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Patients with type II diabetes have an increased risk of subsequent fractures beyond imminent risk period: a survival analysis

Los pacientes con diabetes tipo II tienen mayor riesgo de fracturas subsecuentes más allá del periodo de riesgo inminente: un análisis de supervivencia

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Abstract

Introduction: development of subsequent fragility fractures has been linked to previous fractures, age, biological sex and type 2 diabetes mellitus (T2DM). Diabetes may induce osteometabolic disorders that lead to increased fracture risk, relation with subsequent fractures remains unclear. **Objective:** to establish the impact of previous fractures, age, sex, and type 2 diabetes diagnosis on risk of subsequent fractures in patients who had sustained an index hip fracture in time through a survival analysis. **Material and methods:** retrospective, observational and descriptive study. From a database of 670 records of patients aged ≥ 50 years who had sustained an index hip fracture between 2014-2017, with follow-up at least two months. Retrieved information: previous fracture, age, sex, diabetes and subsequent fracture. Statistical analysis: central tendency, dispersion, frequency and percentages, t-Student, χ^2 test, Kaplan-Meyer method, log-rank test, Cox regression model. **Results:** we included 570 patients, mean age 80.09 ± 9.45 years, 79.8% women. Mean follow-up time 24.8 ± 20.8 months. Subsequent fractures on 96 cases, the mean time to subsequent fracture was 25.9 ± 19.5 months; of these 56.2% occurred within two years after incident fracture. No associations were found between previous fracture (p = 0.3), sex (p = 0.265), and diabetes (p = 0.54) for subsequent fractures. Survival analysis only found association for subsequent fractures with diabetes (p = 0.01) and biological sex (p = 0.03). Cox regression analysis model showed an increased risk only for diabetes (HR = 3.8; p = 0.017; 95% CI 1.275-11.484). **Conclusion:** patients with type 2 diabetes had an increased risk of developing subsequent fractures in time. Men patients develop subsequent fractures earlier.

Resumen

Introducción: *las segundas fracturas por fragilidad han sido vinculadas a fracturas previas, edad, sexo y diabetes. La diabetes puede inducir alteraciones osteometabólicas que incrementan el riesgo de fractura, aunque la relación con segundas fracturas no ha sido aclarada.* ***Objetivo:*** *establecer el impacto de fracturas previas, edad, sexo y diabetes tipo 2 en el riesgo de segun-*

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das fracturas posterior a una fractura índice de cadera en el tiempo a través de un análisis de supervivencia. ***Material y métodos:*** *estudio retrospectivo, observacional y descriptivo, de una base de 670 registros de pacientes ≥ 50 años de edad, con fractura de cadera índice ocurrida entre los años 2014-2017, con seguimiento de al menos dos meses. Los desenlaces considerados fueron: fracturas previas, edad, sexo biológico, diabetes y fracturas subsecuentes. Análisis estadístico: tendencia central, dispersión, frecuencias, porcentajes, t de Student, χ^2, método de Kaplan-Meier, prueba log-rank, modelo de regresión de Cox.* ***Resultados:*** *se incluyeron 570 pacientes, edad media de 80.09 ± 9.45 años, 79.8% sexo femenino. Seguimiento de 24.8 ± 20.8 meses. En 96 casos ocurrieron fracturas subsecuentes en un tiempo de 25.9 ± 19.5 meses; de éstos, 56.2% ocurrió antes de dos años posteriores a la fractura índice. No se observaron asociaciones para segundas fracturas entre fractura previa (p = 0.3), sexo (p = 0.265) y diabetes (p = 0.54). El análisis de supervivencia demostró asociación para segundas fracturas con diabetes (p = 0.01) y sexo biológico (p = 0.03). La regresión de Cox demostró riesgo incrementado para diabetes (HR = 3.8; p = 0.017; IC 95% 1.275-11.484).* ***Conclusiones:*** *los pacientes con diagnóstico de diabetes tipo II que cursaron con fractura incidente de cadera tuvieron incremento del riesgo para segundas fracturas en el tiempo. El sexo masculino tuvo segundas fracturas en forma más temprana.*

