Published in final edited form as:

J Diabetes Complications. 2020 October ; 34(10): 107664. doi:10.1016/j.jdiacomp.2020.107664.

Fracture risk in patients with type 2 diabetes aged 50 years related to HbA1c, acute complications, BMI and SGLT2i-use in the DPV registry

Alexander Eckert^{a,b,*}, Julia K. Mader^c, Marcus Altmeier^d, Steffen Mühlendorfer^e, Anton Gillessen^f, Dhayana Dallmeier^{g,h}, Viral N. Shahⁱ, Christoph Heyer^j, Bettina Hartmann^k, Reinhard W. Holl^{a,b}

^aInstitute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm, Ulm, Germany

^bGerman Centre for Diabetes Research (DZD), Neuherberg, Germany

^cDivision of Endocrinology and Diabetology, Medical University of Graz, Graz, Austria

^dDiabetescenter, Klinikum Dortmund GmbH, Dortmund, Germany

^eDepartment of Gastroenterology, Klinikum Bayreuth, Bayreuth, Germany

^fHerz-Jesu Hospital Münster-Hiltrup, Münster, Germany

^gAGAPLESION Bethesda Clinic, Geriatric Center Ulm, Ulm, Germany

^hDepartment of Epidemiology, Boston University School of Public Health, Boston, USA

ⁱBarbara Davis Center for Diabetes, University of Colorado Anschutz Medical Campus, Aurora, USA

^jDiabetespraxis Viersen, Viersen, Germany

^kHeilig-Geist Hospital Bensheim, Department of Gastroenterology and Diabetology, Bensheim, Germany

1 Introduction

People with diabetes have a higher risk for bone fractures. Low bone-mineral-density (BMD) is one reason for fractures among type-1-diabetes (T1DM) patients.^{1,2} In children with T1DM, impaired bone remodelling is another known risk factor for fractures³.

*Corresponding author at: Institute of Epidemiology and Medical Biometry, ZIBMT, Ulm University, Albert-Einstein-Allee 41, 89081 Ulm, Germany. alexander.eckert@uni-ulm.de.

Author statement

AE analysed the data and wrote the paper. RWH conceived and coordinated the study. The authors JKM, MA, SM, AG, DD, VNS, CH, BH and RWH reviewed the article critically and approved the final version of the manuscript before its submission.

Declarations of interest

The authors declare that there is no duality of interest associated with this manuscript.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

However, type-2-diabetes (T2DM) patients reveal normal or higher BMD than people without diabetes, but still have increased risk of fractures^{1,2}.

Older age, female gender, lower body-mass-index (BMI) and lifestyle factors such as smoking and alcohol consumption increase fracture risk in the general population and in diabetes patients⁴. Longer diabetes duration further enhances fracture risk among T2DM patients¹ and the interplay between skeleton and glucose metabolism may play also a role⁵.

In individuals with T2DM, the risk for any fracture, compared to the general population, is elevated (Odds ratio [95%-CI]: 1.2 [1.1–1.3])⁶. The odds ratio (OR) for specific sites is, hip: 1.4 [1.2–1.6]; forearm: 1.2 [1.0–1.5]. Reasons for increased fracture risk among individuals with T2DM are not yet fully understood, but glycaemic control, falls due to hypoglycaemia⁷, reduced bone quality and some anti-diabetic medications^{2,8,9} are discussed in the literature.

In terms of glycaemic control, there are contradictory findings. Some studies report that high HbA1c impairs bone remodeling¹⁰ and elevates the risk for fractures^{1,7}. Another study reports the highest fracture risk in patients with high HbA1c (>9%; >75 mmol/mol), but also increased fracture risk in patients with low HbA1c (<6.5%; <48 mmol/mol) compared to HbA1c values between 6.5 and 9%¹¹. Still another study reports the highest fracture risk among T2DM patients with HbA1c <6.5%¹².

Reduced bone quality is reflected in lower biomarkers for bone turnover, a lower bone material strength index and advanced glycation end products (AGE). Furthermore, T2DM patients often have increased visceral adipose tissue which might result in impaired bone quality⁸.

However, there is evidence that low BMI is associated with higher risk for hip fractures in subjects aged ≥ 40 years with or without diabetes¹³, while high BMI might be a risk factor for ankle and upper leg fractures in postmenopausal women in the general population¹⁴.

Several medications might have an impact on fracture risk. Sodium-glucose co-transporter-2 inhibitors (SGLT2i) and glitazones were mentioned in a previous study¹⁵. In contrary, another study did not confirm the association between SGLT2i and fracture risk¹⁶. Additionally, insulin and sulphonylurea are suspected to increase fracture risk due to hypoglycaemic events which can lead to falls¹⁷.

The role of HbA1c, BMI, anti-diabetic medications and hypoglycaemia is therefore inconclusive. For diabetic ketoacidosis (DKA), we could not find a study that explicitly investigated the relationship to bone fractures in T2DM patients.

Therefore, the aim was to evaluate glycaemic control, BMI, acute complications and diabetes medication as risk factors for fractures in individuals with T2DM aged ≥ 50 years.

2 Materials and methods

2.1 Participants and data collection

This analysis is based on data from the prospective, multicentre diabetes patient follow-up registry “Diabetes-Patienten-Verlaufsdokumentation” (DPV) which is a standardized electronic health record developed at the Institute of Epidemiology and Medical Biometry, Ulm University, Germany¹⁸. The initiative and analysis of anonymised data was approved by the Ethics Committee of Ulm University (approval number: 202/09) as well as by local review boards.

