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ORIGINAL RESEARCH

Relationship Between α-Glucosidase Inhibitors Application and Bone Mineral Density in Chinese Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study

Xiumei Luo[1,2], Shangjian Li[1,2], Ning Chen[1,2]

[1]Department of Endocrinology, Fudan University Zhongshan Hospital Xiamen Branch, Xiamen, Fujian, People's Republic of China; [2]Xiamen Osteoporosis Specialized Prevention and Treatment Center, Xiamen, Fujian, People's Republic of China

Correspondence: Ning Chen, Department of Endocrinology, Zhongshan Hospital (Xiamen), Fudan University, No. 668 Jinhu Road, Xiamen, 361000, People's Republic of China, Tel/Fax +86-0592-3569583, Email chen.ning@zsxmhospital.com

Purpose: To investigate the correlation between α-glycosidase inhibitors (AGIs) and bone mineral density (BMD) in patients with type 2 diabetes mellitus (T2DM).

Patients and Methods: A total of 251 patients with T2DM admitted to the Zhongshan Hospital, Fudan University (Xiamen Branch) from September 2018 to September 2020 were enrolled. Baseline information of patients was analyzed according to different BMD subgroups. Clinical characteristics and BMD were compared between AGIs Group (n = 58) and non-AGIs group (n = 193). Multiple linear regression model was used to examine the relationship between AGIs application and BMD.

Results: The lower BMD group showed the characteristics of older age, longer duration of diabetes, lower body mass index (BMI) and estradiol (E2). In the AGIs group, the proportion of females, duration of diabetes, incidence of diabetic peripheral vascular disease and the use of sulfonylureas were significantly higher than those in the non-AGIs group ($p < 0.05$), the results of HbA1c, TC, TG, LDL, FT3, FT4 were opposite ($p < 0.05$). Compared with the non-AGIs group, the BMD of femoral neck and lumbar spine in the AGIs group was significantly decreased, FRAX score and the prevalence of osteoporosis were remarkably increased, accompanied by a decrease in β-CTX and P1NP level. Multivariate linear regression analysis showed a significant negative correlation between AGIs and lumbar BMD after adjustment for potential confounding variables (β = −0.053, 95% CI −0.100~0.006, P = 0.029).

Conclusion: This study indicates that the use of AGIs in patients with T2DM is significantly associated with an increased risk of BMD decline, osteoporosis, and fracture.

Keywords: type 2 diabetes mellitus, α-glucosidase inhibitor, BMD, osteoporosis

Introduction

The prevalence of diabetes is increasing globally. According to IDF Diabetes Atlas (11th edition), the number of adults aged 20–79 with diabetes worldwide reached 589 million in 2024 and is expected to rise to 853 million by 2050, with 90% cases being type 2 diabetes mellitus (T2DM).[1] Compared with healthy individuals, patients with T2DM have an increased risk of developing osteoporosis and related fractures (such as hip, spinal, or even any site),[2,3] which may be related to insulin resistance and poor glycemic control,[4] inflammation,[5] hyperosmotic diuresis triggering the loss of calcium and phosphorus, and the impact of hypoglycemic drugs,[6] and other factors that lead to the deterioration of the bone micro-environment. The influence of hypoglycemic drugs on bone mineral density (BMD) is intricately linked to the particular drug in question.[6–11] Several hypoglycemic drugs, such as rosiglitazone[12–15] and canagliflozin,[16] have been shown to adversely affect bone health. Since T2DM patients require the use of hypoglycemic drugs for most of the disease process, the influences of different classes of hypoglycemic drugs on BMD and fracture risk need to be carefully evaluated.

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China is the country with the most extensive use of α-glucosidase inhibitors (AGIs) worldwide.[17] The results of previous researches on the of AGIs on bone mass are extremely inconsistent, and the approaches used to detect and evaluate bone metabolism are often one-sided, so the effects of AGIs on bone health need to be further investigated.

In this study, BMD was measured by dual-energy X-ray absorptiometry (DXA), and the levels of bone metabolism biomarker and FRAX scores for fracture risk were combined to comprehensively analyze the impacts of AGIs application on the BMD and fracture risk of T2DM patients.