INTRODUCTION

Fragility fractures are those that result from low energy trauma or mechanical forces that would not ordinarily result in fracture.[1] These might be associated to osteoporosis, and are a cause of disability, diminished quality of life and increased morbimortality.[2] Its risk increases with age, as well as osteoporosis, in which there is an increased loss of bone mineral content and progressive deterioration of skeletal microarchitecture.[3] Among fragility fractures, major osteoporotic fractures (MOF) are those that occurred in hip, forearm, spine and humerus.[4] An incident or index fracture is a fragility fracture due to osteoporosis that triggers interventions to lower the risk of falls, subsequent fractures and pharmacological treatment. After an incident MOF, it has been described that the risk of a subsequent fracture at one year was 2.7-fold (2.4-3.0) higher than the population risk; while, after a 10 years period the risk ratio was 1.4 (1.2-1.6) and remained above unity for the subsequent 15 years. On the follow-up, 20% of 1,311 cases re-fractured within one year and 34% within two years.[4] Because the risk of a subsequent fracture increases notably within two years after the index fragility fracture, this high-risk period has been defined as imminent risk.[2]

Three main factors have been linked to subsequent fractures: age, sex and previous fractures.[3] According to the study of Johansson,[4] the risk of a subsequent MOF increased risk by 5% each year of age (95% CI: 2-7%) and, was 25% more likely for women than men (95% CI: 9-44%). It has been described that approximately half of the patients who sustained a hip fracture had up to four previous fractures.[2]

In the presence of diabetes mellitus (DM), calcium metabolism might be altered[5] with increased bone turnover and reduced bone mineral density, which in turn may influence the risk of fractures in patients.[6] The strength of the association between DM and risk of fractures has been questioned due to the big variability among reports. Pooled results demonstrated increased risk of total hip, upper arm and ankle fractures in patients with DM.[6] Even though osteometabolic disorders have been described and have been linked to risk of fractures, controversy on the clinical impact of diabetes on fractures persists, and little information has been reported on its impact on subsequent fragility fractures.[7,8]

The aim of this study was to establish the impact of previous MOF, age, sex and type 2 diabetes diagnosis on subsequent fractures in patients who sustained an index hip fracture through a survival analysis.

MATERIAL AND METHODS

We performed a retrospective, observational and descriptive study.

Participants and settings. A database of 670 patients over 50 years of age records from an open population tertiary care concentration hospital with hip fracture from 2014 to 2017 was created, establishing hip fracture as index fracture. The only selection criteria were patients with records of follow-up in outpatient clinic for more than two months.

Outcomes. The information retrieved was age, biological sex, number of previous fractures (besides the index hip fracture), date and site of subsequent fractures and the presence of T2DM. It was approved

by the Institutional Research Ethics Board (register number 42/18).

Previous fractures were considered when the fragility fractures occurred before the index hip fracture; and subsequent fractures as those occurred after the index hip fracture.

Statistical analysis. The statistical analysis was performed with SPSS v17. Quantitative variables were synthetized with central tendency (mean) and dispersion (standard deviation), qualitative variables with frequency and percentages. Quantitative variables were compared with t Student and qualitative with χ^2 test. Survival analysis was performed with Kaplan-Meier method with type II censoring, and log-rank test. P-value was considered positive if it was below 0.05 and standard error (SE). Cox proportional hazards regression model was applied.

RESULTS

We selected 570 patients registers that fulfilled the criteria, the groups aged between 80 to 94 years comprised the 72.9% of subsequent fractures *(Figure 1)*.