495 diabetes centres from Germany, Austria, Switzerland and Luxembourg provided anonymised data on diabetes treatment and outcome to the DPV registry until September 01, 2019. Twice a year participating centres report de-identified data for central analysis at Ulm University. The transferred data are checked for inconsistency or implausibility and reported back to the respective centres for correction, if necessary.

Patients recorded in the DPV initiative were included if they had a clinical diagnosis of T2DM and were ≥ 50 years of age.

2.2 Group selection and fracture sites

Patients were allocated to the fracture group if they had at least one documented fracture at any site during the last 12 months. Fractures were divided into the following sites: hip, spine, lower limb, upper limb, pelvis, skull and others (could not be clearly allocated). Supplementary table 1 shows the inclusion/exclusion criteria and the ICD-10 codes used. Every patient is represented only once in the overall fracture group, even if more than one fracture at different sites was documented. Therefore, the number of patients in the overall fracture group ($n = 4821$) is not equivalent to the sum of patients with fractures at the specific sites ($n = 5200$).

People who had no documented fracture, were allocated to the control group for comparison of demographics and diabetes-related outcomes. Patients that had a documented fracture, that occurred more than 12 months ago or that was documented as “status post” fracture with unknown time-lag were excluded (figure 1).

For each subject the last documented year was analysed. The data were aggregated if the subject had more than one visit in the last documented year.

2.3 Patient data

For descriptive comparison of demographics and diabetes-related outcomes between the fracture group and the control group, the parameters sex, age, height, weight, BMI, diabetes duration, type of treatment, HbA1c (%; mmol/mol), alcohol consumption and smoking were analysed. The parameters HbA1c, BMI, type of treatment, severe hypoglycaemic events per patient-year, events of severe hypoglycaemia with coma per patient-year and DKA events per patient-year were used in multivariable logistic regression models to determine the fracture risk associated with these parameters.

Alcohol consumption was divided into alcohol abuse (a reported consumption of >12g (female) or >24g (male) alcohol per day), and normal or no alcohol consumption reported. Smoking was defined as reported current smoking yes/no. Severe hypoglycaemia was defined as a stage in which the patient required help by another person and severe hypoglycaemia with coma as loss of consciousness. DKA was defined as pH <7.3 and/or bicarbonate <15 mmol/l. HbA1c values were standardised to the Diabetes Control and Complications Trial (DCCT) reference range of 4.05%–6.05% (20.7–42.6 mmol/mol) using the multiple of the mean transformation method to account for different laboratory methods¹⁹.

2.4 Statistical analysis

All statistical analyses were generated using SAS (Statistical Analysis Software, SAS Institute Inc., Cary, NC, USA) Version 9.4. Descriptive statistics were performed for baseline characteristics. The results were shown as median with quartiles for continuous variables using the Kruskal-Wallis-Test to compute unadjusted *p*-values and as proportions for binary variables using the χ^2 -Test.

We used multivariable logistic regression models to calculate the percentage of patients with fractures (PWF) among the different sub-groups for HbA1c, BMI, type of treatment, severe hypoglycaemia, severe hypoglycaemia with coma and DKA.

For these logistic regression models, HbA1c was divided into sub-groups of: “<6.5%”, “≥6.5–<9%” and “≥9%”. Severe hypoglycaemia (with or without coma) was divided into the sub-groups: “0 events”, “1 event”, “>1 event” per patient-year. DKA was categorised as “0 events”, “≥1 event” per patient-year. BMI was analysed in sub-groups of “<25”, “≥25–30”, “≥30–35” and “≥35”.

Diabetes therapy was divided into 5 groups: insulin (patients that received insulin therapy); GL/SU (patients treated with glinides or sulphonylureas, without insulin therapy); SGLT2i (Patients treated with SGLT2i, without insulin or GL/SU treatment); OAD-others (Patients treated with any other OAD, without insulin therapy); lifestyle (no antidiabetic medication).

All regression models were adjusted for age (in groups of “≥50–60”, “≥60–70”, “≥70–80” and “≥80” years), sex, diabetes duration (in groups of “≤2”, “>2–7”, “>7–11”, “>11–18” and “>18” years), and BMI (see above) and were implemented for the whole cohort as well as stratified by sex. Regression models for type of treatment, severe hypoglycaemic events and DKA events were additionally adjusted for HbA1c.

Identical regression models were used for calculation of patients with any fracture and for specific sites (hip, spine, lower limb, upper limb). Regression models for specific sites included patients with fractures at this site and patients without fractures, patients that had a documented fracture at any other site were excluded to ensure a clear comparison. The number of patients with >1 severe hypoglycaemic event, ≥1 DKA event or SGLT2i treatment was too low to be used in regression models for different fracture sites. Therefore, the confounders severe hypoglycaemia (with or without coma), DKA and treatment were only analysed in regression models for any fracture. Results from logistic regression models

were presented as adjusted percentages together with 95%-CI. *P*-values between groups were calculated for all confounders. For HbA1c, BMI and severe hypoglycaemia (with and without coma) *p*-values for trend were additionally calculated. *P*<0.05 indicated a significant difference.

3 Results

3.1 Study population and demographics

Among all patients registered in DPV, 356,277 were aged ≥ 50 years and had a diagnosis of T2DM. 2169 had a documented fracture that occurred more than one year ago or with unclear time allocation. This left 354,108 patients, which represented the study population. 4821 (1.4%) had a recent fracture (figure 1).

