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HYPOGLYCAEMIA IS ASSOCIATED WITH INCREASED RISK OF FRACTURES IN PATIENTS WITH TYPE2 DIABETES MELLITUS: A COHORT STUDY

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Abstract

This study was conducted to determine that if type 2 diabetes is associated with an increased risk of fracture in patients.

This population-based cohort study used data from 2009 to 2017, in which 30,394 participants aged 0–89 years with type 2 diabetes were compared with 303,872 randomly selected age, sex, and practice matched participants without diabetes. Cox regression analysis was used to determine hazard ratios (HRs) for incident fracture in participants with type 2 diabetes.

A total of 334,266 participants, median age 34 years, were monitored for 1.9 million person-years. Hazard ratios were lowest in males and females age < 0.001). Secondary analyses or incident hip fractures identified the highest HR of 5.64 (95% CI 3.55–8.97) in men 60–69 years and the highest HR of 5.63 (95% CI 2.25–14.11) in women 30–39 years.

Type 2 diabetes was associated with increased risk of incident fracture that began in early age and lasts across the life span. Participants with type 2 diabetes sustained a disproportionately greater number of lower extremity fractures. These findings have important public health implications, given the increasing prevalence of type 2 diabetes and the morbidity and mortality associated with hip fractures.

Keywords: *Type 2 Diabetes; Increased risk fracture.*

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INTRODUCTION:

Type 2 diabetes is known as a situation caused by autoimmune-mediated destruction of the pancreatic b-cells. The incidence of type 2 diabetes is finest throughout early age. Though, the majority of the co-morbidities as well as end-organ consequences tend not to demonstrate unless adulthood. Spacious, multinational registry researchers have systematically revealed a progressive incidence of type 2 diabetes within the order of 2–5% annually. Enhancements in treatment have additionally authorized patients with type 2 diabetes to live for a longer period. These two aspects have brought about an increasing number of patients experiencing type 2 diabetes who definitely are in danger of the growth of diabetes-related difficulties (AL-Azawy, JABIR and Al-Ghurabi, 2012).

There happens to be an emerging understanding that diabetes negatively impacts skeletal health and that type 2 diabetes impacts the skeleton a lot more seriously. Studies in humans model has recognized several skeletal abnormalities commonly connected with type 2 and seldom type 2 diabetes, incorporating insufficiencies in bone mineral density (BMD) and bone structure, lowered indicators of bone formation, and diverse adjustments in markers of bone resorption (Alsaadawi, 2016).

Preceding studies as well as two huge meta-analyses stated that type 2 diabetes is related to an improved threat of fracture. Though, the majority of these researches had been carried out in seniors and concentrated on hip fractures. Significantly, most affected individuals formulate type 2 diabetes in earlier age, prior to the accomplishment of optimum bone mass, and as such might be at increased threat of fracture on their life span. Furthermore, due to the fact that hip fractures are usually rare in children and young adults, studies constrained to this consequence may disregard the complete fracture burden in type 2 diabetes (AL-Azawy, JABIR and Al-Ghurabi, 2012).

We applied online database to perform a cohort study to find out whether type 2 diabetes is affiliated with enhanced fracture incidence, to specify age and sex consequence on fracture risk, as well as to figure out whether fracture site division is modified in respondents with type 2 diabetes in comparison with respondents without diabetes. Online database is essentially designed for this task, because it comes with a legitimate origin of diagnosis and fracture data and also has been used to review other complications of type 2 diabetes and then to distinguished fracture incidence in a variety of patient populations across the life span (Alsaadawi, 2016).

STUDY DESIGN AND METHODOLOGY:

Database

We obtained data for this retrospective cohort study from the online database, specifically defined as anonymized longitudinal electronic medical records. Online database provide demographic, medical history, biochemical, and prescription data for more than 10 million patients, derived from the daily records of 587 participating practices. Medical diagnoses in this specific online database are recorded using Read codes, the standard classification system. Data collected from 2009 to 2017 were used for this analysis (Babu, Nakamura and Jurišić Eržen, 2018).