The mean age in the total study population was 80.0 ± 9.4 years old (range 50 to 101). We included 455 women and 115 men (mean age, 80.8 ± 8.9 years and 77.2 ± 10.7 years, respectively); no significant statistical differences were observed between the sex and the group ages. The mean follow-up was 24.8 ± 20.8 months (range 9 to 99). 30.5% of these patients had a diagnosis of type II diabetes mellitus, and 39.3% referred previous fractures.

Subsequent fractures were documented in 96 cases *(Figure 2)*. The mean time to subsequent fractures was 25.9 ± 20.0 months (range 0.5 to 88.7). The 29.2% of subsequent fractures occurred in the first year after index fracture, and 27.1% during the second year, in other words subsequent fractures occurred in the imminent risk period, while the 43.7% of the fractures occurred after the imminent risk period. Of the 570 cases, 44.8% have had previous fractures with no statistical association between previous fracture and subsequent fractures. From the 455-women with index fracture, 17.4% sustained subsequent fractures, compared to the 14.8% in the 115 men (χ^2 = 0.663; p = 0.45 and 1.131; p = 0.28 respectively).

No significative associations were found between the number of previous fractures and having or not subsequent fractures *(Figure 2)*. Subsequent fractures site in the imminent risk period and after are described in *Table 1*, no significative associations were found.

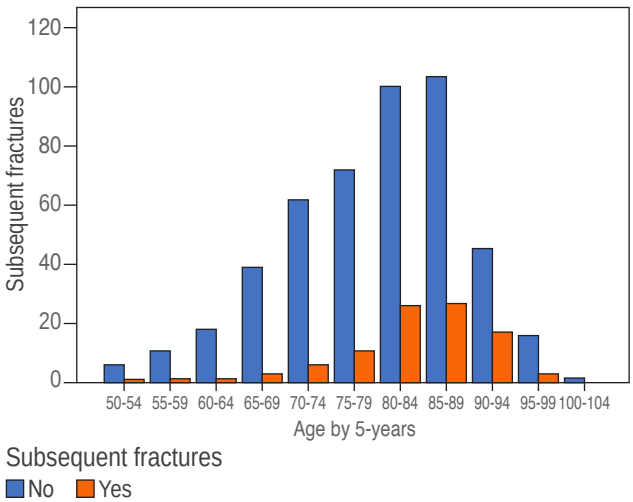


Figure 1: Distribution by 5-year age groups and subsequent fractures. N = 570; χ^2 = 17.277; p = 0.068.

We have tested the association between the presence of diabetes and the subsequent fractures; from the 96 patients that underwent through subsequent fractures, 33.3% had diabetes. We found no significative association between these variables (χ^2 = 0.429; p = 0.544).

Survival analysis

For survival analysis, data from 334 patients were censored if follow-up time was less than two years, and not censored if patients had a follow-up over two years.

When survival analysis was performed between previous and subsequent fractures *(Figure 3A)* we observed that the time for the subsequent fracture in patients with previous fracture was 65.7 ± 8.4 months and with no previous fracture was 74.7 ± 33.2 months. There was no statistical difference between groups (log-rank p = 0.709).

When performing survival analysis for diabetes and subsequent fractures *(Figure 3B)* we observed a difference of about 20% after 20 months of follow-up between individuals with and without diabetes through the time, with statistical significative difference (log-rank p = 0.01). The mean time to have a fracture in patients with diabetes was 54.4 ± 24.3 months and in patients without diabetes 74.7 ± 8.3 months.

The survival analysis for biological sex and subsequent fractures *(Figure 3C)* showed that there is a statistical significative difference in the time to have a second fracture between sexes (log-rank p = 0.039). Men sustained subsequent fractures with a mean time of 27.6 ± 14.3 months, and women with a mean time of 74.7 ± 8.3.