T2DM patients with fractures were more often female (62.7% vs. 47.4%), older and had a longer diabetes duration compared to the control group. Furthermore, patients in the fracture group had lower BMI and lower HbA1c than T2DM patients without fractures (table 1). Individuals with fractures more often consumed a harmful amount of alcohol, but smoked less frequently, compared to patients without fractures. Patients in the fracture group received insulin treatment and lifestyle therapy slightly more often and were less frequently treated with OAD than the control group (table 1).

Stratification by sex showed similar results. However, female T2DM patients in both the fracture group and the control group were older and had longer diabetes duration than male patients. Males smoked and consumed a harmful amount of alcohol more often than females (table 1). Female T2DM patients with fractures received slightly more often insulin therapy than females without fractures. Among male T2DM patients, lifestyle therapy was used more often in the fracture group compared to the control group (table 1).

3.2 Logistic regression models for any fracture

For the whole cohort as well as stratified by sex, PWF increased significantly with lower HbA1c. Highest fracture risk was observed in the “<6.5%” group (table 2).

No significant differences could be observed regarding severe hypoglycaemic events. However, patients with more than one event of hypoglycaemic coma during the last year revealed a significantly ($p<0.01$) higher fracture risk compared to patients without or with only 1 event of hypoglycaemic coma. Same results were found in females ($p<0.01$). Male individuals with T2DM showed a similar (but nonsignificant) tendency (table 2).

T2DM patients in the whole cohort, that had at least one event of DKA during the last year, were at higher risk for any fracture. These results were also valid after stratification for sex (table 2).

Higher fracture risk was observed for people with lower BMI in the whole cohort as well as for females and males separately (table 2). However, for male patients only the sub-groups “<25” and “ ≥ 35 ” were significantly different ($p=0.017$).

In the whole cohort, treatment with SGLT2i and lifestyle therapy were associated with higher fracture risk compared to GL/SU and insulin treatment (all p -values <0.05). Female patients with SGLT2i treatment revealed the highest fracture risk compared to other treatment-groups (table 2). Male patients on lifestyle therapy had the highest PWF among all sub-groups. For females treated with SGLT2i, fracture risk was significantly increased compared to treatment with insulin ($p=0.011$) and GL/SU ($p=0.003$). Differences to the OAD-others ($p=0.053$) or the lifestyle group ($p=0.086$) were not significant. Male patients in the lifestyle group had significantly higher fracture risk than individuals treated with insulin ($p=0.003$) or GL/SU ($p<0.001$), but no significant association to SGLT2i could be observed (table 2).

Among treatment-groups, patients on insulin had the longest diabetes duration. Patients in the SGLT2i group were younger and more often male, consumed more alcohol and smoked more often compared to all other treatment groups. (supplementary table 2). However, even after additional adjustment for self-reported alcohol consumption and smoking, results for treatment groups were similar and still significant.

3.3 Logistic regression models stratified by fracture site

In the whole cohort and in female patients, low HbA1c was associated with higher fracture risk for hip ($p<0.001$), spine ($p<0.05$) and lower limb ($p<0.01$), but not for upper limb. In male patients, only hip ($p=0.002$) and lower limb ($p<0.001$) fractures were associated with lower HbA1c (figure 2) (all p -values for trend-analysis).

In the whole cohort, BMI was inversely associated with the risk for hip ($p<0.001$) and spine ($p=0.002$) fractures, but lower limb fractures were related to higher BMI ($p=0.022$). In female patients, hip ($p<0.001$) and spine ($p=0.014$) fractures were inversely related to BMI, while in male patients, only hip fractures were inversely associated ($p<0.001$) and lower limb fractures were associated to higher BMI ($p=0.004$; all p -values for trend-analysis). No trend was observable for upper limb fractures in association with BMI (figure 3).

4 Discussion

We investigated the association between diabetes-related parameters and fracture risk among people with T2DM ≥ 50 years. Our results indicate that low HbA1c, low BMI, hypoglycaemic coma, DKA and SGLT2i treatment is associated with higher fracture rates.

Several studies reported that poor glycaemic control is associated with reduced bone remodeling¹⁰ and therefore with a higher risk of fractures in elderly T2DM patients^{1,7}. One reason could be the high amount of AGE that are a result of long-lasting high blood glucose levels⁸, but we could not confirm that high HbA1c is related to fracture risk among T2DM patients ≥ 50 years of age in the DPV registry. This could be due to the cross-sectional nature of this study, which did not allow us to evaluate possible long-term effects of high HbA1c. Other studies found higher fracture risk in individuals with T2DM ≥ 65 years with very low or very high HbA1c^{11,20}. However, results of the current study did not change, even after analysing only T2DM patients ≥ 65 years. Another study found higher fracture risk in T1DM patients with high HbA1c, but no relation between glycaemic control and

fracture risk among T2DM patients²¹. This is in line with findings by Cutrim et al. that could not confirm an association between high HbA1c and bone resorption²². Altogether, the current knowledge about the relation between glycaemic control and fracture risk in T2DM remains largely unclear.

Our results support the findings by Lee et al. who observed highest fracture risk in T2DM patients with HbA1c <6.5%¹². One reason might be that people with T2DM and low HbA1c are at higher risk for hypoglycaemic events²³, causing falls and fractures²⁴. This would be in line with our findings on higher fracture risk among patients with more than one event of hypoglycaemic coma. Other studies confirmed that hypoglycaemia is a risk factor for fractures in T2DM patients²⁵, and that more events of hypoglycaemia per year result in higher fracture rate²⁶. These studies, however, did not differentiate between (severe) hypoglycaemic events with or without coma. The present study suggests that only several events of hypoglycaemic coma per patient-year increase fracture risk.