Materials and Methods

Study Population

A total of 251 patients with T2DM admitted to the Zhongshan Hospital, Fudan University (Xiamen Branch) from September 2018 to September 2020 were enrolled. All patients met the 2018 American Diabetes Association's (ADA's) criteria for the diagnosis and classification of diabetes and were negative for serum glutamic acid decarboxylase antibodies, including 149 males and 102 females, and all patients underwent DXA scan. Medical records of the patients were reviewed to confirm their medication status. According to whether AGIs (including acarbose and voglibose) were used at admission, the patients were divided into the AGIs group and the Non-AGIs group. In addition, the AGIs group was required to have received the drug for at least 3 months prior to enrollment, while the non-AGIs group had no history of relevant drug use within 3 months prior to enrollment.

Exclusion criteria include: (1) previously and currently diagnosed with type 1 diabetes, secondary diabetes, and special type diabetes; (2) age ≤ 18 years; (3) estimated glomerular filtration rate (eGFR) < 60 mL/(min ·1.73m2); (4) use of estrogen, progestogen, glucocorticoids, bisphosphonates, desmuximab and other agents that may affect BMD within the past six months; (5) presence of any disease prone to secondary osteoporosis, such as hyperparathyroidism, multiple myeloma, autoimmune diseases; (6) long-term bed rest leading to bone loss; (7) metal implants affecting BMD detection; (8) presence of psychiatric disease, infection or stress state, severe organ dysfunction, and any other conditions considering unsuitable for inclusion.

Information and Data Collection

Demographic and clinical information for all patients were obtained from the medical records and interviews, including age, gender, smoking history, drinking history, duration of T2DM, diabetic complications and hypoglycemic drug use. Height, weight, waist circumference, hip circumference, and blood pressure data were measured, and body mass index (BMI) and waist-to-hip ratio were calculated.

Laboratory indicators were based on early-morning venous blood after an overnight fast of 8 hours, and the detection items included: (1) Bone turnover markers: carboxy-terminal β-crosslinking telopeptide of type 1 collagen (β-CTX), type I procollagen amino-terminal peptide (P1NP), osteocalcin (OC) and 25-hydroxy vitamin D3 (25OHD). (2) Blood biochemical indicators: triacylglycerol (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), calcium (Ca), phosphorus (P), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), uric acid (UA), blood creatinine (CREA) and eGFR. (3) Glycometabolic indicators: glycated hemoglobin (HbA1c), fasting blood glucose (FBG), fasting insulin, and the HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) was calculated according to the formula: fasting blood glucose ($mmol \cdot L^{-1}$) × fasting insulin ($\mu U \cdot mL^{-1}$)/22.5.[18] (4) Hormone indicators: thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), parathyroid hormone (PTH), estradiol (E2). Above indicators were determined by using the same methods as previously described.[19]

Definition of Osteoporosis and Assessment of Fracture Risk

Based on the Chinese guidelines for osteoporosis (2022 version),[20] the definition of osteoporosis should include any one of the following three items: ① Minimum T-score of BMD ≤−2.5. ② Hip or vertebral fragility fractures, regardless of

BMD measurement. ③ Fragility fractures of the proximal humerus, pelvis, or distal forearm with −2.5 < T-score < −1.0. BMD was measured by DXA (QDR4500A, Hologic Inc., Waltham MA, USA) at the femoral neck and lumbar spine (L1-L4), with a dedicated technician from the Department Medical Imaging responsible for the assessments. Fracture Risk Assessment Tool (FRAX) score[21] was used to assess the 10-year probability of a major osteoporotic fracture and hip fracture.

Statistical Analysis

Data conforming to the normal distribution were expressed as mean ± standard deviation (SD), and *T*-test is used for statistical difference analysis. Non-normally distributed data were represented in terms of the median (P25, P75), and *T*-test was applied after the data was transformed into a normal distribution. Non-parametric test was conducted for data that could not be converted to normal. Group differences between the BMD tertiles were analyzed by ANOVA. Count data were expressed as n (%) and χ^2 test was used. Multiple linear regression analysis was applied to explore the influence of AGIs on bone mass, with BMD as the dependent variable and related factors as covariates. Data were analyzed by SPSS 27.0 software, and statistical graphs were plotted by GraphPad Prism 9.0. $P < 0.5$ was considered statistically significant.