Cox regression analysis

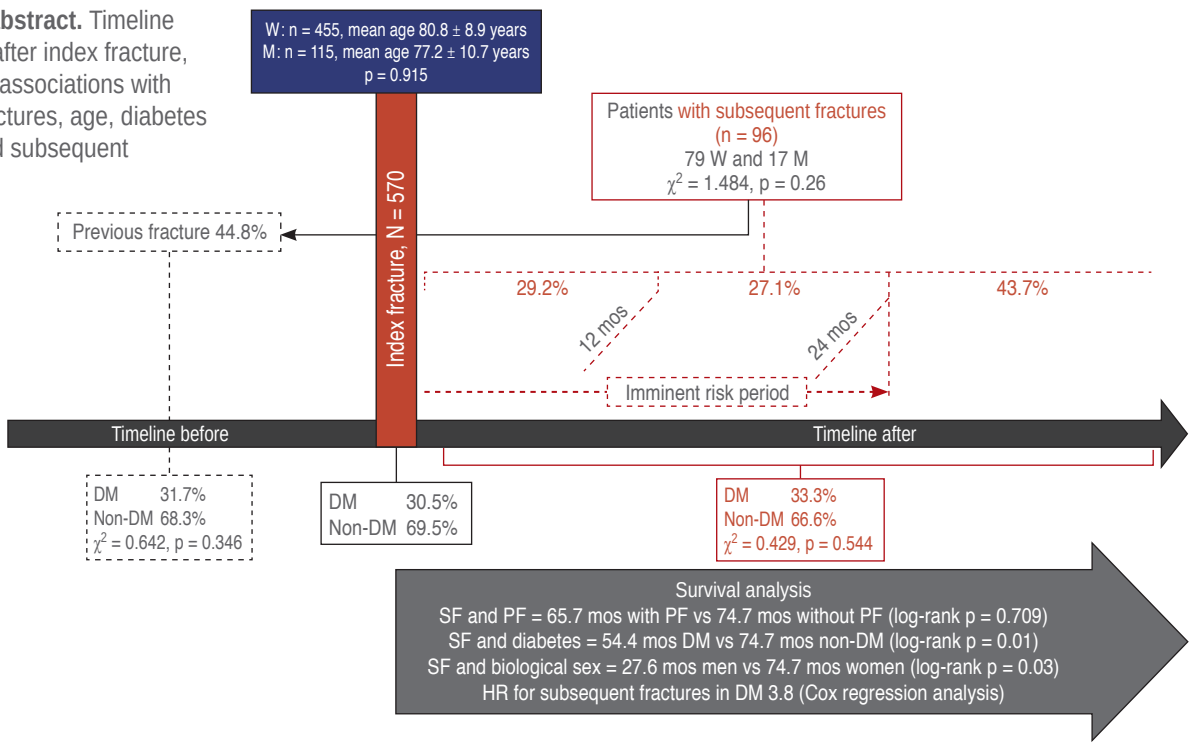
Cox regression analysis included diabetes, previous fracture, biological sex and age. Of these variables, only diabetes was included in the final equation model. Hazard ratio was 3.827 (p = 0.017; 95% CI 1.275-11.484).

DISCUSSION

The most studied outcomes associated with subsequent fractures are previous fractures, age and biological sex.[2,9-12] Even though the association of bone metabolism and diabetes is well documented, it has not been included in 10-year fracture risk calculation. Recents efforts have tried to confirm the relationship between the degree of metabolic compensation in T2DM and the 10-year probability for major osteoporotic fracture (MOF). One of the proposed algorithms included T2DM as a clinical risk factor, through HbA1c[13] which has not been included yet in fracture risk assessment tool (FRAX). HbA1c has been considered as an important indicator of glycemic control as it reflects glycemic history of the preceding two to three months.[14] Interestingly, in our study the only presence of T2DM increases 3.8 fold the risk of subsequent MOF in time, without consideration of metabolic control.