Study Cohort

The analysis sample had been obtained from respondents 0–89 years of age with appropriate records for research according to inspections carried out by the data vendor. Respondents were also deemed revealed considering they had a nonspecific diabetes Read code (e.g., “diabetes mellitus”) and had been ,35 years old with the initial diabetes code, possessed a prescription for insulin among 12 months with the first diabetes code, and lacked a prescription for oral or other anti-diabetic medication within 12 months of the first diabetes code (Berlin, Sachon and Grimaldi, 2017).

Respondents who have no diagnosis codes suggestive of diabetes were regarded as being unexposed to diabetes. Each type 2 diabetes participant was coordinated with approximately 10 randomly preferred respondents which has no diabetes codes based on age of diabetes respondents (3-year age-groups up to 30 years and 5-year age-groups thereafter) at the beginning of follow-up, sex, and practice. The ultimate study example consequently contained all internet based registered respondents fulfilling the criteria for type 2 diabetes and a random sample of matched online participants without exposure to diabetes To diminish the risk of misclassifying prevalent fractures as incident fractures, the start of the follow-up period for participants was the latest of 6 months after registration with the practice, the date that the practice started using the Vision software, and the date of the first diagnosis code meeting criteria for exposure (Babu, Nakamura and Jurišić Eržen, 2018).

Follow-up for unexposed issues started on the very same date as compared to their coordinated exposed participant. The follow-up course concluded together with the last collection date towards the practice, and subjects had been censored during the time of transfer out of their practice, death, or preliminary fracture event. Since the median observation period

was 4.7 years, using age at the start of observation would generate misleading information regarding age-specific hazards. Therefore, the data set had multiple records for 92.8% of the participants, with each record representing the time followed up in a given year of life (Jafari and Britton, 2015).

Primary Outcomes

The particular results of incident fracture were considered the initial incident of a diagnosis code in keeping with fracture throughout the research period. Incident fractures had been additionally categorized based upon anatomic site as follows: vertebral, skull/face, pelvis, rib/thorax, clavicle/ scapula, humerus/elbow, forearm/wrist, hand, femur/hip, lower leg/ankle, and foot. Fractures were encrypted as multi-site if there have been codes for 2 or more sites on a single date and classified by the site-specific code if the site-specific and a nonspecific code were simultaneously registered on the identical date. Surgically induced fractures and fractures attributed to birth trauma or metastatic bone disease were excluded. Secondary analyses defining incident hip fracture as the outcome of interest were also performed (Ntouva et al., 2018).

Covariates

Conditions identified by diagnosis codes as covariates of interest were hypothyroidism, hyperthyroidism, adrenal insufficiency, celiac disease, inflammatory bowel disease, vitamin D deficiency, and fracture before the start of the follow-up period, diabetic retinopathy, and diabetic neuropathy. All variables, with the exception of prior fracture, were treated as time-varying covariates. Prescription codes were used to assess for an effect of exposure to corticosteroids. Laboratory covariates analysed included haemoglobin A_{1C} (HbA1c), which was collected and averaged over the study period, and creatinine, which was used to define the presence or absence of chronic kidney disease (CKD) in participant. CKD was defined as two creatinine measures consistent with an estimated glomerular filtration rate (eGFR) of, 60 mL/min/ 1.73 m2 separated by .90 days and treated as a time-varying covariate. eGFR was calculated using the Modification of Diet in Renal Disease study equation (Singh, 2017).

The eGFR could not be reliably calculated in the paediatric population because of a large amount of missing height data, which is necessary for the calculation of eGFR in children. Given the extremely low incidence of CKD in the paediatric population (27, 28), participants, 18 years were considered unexposed to CKD. BMI within 1 year before the start of follow-up was included; the closest reading to the start of follow-up was analysed for participants with more than one reading. Participants were considered to be exposed to smoking if they were identified as past or current smokers before the start of follow-up (Ntouva et al., 2018).