Low BMI was a risk factor for hip and spine fractures, which is in accordance with another study that revealed that low BMI is associated with higher hip fracture risk in people with diabetes and in people without diabetes aged ≥ 40 years¹³. Fat deposits might protect against hip fractures indicated by falls⁴. However, another study reported that high BMI enhances the risk for ankle and upper leg fractures. This is in line with our findings on lower limb fractures that were more frequent in patients with higher BMI. The authors supposed that the higher impact of falls in people with higher BMI together with the absence of fat deposits at the ankle and leg could make these locations more prone to fractures in obese individuals¹⁴.

DKA occurs more often in T1DM patients than in T2DM patients, but in the last decades more events of DKA were ascertained in both T1DM and T2DM^{27,28}. Furthermore, DKA is often serious in T2DM patients²⁹. One reason for the higher fracture rate among individuals with DKA could be the frequent severe form of DKA in T2DM, that can lead to weakness, lethality and even to coma³⁰. Another possible explanation could be, that one risk factor for DKA is alcohol abuse³¹, which was more frequent in the fracture group compared to the control group in the present study and was stated as a risk factor for fractures, especially for hip fractures in older men, in previous studies^{32,33}. A third explanation might be the possible association between SGLT2i medication and DKA, that is currently discussed in the literature^{34,35}. At least in female patients, these two parameters could play a role, as in women, medication with SGLT2i was related to higher fracture risk in the present study. However, there is evidence that SGLT2i increase the mean total ketone body concentration, but not necessarily the risk for ketoacidosis³⁶.

This leads to diabetes treatment in relation to fracture risk. Previous studies reported that medication with insulin or GL/SU is a risk factor for hypoglycaemia^{37,38}. SGLT2i are under suspicion to play a role in BMD and fracture risk, but contradictory results were presented in the literature^{15,39,40}. We could not confirm that insulin therapy or medication with GL/SU increases fracture risk compared to other treatments. In fact, in males, the highest PWF was observed in the lifestyle group. Possibly, these patients have less severe medical conditions and therefore are more active. The higher activity of this sub-group in connection with a

higher amount of sport fractures in men compared to women (18% vs. 10% of limb fractures)⁴¹ might be one explanation why male patients with lifestyle therapy had more fractures. In the whole cohort and especially in female patients, medication with SGLT2i revealed the highest risk for any fracture. Individuals in the SGLT2i group were younger, which is in line with another study that compared the age-dependant use of anti-diabetic medications.⁴² From this, one can assume that patients in the SGLT2i treatment-group are more active and therefore have higher fracture risk. The association of SGLT2i with DKA^{34,35} might be another reason for the higher fracture risk compared to other treatments. However, further evaluation is required whether all SGLT2i are related to fracture risk, or if only canagliflozin has a detrimental effect on BMD and fracture risk, as suggested in previous studies^{15,43}. The effect of SGLT2i on calcium-phosphate metabolism in terms of increased serum phosphate may also contribute to reduced bone strength and higher fracture risk⁴⁴. Furthermore, the acid buffering capacity (e.g. ketoacids) of the bone might support the consideration of an interaction between post-menopausal osteoporosis in women and bone resorption.⁴⁵

Most of the published studies on fractures among people with T2DM concentrated on any fracture or on few specific fracture sites, often hip fractures. One of the strengths of the present study was that we analysed 4 specific fracture sites separately and we could show that HbA1c and BMI differently affect fracture risk at specific sites. Another strength was that we had data available from more than 350,000 T2DM patients from the DPV registry. One limitation of the present study was the difficulty to allocate some fractures to a specific site, because some fracture sites were included in more than one ICD-10 code, for example lumbar spine (supplementary table 1). Another difficulty was the temporal assignment of the fractures, as this was not always clearly documented. We cannot rule out that some patients were excluded, because their fracture was only documented as “status post”, but sustained the fracture during the last 12 months and therefore should have been included. Additionally, some fractures probably have never been documented in this diabetes registry, and therefore we might have underestimated the number of patients with fractures. Furthermore, longitudinal studies might reveal different associations between HbA1c and fracture risk. Another limitation was that we had no information on fracture cause (spontaneous, traumatic, etc.) as well as on BMD, vitamin D levels or osteoporosis.

In conclusion, low HbA1c was associated with higher risk of any, hip, spine and lower extremity fractures in T2DM patients ≥ 50 years of age. BMI showed an inverse relationship to the risk for any, hip and spine fractures, whereas lower limb fractures were associated with high BMI. More than one event of hypoglycaemic coma as well as at least one event of DKA per patient-year increased the risk for any fracture. SGLT2i and lifestyle therapy revealed the highest fracture risk in the whole cohort. In male patients, lifestyle therapy and in female patients, medication with SGLT2i was associated with the highest fracture risk. It seems that insufficient glycaemic control is not a predictor for fracture risk in individuals with T2DM ≥ 50 years, but caution is required in patients with low HbA1c to prevent hypoglycaemic coma. SGLT2i treatment might be detrimental, at least in female patients. Even if DKA is rare in T2DM patients, it seems to be related to fractures and because the DKA rate increased in T2DM patients during the last decades²⁸, this is an important topic for further research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to thank all participating centres, especially the collaborating centres in this investigation, of the DPV initiative. Special thanks to Andreas Hungele and Ramona Ranz for support and the development of the DPV documentation software and Katharina Fink and Esther Bollow for the DPV data management (in each case clinical data manager, Ulm University). The list of all contributing centres is given in supplementary list 1.