Results

Demographic and Clinical Characteristics of the Population Stratified by BMD

The patients were divided into groups by tertiles of femoral neck BMD and lumbar spine total BMD, respectively. The demographic and clinical characteristics of different BMD patients were compared in Table 1. In all groups, patients with lower BMI and E2 levels tended to have lower BMD. In the femoral neck BMD subgroups, the decrease of BMD was

Table 1 Demographic and Clinical Characteristics of the Population Stratified by BMD

	Femoral Neck BMD				Lumbar Spine Total BMD			
	<0.67(n = 81)	0.67~0.79(n = 85)	>0.79(n = 85)	P	<0.88(n = 84)	0.88~1.01(n = 82)	>1.01(n = 85)	P
Age (years)	61.52 ± 9.43	55.80 ± 11.98	55.90 ± 12.83	0.002	58.19 ± 12.22	55.35 ± 11.34	59.72 ± 11.45	0.052
Gender, n (%)				0.992				0.996
Male	48 (59.3)	50 (58.8)	51 (60.0)		50(59.5)	49(59.8)	52(61.2)	
Female	33 (40.7)	35 (41.2)	34 (40.0)		34(40.5)	33(40.2)	33(38.8)	
SBP (mmHg)	132.20 ± 16.03	132.98 ± 17.46	129.06 ± 17.09	0.291	128.84 ± 15.82	131.34 ± 16.98	133.21 ± 17.41	0.244
HBP (mmHg)	82.09 ± 9.43	83.27 ± 10.04	81.28 ± 10.45	0.440	82.02 ± 9.06	82.71 ± 10.28	81.38 ± 10.54	0.691
BMI (kg/m2)	22.8(21.3, 25.2)	25.5(22.8, 27.3)	25.5(23.2, 28.8)	<0.001	22.9(21.3, 25.2)	25.2(22.6, 26.9)	26.0(23.2, 29.1)	<0.001
Waist-to-hip ratio	0.93 ± 0.06	0.95 ± 0.06	0.94 ± 0.07	0.118	0.93 ± 0.06	0.94 ± 0.06	0.94 ± 0.07	0.355
Diabetes duration (years)	8.6(2.8, 13.5)	4.7(1.1, 10.8)	6.0(0.9, 9.8)	0.011	7.3(1.5, 12.3)	7.2(2.3,11.8)	5.1(0.9, 9.8)	0.908
Complications of diabetes, n (%)								
Diabetic peripheral vascular disease	63(77.8)	56(65.8)	52(61.2)	0.139	55(65.4)	59(71.9)	57(67.1)	0.648
Diabetic nephropathy	13(16.0)	13(15.3)	14(16.5)	0.759	12(13.6)	14(17.1)	15(17.6)	0.325
Diabetic retinopathy	26(32.1)	24(28.2)	23(27.1)	0.560	22(26.2)	24(29.3)	27(31.7)	0.610
Diabetic peripheral neuropathy	12(14.8)	13(15.3)	10(11.7)	0.802	11(12.3)	15(18.3)	11(12.9)	0.492
Diabetes treatment, n (%)								
Insulin	29(35.8)	25(29.4)	26(30.6)	0.516	25(29.6)	24(29.2)	29(34.1)	0.509
Metformin	36(44.4)	47(55.3)	40(47.1)	0.286	40(48.1)	47(57.3)	39(45.9)	0.297
TZD	5(6.2)	5(5.9)	6(7.1)	0.935	7(8.3)	4(4.9)	5(5.8)	0.262
GLP-1RA	0(0.0)	0(0.0)	1(1.2)	0.366	0(0.0)	0(0.0)	1(1.2)	0.382
SGLT2i	0(0.0)	1(1.2)	0(0.0)	0.373	1(1.2)	0(0.0)	0(0.0)	0.355
DPP4i	18(22.2)	18(21.2)	14(16.5)	0.392	14(16.6)	17(20.7)	19(22.3)	0.573
Sulfonylurea	23(28.4)	28(32.9)	29(34.1)	0.384	28(33.3)	22(26.8)	30(35.2)	0.473
Glinide	11(13.5)	5(5.9)	6(7.0)	0.139	8(9.5)	5(6.1)	10(11.7)	0.153
AGI	24(29.6)	17(20.0)	17(20.0)	0.182	27(32.1)	12(14.6)	19(22.4)	0.018

(*Continued*)

Table 1 (Continued).