Analysis

Standard comprehensive statistics were utilized to report participant and disease attributes. Prolonged parameters are revealed as median and interquartile range (IQR) and particular aspects as proportions. The x2 test was applied to examine for group variations between proportions. Cox proportional hazards evaluation was operated to evaluate the incidence of fracture in respondents with type 2 diabetes compared to that of matched unexposed participants. Multi-variable Cox regression analysis was adopted to evaluate confounding by covariates of interest. Final systems were stratified through category of age (<20, 20–29, 30–39, 40–49, 50– 59, 60–69, and ± 70 years) after age was found to be a substantial forecaster of fracture and to violate the expectation of proportionality of hazards residuals). Throughout each age stratum, models were again assessed for proportionality of hazards and further stratified where appropriate. Multi-variable Cox regression analyses were further carried out in precisely the respondents with type 2 diabetes to determine if higher HbA1c was associated with an increased risk of fracture. Age was not found to violate the assumption of proportional hazards in these models, so it was included as a continuous variable (Singh, 2017).

RESULTS:

Cohort Characteristics

We identified 30,394 participants with type 2 diabetes and 303,872 age, sex, and practice matched participants without diabetes (Table 1). The follow-up time was longer for participants without diabetes (4.7 years [IQR 2–9]) compared with those with type 2 diabetes (3.89 [IQR 1.5– 7.7]). Males comprised 56.1% of the study cohort, consistent with the known higher prevalence of type 2 diabetes in males. The median average HbA_{1c} was 8.5% (69 mmol/mol; IQR 7.6–9.5% [60–80 mmol/mol]) in the 24,533 type 2 diabetes participants with HbA_{1c} data available for analysis.

The median BMI was 25 kg/m2 in both groups. BMI data were available in 51.6% of participants with type 2 diabetes and in 14.4% of participants without diabetes. History of fracture before the start of the study follow-up was more common in participants with type 2 diabetes (19.6% vs. 17%).

	n = 30,394	*n* = 303,872	*P* value
Male, *n* (%)	17,047 (56.1)	170,421 (56.1)	
Age at start of follow-up, median (IQR), years	35 (24–50)	35 (24–50)	
Follow-up time, median (IQR), years	3.8 (1.5–7.7)	4.7 (2–9)	<0.001
BMI,[2] median (IQR), kg/m^2	25.4 (22.7–28.7)	25.5 (22.4–29.2)	0.33
Overweight,[3] *n* (%)	5,442 (34.7)	14,249 (32.5)	<0.001
Obese,[4] *n* (%)	3,025 (19.3)	9,595 (21.9)	0.01
Smoking,[5] *n* (%)	9,512 (39.8)	79,640 (37)	<0.001
Prior fracture, *n* (%)	5,952 (19.6)	51,641 (17)	<0.001
CKD,[6] *n* (%)	3,695 (12.2)	14,064 (4.6)	<0.001
Celiac disease, *n* (%)	496 (1.6)	698 (0.2)	<0.001
Hypothyroidism, *n* (%)	3,018 (9.9)	8,913 (2.9)	<0.001
Hyperthyroidism, *n* (%)	620 (2)	2,155 (0.7)	<0.001
Adrenal insufficiency, *n* (%)	101 (0.3)	52 (0.02)	<0.001
Cystic fibrosis, *n* (%)	161 (0.5)	122 (0.04)	<0.001
Systemic corticosteroid exposure, *n* (%)	5,489 (18.1)	50,681 (16.7)	<0.001
Diabetic retinopathy, *n* (%)	6,304 (20.7)	–	–
Diabetic neuropathy, *n* (%)	710 (2.3)	–	–
HbA_{1c},[7] median (IQR), %	8.5 (7.6–9.5)	5.6 (5.3–6)	
HbA_{1c},[7] median (IQR), mmol/mol	69 (60–80)	38 (34–42)	<0.001