Funding

This Study was supported through the German Federal Ministry for Education and Research within the German Centre for Diabetes Research (DZD, 82DZD0017G). Further financial support was received by the German Robert Koch Institute (RKI) and the German Diabetes Association (DDG). Sponsors were not involved in data acquisition or analysis. VNS is supported by NIH grants (1K23AR075099 and 1R01DK122554).

References

1. Napoli N, Chandran M, Pierroz DD, et al. Mechanisms of diabetes mellitus-induced bone fragility. *Nat Rev Endocrinol*. 2017;13(4):208–219. doi: 10.1038/nrendo.2016.153. [PubMed: 27658727]
2. Costantini S, Conte C. Bone health in diabetes and prediabetes. *World J Diabetes*. 2019;10(8):421–445. doi: 10.4239/wjd.v10.i8.421. [PubMed: 31523379]
3. Faienza MF, Ventura A, Delvecchio M, et al. High sclerostin and dickkopf-1 (DKK-1) serum levels in children and adolescents with type 1 diabetes mellitus. *J Clin Endocrinol Metab*. 2017;102(4):1174–1181. doi: 10.1210/jc.2016-2371. [PubMed: 28388723]
4. Starup-Linde J, Frost M, Vestergaard P, Abrahamsen B. Epidemiology of fractures in diabetes. *Calcif Tissue Int*. 2017;100(2):109–121. doi: 10.1007/s00223-016-0175-x. [PubMed: 27444009]
5. Faienza MF, Luce V, Ventura A, et al. Skeleton and glucose metabolism: A bone-pancreas loop. *Int J Endocrinol*. 2015;2015:758148. doi: 10.1155/2015/758148. [PubMed: 25873957]
6. Vestergaard P, Rejnmark L, Mosekilde L. Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. *Diabetologia*. 2005;48(7):1292–1299. doi: 10.1007/s00125-005-1786-3. [PubMed: 15909154]
7. Komorita Y, Iwase M, Fujii H, et al. Both hypo and hyperglycaemia are associated with increased fracture risk in Japanese people with type 2 diabetes: the Fukuoka diabetes registry. *Diabetic Medicine*. 2019. doi: 10.1111/dme.14142.
8. Poiana C, Căpatina C. Osteoporosis and fracture risk in patients with type 2 diabetes mellitus. *Acta endocrinologica (Bucharest, Romania : 2005)*. 2019;15(2):231–236. doi: 10.4183/aeb.2019.231.
9. Sellmeyer DE, Civitelli R, Hofbauer LC, Khosla S, Lecka-Czernik B, Schwartz AV. Skeletal metabolism, fracture risk, and fracture outcomes in type 1 and type 2 diabetes. *Diabetes*. 2016;65(7):1757–1766. doi: 10.2337/db16-0063. [PubMed: 27329951]
10. Ha M, Chen J, Zhang X, Yang H, Liu C. Relationships of social support, health-promoting lifestyles, glycemic control, and bone turnover among adults with type 2 diabetes. *Jpn J Nurs Sci*. 2020;17(1):e12280. doi: 10.1111/jjns.12280. [PubMed: 31286684]
11. Conway BN, Long DM, Figaro MK, May ME. Glycemic control and fracture risk in elderly patients with diabetes. *Diabetes Res Clin Pract*. 2016;115:47–53. doi: 10.1016/j.diabres.2016.03.009. [PubMed: 27242122]
12. Lee RH, Sloane R, Pieper C, et al. Glycemic control and insulin treatment alter fracture risk in older men with type 2 diabetes mellitus. *J Bone Miner Res*. 2019;34(11):2045–2051. doi: 10.1002/jbmr.3826. [PubMed: 31269274]
13. Huang HL, Pan CC, Hsiao YF, et al. Associations of body mass index and diabetes with hip fracture risk: A nationwide cohort study. *BMC Public Health*. 2018;18(1):1325–y. doi: 10.1186/s12889-018-6230-y. [PubMed: 30497430]