	Femoral Neck BMD				Lumbar Spine Total BMD			
	<0.67(n = 81)	0.67~0.79(n = 85)	>0.79(n = 85)	P	<0.88(n = 84)	0.88~1.01(n = 82)	>1.01(n = 85)	P
Cardiovascular disease, n (%)	9(11.1)	8(9.4)	9(10.6)	0.703	9(10.7)	10(12.2)	8(9.4)	0.583
Smoking history, n (%)	32 (39.5)	31 (36.4)	26 (30.6)	0.436	29(34.5)	27(32.9)	36(42.3)	0.335
Drinking history, n (%)	18 (22.2)	23 (27.1)	21 (24.7)	0.717	19(22.2)	27(32.9)	19(22.4)	0.197
HbA1c (%)	8.7(7.2,10.4)	9.0(7.8,10.5)	8.7(7.0,10.8)	0.771	8.9(7.2, 10.4)	8.9(7.5,10.6)	8.7(7.0,10.8)	0.498
HOMA-IR	2.5(1.4, 3.9)	2.5(1.6, 3.7)	3.0(1.6, 4.7)	0.188	2.5(1.5, 3.8)	2.4(1.6, 3.6)	3.0(1.6, 4.9)	0.633
TC (mmol/L)	4.3(3.7, 5.4)	4.3(3.8, 5.0)	4.3(3.9, 5.1)	0.905	4.4(3.6, 5.5)	4.4(3.8, 5.1)	4.3(3.9, 5.0)	0.586
TG (mmol/L)	1.4(1.0, 1.9)	1.7(1.2, 2.4)	1.6(1.2, 2.4)	0.277	1.5(1.0, 1.9)	1.7(1.2, 2.7)	1.6(1.2, 2.4)	0.447
LDL (mmol/L)	2.48 ± 0.95	2.53 ± 1.02	2.69 ± 1.03	0.009	2.51 ± 0.93	2.53 ± 1.06	2.59 ± 1.01	0.864
HDL (mmol/L)	1.1(0.9, 1.3)	1.1(0.9, 1.3)	1.1(0.9,1.3)	0.341	1.1(0.9, 1.4)	1.1(0.9, 1.3)	1.1(0.9, 1.3)	0.141
ALT (U/L)	18.0(14.0, 27.0)	22.0(14.0, 33.1)	19.0(13.0, 32.5)	0.896	20.5(14.3, 27.8)	21.0(14.0, 34.0)	19.0(14.0, 26.0)	0.564
AST (U/L)	17.5(14.0, 21.7)	17.0(13.0, 23.0)	17.0(14.0, 24.0)	0.966	18.0(14.0, 23.8)	17.0(13.0, 25.0)	17.0(14.0, 23.0)	0.928
BUN (mmol/L)	6.19 ± 2.12	5.73 ± 1.98	5.80 ± 2.69	0.382	5.82 ± 2.10	5.87 ± 1.84	5.92 ± 2.75	0.958
CREA (μmol/L)	74.63 ± 22.89	74.59 ± 25.42	78.19 ± 30.82	0.715	70.00 ± 19.66	76.11 ± 22.88	81.20 ± 45.15	0.078
eGFR (mL/min/1.73m2)	87.59 ± 19.20	92.39 ± 20.16	91.26 ± 21.87	0.297	93.55 ± 17.11	90.27 ± 19.44	87.46 ± 23.67	0.159
UA (μmol/L)	335.49 ± 95.83	352.14 ± 88.55	366.15 ± 106.45	0.136	326.91 ± 89.79	364.49 ± 102.55	363.46 ± 94.51	0.019
TSH (uIU/mL)	1.9(1.3, 2.5)	1.8(1.3, 3.1)	2.0(1.2, 3.0)	0.513	2.0(1.2, 2.8)	1.8(1.3, 2.8)	1.9(1.1, 3.0)	0.362
FT3 (pmol/L)	4.3(3.9, 4.8)	4.3(3.9, 4.8)	4.2(3.9, 4.6)	0.804	4.3(3.9, 4.8)	4.3(3.9, 4.8)	4.2(3.9, 4.6)	0.439
FT4 (pmol/L)	16.62 ± 2.31	17.17 ± 2.88	16.55 ± 2.76	0.011	16.66 ± 2.45	16.89 ± 3.37	16.72 ± 2.12	0.848
E2 (pmol/L)	53.7(19.4, 98.8)	60.1(20.2, 105.9)	84.6(31.0,127.4)	0.013	54.4(19.6, 94.4)	60.2(19.9,104.9)	88.7(31.5,133.3)	<0.001
PTH (pg/mL)	35.3(27.5, 45.3)	32.9(26.4, 40.6)	34.3(25.9, 44.0)	0.499	35.5(27.5, 46.8)	31.8(26.6, 39.0)	35.0(25.8, 44.0)	0.435
Ca (mmol/L)	2.31 ± 0.11	2.33 ± 0.11	2.31 ± 0.11	0.506	2.31 ± 0.13	2.33 ± 0.09	2.30 ± 0.11	0.212
P (mmol/L)	1.19 ± 0.18	1.23 ± 0.17	1.26 ± 0.19	0.114	1.22 ± 0.17	1.27 ± 0.19	1.20 ± 0.17	0.018