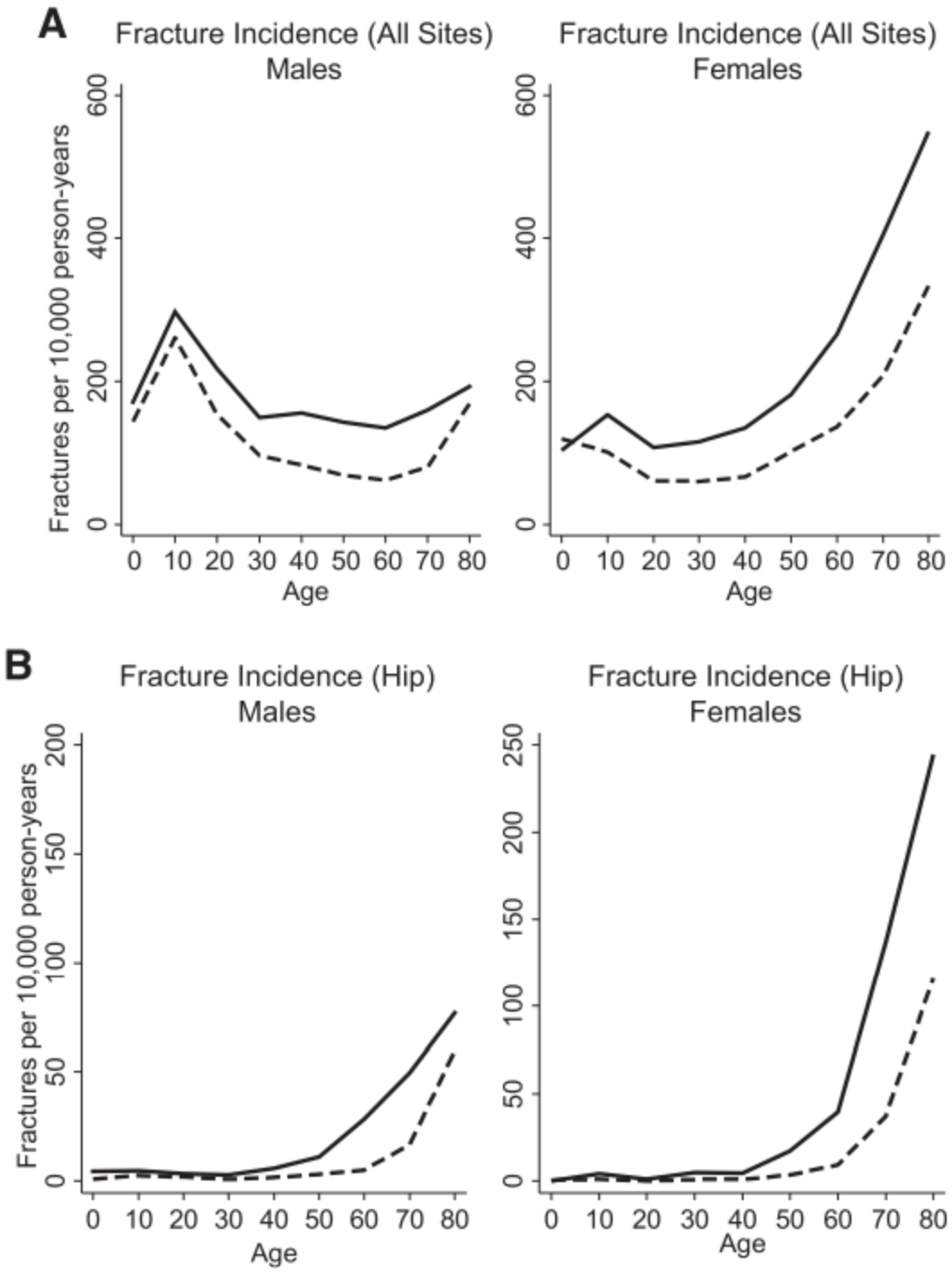
The incidence among all various other covariates appealing was increasing in respondents with type 2 diabetes, as anticipated. Diagnosis codes for diabetic retinopathy and diabetic neuropathy had been contained in 6,304 (20.7%) and 710 (2.3%) of respondents with type 2 diabetes, respectively.