Skeletal growth is inhibited at an early age in absence of insulin and low levels of IGF-1 in type 1 diabetes mellitus, terminal differentiation of mesenchymal stem cells to osteoblasts is suppressed in addition to increased osteoclastic activity, leading to inadequate accumulation of bone to reach peak bone mass. In T2DM there is a multifactorial effect, which includes low levels of insulin, hyperglycemia,

Graphical abstract. Timeline before and after index fracture, considering associations with previous fractures, age, diabetes mellitus, and subsequent fractures



At the index fracture, 30.5% of patients (n = 570) had the diagnosis of DM. During follow up, among patients who developed SF, 33.3% (n = 96) had been diagnosed with DM. In Cox regression analysis only DM was considered for the final equation model.
W = women. M = men. DM = diabetes mellitus. HR = hazard ratio. SF = subsequent fractures. PF = previous fractures.

Figure 2: Graphical abstract.

Table 1: Subsequent fracture distribution in time by age five years groups.

	Spine		Humerus		Distal radius		Hip		Distal femur		Other	
Years	≤ 2	> 2	≤ 2	> 2	≤ 2	> 2	≤ 2	> 2	≤ 2	> 2	≤ 2	> 2
Age												
55-59	2											
60-64							2	1				
65-69	1		1	1	1	1		3	1			
70-74				1				2			1	1
75-79	1				2		5			1	1	2
80-84	2				3	1	6	8		1	2	1
85-89			1	3	3	2	6	6	2		2	1
90-94			1				5			2	2	
95-99						1		2				1
100-104			1									
Total	6	0	4	5	9	5	24	22	3	4	8	6
n (%)	6 (6.2)		9 (9.4)		14 (14.6)		46 (47.9)		7 (7.3)		14 (14.6)	

Pearson's χ^2: ≤ 2 years 56.045; p = 0.47. > 2 years 40.93; p = 0.055.
≤ 2: up to 2 years, > 2: more than 2 years.

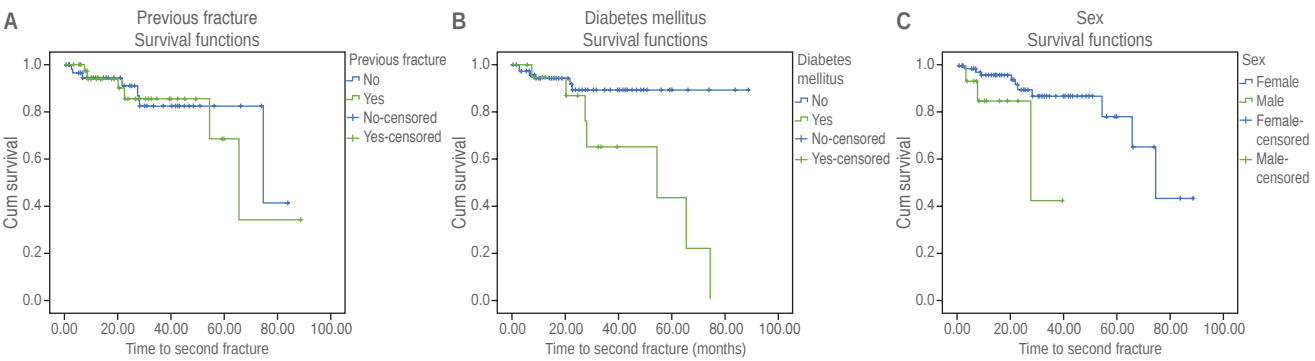


Figure 3: Kaplan-Meier survival analysis for subsequent fractures: previous fracture, diabetes, and biological sex (N = 570). SE = standard error. Cum = add Kaplan-Meier cumulative.

development and fixation of advanced glycation end products (AGEs), chronic inflammation and microvascular disease. These conditions decrease bone resistance by affecting architecture and biomechanical properties.[15,16] But there is controversy of the clinical significance of the association of diabetes and risk of fractures.[7,8]