14. Compston JE, Watts NB, Chapurlat R, et al. Obesity is not protective against fracture in postmenopausal women: GLOW. *Am J Med.* 2011;124(11):1043–1050. doi: 10.1016/j.amjmed.2011.06.013. [PubMed: 22017783]
15. Wolverson D, Blair MM. Fracture risk associated with common medications used in treating type 2 diabetes mellitus. *Am J Health Syst Pharm.* 2017;74(15):1143–1151. doi: 10.2146/ajhp160319. [PubMed: 28743778]
16. Cheng L, Li YY, Hu W, et al. Risk of bone fracture associated with sodium-glucose cotransporter-2 inhibitor treatment: A meta-analysis of randomized controlled trials. *Diabetes Metab.* 2019;45(5):436–445. doi: S1262–3636(19)30025–4 [pii]. [PubMed: 30738154]
17. Hidayat K, Du X, Wu MJ, Shi BM. The use of metformin, insulin, sulphonylureas, and thiazolidinediones and the risk of fracture: Systematic review and meta-analysis of observational studies. *Obes Rev.* 2019;20(10):1494–1503. doi: 10.1111/obr.12885. [PubMed: 31250977]
18. Hofer SE, Schwandt A, Holl RW, Austrian/German DPV Initiative. Standardized documentation in pediatric diabetology: Experience from Austria and Germany. *J Diabetes Sci Technol.* 2016;10(5):1042–1049. doi: 10.1177/1932296816658057. [PubMed: 27381028]
19. Rosenbauer J, Dost A, Karges B, et al. Improved metabolic control in children and adolescents with type 1 diabetes: A trend analysis using prospective multicenter data from Germany and Austria. *Diabetes Care.* 2012;35(1):80–86. doi: 10.2337/dc11-0993. [PubMed: 22074726]
20. Baltrusaitis SL, Grabarczyk T. Glycemic control and 10-year odds of all-cause fractures in elderly veterans with type 2 diabetes. *Diabetes Res Clin Pract.* 2019;151:46–55. doi: S0168–8227(18)31082–9 [pii]. [PubMed: 30904745]
21. Vavanikunnel J, Charlier S, Becker C, et al. Association between glycemic control and risk of fracture in diabetic patients: A nested case-control study. *J Clin Endocrinol Metab.* 2019;104(5):1645–1654. doi: 10.1210/je.2018-01879. [PubMed: 30657918]
22. Cutrim DM, Pereira FA, de Paula FJ, Foss MC. Lack of relationship between glycemic control and bone mineral density in type 2 diabetes mellitus. *Braz J Med Biol Res.* 2007;40(2):221–227. doi: S0100–879X2007000200008. [PubMed: 17273658]
23. Yu S, Fu AZ, Engel SS, Shankar RR, Radican L. Association between hypoglycemia risk and hemoglobin A1C in patients with type 2 diabetes mellitus. *Curr Med Res Opin.* 2016;32(8):1409–1416. doi: 10.1080/03007995.2016.1176017. [PubMed: 27053004]
24. Chiba Y, Kimbara Y, Kadera R, et al. Risk factors associated with falls in elderly patients with type 2 diabetes. *J Diabetes Complications.* 2015;29(7):898–902. doi: 10.1016/j.jdiacomp.2015.05.016. [PubMed: 26122285]
25. Ntouva A, Toulis KA, Keerthy D, et al. Hypoglycaemia is associated with increased risk of fractures in patients with type 2 diabetes mellitus: A cohort study. *Eur J Endocrinol.* 2019;180(1):51–58. doi: 10.1530/EJE-18-0458. [PubMed: 30400051]
26. Hung YC, Lin CC, Chen HJ, et al. Severe hypoglycemia and hip fracture in patients with type 2 diabetes: A nationwide population-based cohort study. *Osteoporos Int.* 2017;28(7):2053–2060. doi: 10.1007/s00198-017-4021-4. [PubMed: 28374044]
27. Benoit SR, Hora I, Pasquel FJ, Gregg EW, Albright AL, Imperatore G. Trends in emergency department visits and inpatient admissions for hyperglycemic crises in adults with diabetes, United States 2006–2015. *Diabetes Care.* 2020. doi: 10.1007/dc192449.
28. Zhong VW, Juhaeri J, Mayer-Davis EJ. Trends in hospital admission for diabetic ketoacidosis in adults with type 1 and type 2 diabetes in England, 1998–2013: A retrospective cohort study. *Diabetes Care.* 2018;41(9):1870–1877. doi: 10.2337/dc17-1583. [PubMed: 29386248]
29. Barski L, Nevzorov R, Jotkowitz A, et al. Comparison of diabetic ketoacidosis in patients with type-1 and type-2 diabetes mellitus. *Am J Med Sci.* 2013;345(4):326–330. doi: S0002–9629(15)30697–2. [PubMed: 23377164]
30. Misra S, Oliver NS. Diabetic ketoacidosis in adults. *BMJ.* 2015;351:h5660. doi: 10.1136/bmj.h5660. [PubMed: 26510442]
31. Berndt M, Lehnert H. Diabetische ketoazidose. *Diabetologe.* 2014;10(8):638–644. doi: 10.1007/s11428-014-1266-9.