Fracture Incidence

During the study period, incident fractures occurred in 2,615 participants (8.6%) with type 2 diabetes compared with 18,624 participants (6.1%) without diabetes. The fracture incidence per 10,000-person years is shown for each decade of life for males and females in (Fig. 1A). The incidence in males was greatest in the 10- to 20-year age bracket, at 297.2 and 261.3 fractures per 10,000 person-years in participants with and without type 2 diabetes, respectively. The fracture incidence in women was greatest in the 80- to 90-year age bracket, at 549.1 and 333.9 fractures per 10,000 person-years in participants with and without type 2 diabetes, respectively. Hip fracture incidence (Fig. 1B) was greatest in the 80- to 90- year age bracket for both sexes, at 76.7 and 59.6 fractures per 10,000-person years in men and 244.5 and 116.1 fractures per 10,000 person-years in women, for participants with and without type 2 diabetes, respectively (Vavlukis, 2016).

Fracture Site Distribution

The distribution of fracture site differed for males and females with type 2 diabetes compared with those without diabetes (Supplementary Fig. 1A). Fractures involving the lower extremity (hip/femur, lower leg/ankle, foot) comprised a greater percentage of all fractures in participants with type 2 diabetes compared with those without diabetes (31.1% vs. 25.1% in male subjects and 39.3% vs. 32% in females, P , 0.001 for both sexes; Supplementary Fig. 1B). Hip fractures alone comprised 5.5% and 11.6% of all fractures in males and females with type 2 diabetes, compared with 4.1% and 8.6% in males and females without diabetes (P = 0.04 for males and P = 0.001 for females). Participants with type 2 diabetes with a lower extremity fracture were more likely to have retinopathy (30% vs. 22.5%, P, 0.001) and neuropathy (5.4% vs. 2.9%, P = 0.001) compared with those with fractures at other sites. The median average HbA_{1c} did not differ between the two groups.



