)