32. Sogaard AJ, Ranhoff AH, Meyer HE, et al. The association between alcohol consumption and risk of hip fracture differs by age and gender in cohort of norway: A NOREPOS study. *Osteoporos Int.* 2018;29(11):2457–2467. doi: 10.1007/s00198-018-4627-1. [PubMed: 30006884]
33. Zhang X, Yu Z, Yu M, Qu X. Alcohol consumption and hip fracture risk. *Osteoporos Int.* 2015;26(2):531–542. doi: 10.1007/s00198-014-2879-y. [PubMed: 25266483]
34. Patoulas D, Manafis A, Mitas C, et al. Sodium-glucose cotransporter 2 inhibitors and the risk of diabetic ketoacidosis; from pathophysiology to clinical practice. *Cardiovasc Hematol Disord Drug Targets.* 2018;18(2):139–146. doi: 10.2174/1871529X18666180206123149. [PubMed: 29412120]
35. Sharma PV, Jobanputra YB, Lewin K, Bagatell S, Lichtstein DM. Diabetic ketoacidosis in patients with type 2 diabetes on sodium-glucose cotransporter-2 inhibitors - A case series. *Rev Recent Clin Trials.* 2018;13(2):156–160. doi: 10.2174/1574887113666180314101436. [PubMed: 29542418]
36. Inagaki N, Kondo K, Yoshinari T, Kuki H. Efficacy and safety of canagliflozin alone or as add-on to other oral antihyperglycemic drugs in japanese patients with type 2 diabetes: A 52-week open-label study. *J Diabetes Investig.* 2015;6(2):210–218. doi: 10.1111/jdi.12266.
37. Silbert R, Salcido-Montenegro A, Rodriguez-Gutierrez R, Katabi A, McCoy RG. Hypoglycemia among patients with type 2 diabetes: Epidemiology, risk factors, and prevention strategies. *Curr Diab Rep.* 2018;18(8):53–0. doi: 10.1007/s11892-018-1018-0. [PubMed: 29931579]
38. Schloot NC, Haupt A, Schutt M, et al. Risk of severe hypoglycemia in sulfonylurea-treated patients from diabetes centers in germany/austria: How big is the problem? which patients are at risk? *Diabetes Metab Res Rev.* 2016;32(3):316–324. doi: 10.1002/dmrr.2722. [PubMed: 26409039]
39. Li X, Li T, Cheng Y, et al. Effects of SGLT2 inhibitors on fractures and bone mineral density in type 2 diabetes: An updated meta-analysis. *Diabetes Metab Res Rev.* 2019;35(7):e3170. doi: 10.1002/dmrr.3170. [PubMed: 30983141]
40. Hidayat K, Du X, Shi BM. Risk of fracture with dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors in real-world use: Systematic review and meta-analysis of observational studies. *Osteoporos Int.* 2019;30(10):1923–1940. doi: 10.1007/s00198-019-04968-x. [PubMed: 31134305]
41. Meisinger C, Wildner M, Stieber J, Heier M, Sangha O, Doring A. Epidemiology of limb fractures. *Orthopade.* 2002;31(1):92–99. doi: 10.1007/s132-002-8281-x. [PubMed: 11963475]
42. Bohn B, Bohn B, Bramlage P, et al. Welche patienten mit typ-2-diabetes bekommen neue antidiabetika? *Diabetologie.* 2019;15(2):96–103. doi: 10.1007/s11428-018-0411-2.
43. Kaneko M, Narukawa M. Effects of sodium-glucose cotransporter 2 inhibitors on amputation, bone fracture, and cardiovascular outcomes in patients with type 2 diabetes mellitus using an alternative measure to the hazard ratio. *Clin Drug Investig.* 2019;39(2):179–186. doi: 10.1007/s40261-018-0731-4.
44. de Jong MA, Petrykiv SI, Laverman GD, et al. Effects of dapagliflozin on circulating markers of phosphate homeostasis. *Clin J Am Soc Nephrol.* 2019;14(1):66–73. doi: 10.2215/CJN.04530418. [PubMed: 30559106]
45. Bushinsky DA, Frick KK. The effects of acid on bone. *Curr Opin Nephrol Hypertens.* 2000;9(4):369–379. doi: 10.1097/00041552-200007000-00008. [PubMed: 10926173]

Highlights

- Fracture risk among adults with T2D is associated with low HbA1c
- SGLT2-use, especially in women, is related to bone fractures in T2D
- The relation of BMI to fracture risk varies between fracture sites

Figure 1. Inclusion and exclusion criteria and group formation

Fracture group = patients with a documented fracture during the last 12 months; Control group = patients who never had a documented fracture; Previous fracture = patients that had a documented fracture that did not occur during the last 12 months or that was only documented as “status post” with unknown time-lag; DPV = diabetes prospective follow-up registry.

Figure 2. Percentage of patients with fractures at certain sites in relation to HbA1c. Whole cohort and stratified by sex. Results from adjusted regression models.

Data are shown as % of patients with fractures [SD] adjusted for age, sex, diabetes duration and BMI. HbA1c = haemoglobin A1c; LL = lower limb; UL = upper limb.

Figure 3. Percentage of patients with fractures at certain sites in relation to BMI. Whole cohort and stratified by sex. Results from adjusted regression models.

Data are shown as % of patients with fractures [SD] adjusted for age, sex and diabetes duration. BMI = body-mass index; LL = lower limb; UL = upper limb.

Table 1.

Baseline characteristics of fracture group compared to control group. Entire cohort and stratified by sex.

Characteristic	All		Female		Male	
	Control group	Fracture group	Control group	Fracture group	Control group	Fracture group
N (%)	349,287	4,821 (1.4)	165,538	3,025 (1.8)	183,749	1,796 (1.0)
Sex [% female]	47.4	62.7				
Age [y]	71.6 [63.2; 78.8]	77.8 [69.7; 83.4]**	73.6 [65.2; 80.7]	79.8 [73.0; 85.0]**	69.8 [61.8; 77.0]	73.7 [65.7; 80.7]**
Diabetes duration [y]	9.2 [3.5; 15.8]	11.5 [6.6; 18.8]**	9.6 [3.7; 16.3]	11.7 [6.9; 18.9]**	8.8 [3.2; 15.5]	11.3 [6.3; 18.6]**
Height [cm]	168 [162; 175]	166 [160; 173]	162 [158; 167]	162 [158; 167]	175 [170; 180]	175 [170; 180]
Weight [kg]	84.7 [73.0; 98.0]	79.0 [67.3; 92.0]**	79.0 [68.0; 92.0]	74.0 [64.0; 86.8]**	89.2 [79.0; 102.0]	87.0 [76.9; 100.0]**
BMI [kg/m ²]	29.5 [26.0; 33.8]	28.2 [24.9; 32.4]**	30.0 [26.0; 34.7]	28.1 [24.6; 32.5]**	29.2 [26.1; 33.1]	28.4 [25.4; 32.1]**
HbA1c MOM-DCCT [%]	7.1 [6.3; 8.3]	6.8 [6.1; 7.9]**	7.1 [6.3; 8.3]	6.8 [6.1; 7.8]**	7.1 [6.3; 8.4]	6.9 [6.2; 7.9]**
HbA1c MOM-DCCT [mmol/mol]	54 [45; 68]	51 [43; 63]**	54 [45; 67]	51 [43; 62]**	54 [45; 68]	52 [44; 63]**
Smokers [%]	11.8	8.2**	8.2	5.5**	15.0	13.0
Alcohol abuse [%]	3.0	5.1**	1.2	2.7**	4.7	9.2**
Insulin therapy [%]	50.0	51.1	50.1	52.6*	49.8	48.6
SGLT2i therapy [%]	5.7	5.6	4.4	5.7	6.8	5.5
Glinide/sulfonylurea therapy [%]	8.5	8.0	8.6	8.4	8.5	7.2
Other OADs therapy [%]	16.6	14.6**	15.9	14.1*	17.2	15.4
Lifestyle therapy [%]	23.9	25.5	24.6	24.0	23.3	28.0**