Source: Vavlukis, 2016

Table 2—Crude and adjusted HRs for incident fracture

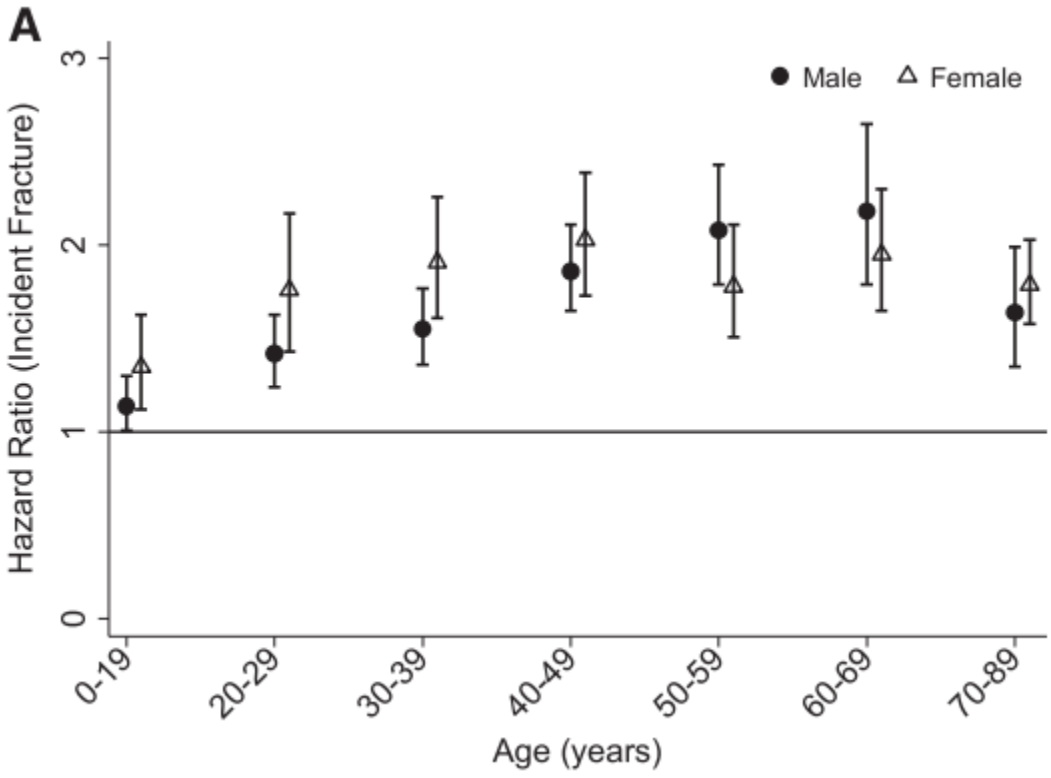
A. All fracture sites

Age-group	Person-years (n[1])	Crude HR (95% CI)	Adjusted HR[2] (95% CI)	Person-years (n[1])	Crude HR (95% CI)	Adjusted HR[2] (95% CI)
	Males			Females		
0–19 years	112,460 (30,623)	1.14 (1.01–1.29)[4]	1.14 (1.01–1.29)[4]	98,851 (26,525)	1.35 (1.12–1.63)[5]	1.35 (1.12–1.62)[5]
20–29 years	132,639 (34,860)	1.42 (1.24–1.63)[4]	1.40 (1.22–1.60)[4]	113,175 (32,587)	1.76 (1.43–2.17)[4]	1.72 (1.39–2.12)[4]
30–39 years	202,109 (42,878)	1.55 (1.36–1.77)[6]	1.50 (1.31–1.71)[6]	158,358 (29,776)	1.91 (1.61–2.26)[6]	1.77 (1.49–2.12)[6]
40–49 years	224,241 (31,804)	1.86 (1.65–2.11)[6]	1.78 (1.57–2.01)[6]	153,547 (19,337)	2.03 (1.73–2.39)[6]	1.82 (1.53–2.16)[6]
50–59 years	168,936 (20,957)	2.07 (1.78–2.41)[6]	1.97 (1.69–2.31)[6]	106,941 (13,582)	1.78 (1.51–2.11)[6]	1.69 (1.42–2.01)[6]
60–69 years	117,089 (14,077)	2.18 (1.79–2.65)[6]	2.00 (1.63–2.45)[6]	84,277 (11,235)	1.95 (1.65–2.30)[6]	1.76 (1.49–2.10)[6]
70–89 years	111,447 (12,268)	1.64 (1.35–1.99)[6]	1.55 (1.27–1.89)[6]	106,952 (13,757)	1.79 (1.58–2.03)[6]	1.69 (1.49–1.92)[6]

B. Hip fracture

Age-group	Person-years (n[1])	Crude HR (95% CI)	Adjusted HR[3] (95% CI)	Person-years (n[1])	Crude HR (95% CI)	Adjusted HR[2] (95% CI)
	Males			Females		
0–29 years	263,584 (65,483)	2.01 (0.99–4.10)	1.90 (0.92–3.93)	218,777 (59,112)	4.71 (1.45–15.28)[4]	4.69 (1.44–15.23)[4]
30–39 years	211,666 (42,878)	3.42 (1.25–9.32)[4]	3.38 (1.24–9.25)[4]	162,501 (29,776)	5.63 (2.25–14.11)[6]	4.16 (1.52–11.43)[5]
40–49 years	234,658 (31,804)	3.59 (1.86–6.91)[6]	2.56 (1.24–5.29)[4]	158,903 (19,337)	4.55 (1.75–11.85)[5]	2.10 (0.65–6.78)
50–59 years	175,743 (20,957)	3.64 (2.07–6.41)[6]	3.23 (1.79–5.84)[6]	111,739 (13,582)	5.06 (2.80–9.14)[6]	4.38 (2.31–8.31)[6]
60–69 years	120,950 (14,077)	5.64 (3.55–8.97)[6]	5.21 (3.2–8.47)[6]	89,406 (11,235)	4.22 (2.73–6.56)[6]	3.21 (2.00–5.16)[6]
70–89 years	115,389 (12,268)	1.99 (1.43–2.78)[6]	1.71 (1.21–2.4)[5]	116,740 (13,757)	2.6 (2.13–3.18)[6]	2.34 (1.91–2.87)[6]

[1]Based on age at study entry. [2]Adjusted for exposure to steroid medication, history of prior fracture, and presence of chronic kidney disease. [3]Adjusted for exposure to steroid medication, history of prior fracture, presence of chronic kidney disease, and hypothyroidism. [4]$P < 0.05$. [5]$P < 0.01$. [6]$P < 0.001$.