Patients with T2DM have shown higher levels of bone mineral density (BMD) than patients of the same age and gender without diabetes, nonetheless there is association with higher risk of osteoporotic fractures in these patients independent of FRAX estimate.[17-19] Multivariable Cox proportional hazards models have been previously implemented to establish if diabetes is associated with incident hip fractures or MOF; after controlling age, sex, medication use and FRAX risk fractures including BMD, this analysis failed to identify 10-year probabilities of fracture between diabetic/non diabetic (11.1 ± 7.2 versus non diabetic 10.9 ± 7.3: p = 0.116).[18] Age and diabetes duration have been tested,

with the latter found to be an independent risk factor for MOF (HR 1.32; 95% CI 1.2-1.46).

Study limitations: in our study we did not consider the time of clinical course with diabetes diagnosis; in diabetes type 1 it has been shown that the risk of fracture extends through lifespan with hip fractures incidence between 10 to 15 years before non diabetic patients.[20] Our results did not show differences in the mean time for the occurrence of a subsequent fracture between type 2 diabetic patients and non-diabetic patients, this is probably due to the high standard error observed in the diabetic group. Nevertheless, Cox regression model demonstrated 3.8-fold higher risk after the imminent risk period of patients with diabetes diagnosis, regardless the time of evolution and metabolic control, ruling out the effect of age, sex and previous fracture.

The proposal of Ferrari[21] for the management of bone fragility in adults with diabetes, considers previous fracture as a strong predictor for subsequent fractures in diabetic and non-diabetic patients. Therefore, they suggested to initiate treatment for osteoporosis when diabetic patients meet the intervention guidelines for the general population, and otherwise, treatment should be considered at more favorable FRAX and BMD values in diabetic than in non-diabetic patients. Hence BMD and FRAX underestimate the risk of fracture in this population.

Previous fracture, biological sex and age, have been proved as individual factors associated to higher risk for subsequent fractures, the influence of type 2 diabetes is still under study.

Previous fracture has shown a high incidence of fractures after one year 10%, within two years 18% and five years 31%,[22] this high risk for mayor osteoporotic fractures is sustained for up to 10 years.[23] From the 96 patients who presented subsequent fracture, 44.8% had previous fracture, we failed to find association between this two variables, even in the survival analysis. This finding may be due to the fact that we searched for major osteoportic fractures, and under-registered minor osteoportic fractures could highlight this variable effect. Usually minor osteoporotic fractures include ribs, pelvis, midshaft and distal femur, distal humerus, proximal forearm, tibia and fibula, clavicle, scapula and sternum, fractures at the ankle, face, foot, hand, patella and skull are considered as non-osteoporotic fractures.[24] This considerations should be reconsidered in type 2 diabetes, due to its effect on bone quality.

Hazard ratio for subsequent fracture MOF after a major or minor osteoporotic fracture is age dependent at 10 years after, showing a progressively decreasing gradient. In the Reykjavik study cohort for an incident hip fracture in a woman aged 40 years HR was 47.6, which fell to 1.1 at the age of 90 years.[24] Subsequent fractures occurred in 86% of 96 subsequent fractures, with no association or effect in other variables.

In 10 years follow-up after an incident fracture hazard ratios (HR) for subsequent MOF are greater in men than in women, for example in hip fracture the increase in HR in men relative to women was 1.27 (95% CI = 1.03-1.55).[24] In our study we found only association with biological sex, and subsequent fractures were observed earlier in follow-up time for men (mean time of 27 months for men and 74.7 months for women). When this variable was included in the cox regression analysis it lost significance for the model.

CONCLUSIONS

Patients with type 2 diabetes diagnosis had 3.8 more risk of subsequent fractures in time establish through a survival analysis and hazard ratio. About 50% of subsequent MOF occurred after the imminent risk period, influenced by biological sex as they occurred earlier in time for men. The group of patients over 70 years of age is a particular group, as it registered 86% of subsequent fractures.

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