Data are presented as median [lower quartile; upper quartile] or %

* indicates a *p*-value <0.05 between fracture group and control group

** indicates a *p*-value <0.01 between fracture group and control group

Fracture group = patients that had a documented fracture during the last 12 months; Control group = patients that never had a documented fracture; BMI = bodymass-index; HbA1c = haemoglobin A1c; SGLT2i = sodium-glucose transport protein 2 inhibitors; OAD-others = patients treated with any oral antidiabetic medication (except: glinides, sulphonylurea, SGLT2i).

Table 2.

Percentage of patients with fractures at any site stratified by diabetes-related parameters adjusted for demographics

Confounder	Sub-groups				p-value	p-value ^a
	<25	>=25-30	>=30-35	>=35		
BMI						
N (all)	57,109	107,988	82,332	63,055		
all	1.24 [1.16-1.33]	1.06 [0.99-1.12]	0.94 [0.88-1.01]	0.90 [0.83-0.98]	p < 0.001	p < 0.001
female	1.70 [1.57-1.85]	1.46 [1.35-1.57]	1.22 [1.12-1.33]	1.23 [1.11-1.35]	p < 0.001	p < 0.001
male	0.92 [0.82-1.04]	0.78 [0.72-0.85]	0.77 [0.69-0.85]	0.70 [0.61-0.81]	p = 0.004	p = 0.026
HbA1c						
N (all)	101,998	6.5-9%	>9%			
all	1.15 [1.08-1.22]	0.92 [0.87-0.97]	0.73 [0.66-0.80]		p < 0.001	p < 0.001
female	1.55 [1.44-1.67]	1.21 [1.13-1.29]	0.94 [0.83-1.07]		p < 0.001	p < 0.001
male	0.87 [0.79-0.95]	0.73 [0.67-0.79]	0.57 [0.49-0.67]		p < 0.001	p < 0.001
Severe hypoglycaemia						
N (all)	334,514	1 event	> 1 event			
all	0.95 [0.92-0.99]	0.81 [0.68-0.97]	0.91 [0.65-1.28]		p = 0.158	p = 0.788
female	1.27 [1.21-1.34]	0.97 [0.77-1.21]	1.25 [0.83-1.89]		p = 0.083	p = 0.497
male	0.74 [0.69-0.78]	0.77 [0.58-1.04]	0.66 [0.36-1.19]		p = 0.973	p = 1.000
Hypoglycaemic coma						
N (all)	339,346	1 event	> 1 event			
all	0.95 [0.91-0.99]	0.81 [0.66-0.99]	2.34 [1.43-3.83]		p = 0.799	p = 1.000
female	1.27 [1.20-1.34]	0.98 [0.76-1.27]	3.48 [1.96-6.12]		p = 0.853	p = 1.000
male	0.74 [0.69-0.78]	0.75 [0.53-1.06]	1.38 [0.51-3.65]		p = 0.514	p = 1.000
DKA						
N (all)	345,816	> 1 event				
all	0.94 [0.91-0.98]	2.11 [1.53-2.88]			p < 0.001	p < 0.001
female	1.26 [1.19-1.33]	2.67 [1.80-3.94]			p < 0.001	p = 0.002
male	0.73 [0.69-0.78]	1.78 [1.05-2.98]			p = 0.001	p = 0.008
Therapy						
N (all)	Glin./Sulfn.	Insulin	Lifestyle	SGLT2i	OAD-others	
	27,071	176,974	90,448	3,204	56,411	

Confounder	Sub-groups			p-value	p-value ^a
all	0.76 [0.67–0.87]	0.90 [0.85–0.95]	1.10 [1.02–1.18]	1.46 [1.04–2.04]	0.98 [0.89–1.07]
female	1.06 [0.90–1.25]	1.19 [1.11–1.28]	1.40 [1.27–1.54]	2.53 [1.61–3.93]	1.33 [1.19–1.50]
male	0.54 [0.43–0.67]	0.70 [0.64–0.76]	0.91 [0.81–1.03]	0.87 [0.52–1.44]	0.74 [0.64–0.85]

All data are shown as % of patients with fractures [lower confidence interval - upper confidence interval] adjusted for age, sex, diabetes duration, BMI and HbA1c (except the regression model for BMI). Numbers in bold face represent sub-groups that revealed significantly ($p < 0.05$) more patients with fractures than at least one other subgroup. BMI = body-mass-index; HbA1c = haemoglobin A1c; DKA = diabetic ketoacidosis; Glin. = glinides; Sulfn. = sulphonylurea; SGLT2i = sodiumglucose transport protein 2 inhibitors; OAD-others = patients treated with any oral antidiabetic medication (except: glinides, sulphonylurea, SGLT2i).

^a p-value additionally adjusted for multiple comparisons