DISCUSSION AND CONCLUSION:

This particular population-based cohort research discovered that respondents with type 2 diabetes of all ages had an increased risk of fracture. Furthermore, fractures in respondents with type 2 diabetes have been more inclined to incorporate the reduced intensity. Specifically, for our knowledge, this is actually the initial research to demonstrate that the elevated fracture risk in type 2 diabetes begins in childhood. This particular learning offers significant repercussions for professionals planning future studies and to ensure clinicians caring for patients in this population. Although peak bone mass is attained by the end of the third decade of life, peak bone accrual occurs in adolescence in conjunction with the pubertal growth spurt. This critical time for bone accrual may represent a period of increased skeletal vulnerability and also a window of opportunity for the implementation of therapies to improve bone formation. This is an especially important consideration in the population with type 2 diabetes, because the incidence of this disease peaks in early adolescence. Three-quarters of individuals will develop the condition before 18 years of age, and therefore before attainment of peak bone mass. The development and evaluation of therapies aimed at increasing bone formation and strength in adolescence may lead to a lifelong reduction in fracture risk (Vavlukis, 2016).

In summary, our study found that participants of all ages with type 2 diabetes were at increased risk of fracture. The adverse effect of type 2 diabetes on the skeleton is an under recognized complication that is likely to grow into a significant public health burden given the increasing incidence and prevalence of this disease. Further research is needed to elucidate the natural history and pathophysiology of skeletal fragility in type 2 diabetes. Our novel finding that children with type 2 diabetes were already at increased risk of fracture suggests that therapeutic interventions aimed at children and adolescents may have an important effect on reducing lifelong fracture risk.

REFERENCES:

1. AL-Azawy, V., JABIR, D. and Al-Ghurabi, D. (2012). A comparative Study on Serum Leptin and Adiponectin levels in Periodontitis Patients with and without Diabetes Mellitus Type2. *International Journal of Scientific Research*, 3(5), pp.1-4.
2. Alsaadawi, T. (2016). Smoking is Associated with Increased Risk of Osteoporosis in Diabetes Mellitus Patients. *Journal of Bone Reports & Recommendations*, 02(04).
3. Babu, G., Nakamura, A. and Jurišić Eržen, D. (2018). Commentary: Short Body Height and Pre-pregnancy Overweight for Increased Risk of Gestational Diabetes Mellitus: A Population-Based Cohort Study. *Frontiers in Endocrinology*, 9.
4. Berlin, I., Sachon, C. and Grimaldi, A. (2017). Identification of factors associated with impaired hypoglycaemia awareness in patients with type 1 and type 2 diabetes mellitus. *Diabetes & Metabolism*, 31(3), pp.246-251.
5. Jafari, B. and Britton, M. (2015). Hypoglycaemia in elderly patients with type 2 diabetes mellitus: a review of risk factors, consequences and prevention. *Journal of Pharmacy Practice and Research*, 45(4), pp.459-469.
6. Ntouva, A., Toulis, K., Keerthy, D., Adderley, N., Hanif, W., Thayakaran, R., Gokhale, K., Thomas, G., Khunti, K., Tahrani, A. and Nirantharakumar, K. (2018). Hypoglycaemia is associated with increased risk of fractures in patients with type 2 diabetes mellitus: a cohort study. *European Journal of Endocrinology*, pp.51-58.
7. Shin, S. and Kim, H. (2016). The effect of sitagliptin on cardiovascular risk profile in Korean patients with type 2 diabetes mellitus: a retrospective cohort study. *Therapeutics and Clinical Risk Management*, p.435.
8. Singh, P. (2017). "A STUDY OF LIFESTYLE INTERVENTIONS IN PATIENTS WITH TYPE2 DIABETES MELLITUS". *World Journal of Pharmacy and Pharmaceutical Sciences*, pp.1591-1602.
9. Subbiah, E. (2017). A Study on The Prevalence And Risk Factors Associated with Peripheral Vascular Disease In Type2 Diabetes Mellitus. *IOSR Journal of Dental and Medical Sciences*, 16(05), pp.46-52.
10. Vavlukis, M. (2016). Are diabetes mellitus and lipoprotein(a) independently or causally associated with an increased cardiovascular risk?. *The Anatolian Journal of Cardiology*.