Abbreviations: SBP, systolic blood pressure; HBP, diastolic blood pressure; BMI, body mass index; TZD, trazodone; GLP-1RA, glucagon-like peptide 1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor; DPP4i, dipeptidyl peptidase 4 inhibitor; AGI, α-glucosidase inhibitor; HbA1c, glycated hemoglobin; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; TC, total cholesterol; TG, triacylglycerol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CREA, blood creatinine; eGFR, estimated glomerular filtration rate; UA, uric acid; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; E2, estradiol; PTH, parathyroid hormone; Ca, blood calcium; P, Blood inorganic phosphorus.

accompanied by the increase of patient's age, the prolongation of diabetic course and the decline of LDL and FT4 levels ($P < 0.05$), and there were no significant differences in the use of hypoglycemic agents. However, in the lumbar spine BMD subgroups, the proportion of patients with AGIs application in the lowest BMD group was obviously higher and the uric acid level was notably lower than that in the other two groups ($P < 0.05$), while there were no marked deviations in age, diabetes course, LDL and FT4 levels among the groups. No striking differences between groups were found for any of the other analyzed indicators in both femoral neck BMD and lumbar spine BMD groups.

Comparison of Basic Data Between T2DM Patients with and without AGIs Application

Of the 251 T2DM patients included, 58 received AGIs therapy and 193 did not. The AGIs group consisted of 26 males and 32 females, and the non-AGIs group consisted of 123 males and 70 females. Table 2 showed that compared with the Non-AGIs group, the AGIs group had obvious higher proportion of female, longer diabetes course, more patients with concomitant diabetic peripheral vascular lesions, and sulfonylurea application, and had significant lower values of HbA1c, TC, TG, LDL, FT3, and FT4 (all $P < 0.05$). The remaining parameters between the two groups were not statistically significant.

Comparison of the Risk of Osteoporosis and Fracture Between the AGIs Group and the Non-AGIs Group

The comparison of BMD, FRAX score and prevalence of osteoporosis between AGIs group and Non-AGIs group were presented in Table 3. The results showed that the BMD of both femoral neck and lumbar spine were significantly lower and the FRAX score was notably higher in the AGIs group than those in the Non-AGIs group ($P < 0.05$), indicating

Table 2 Comparison of Basic Data Between Non-AGIs and AGIs Groups

	Non-AGIs Group (n = 193)	AGIs Group (n = 58)	P
Age (years)	56.07 ± 11.54	63.45 ± 10.43	0.308
Gender, n (%)			0.016
Male	123(63.7)	26(44.8)	
Female	70(36.3)	32(55.2)	
SBP (mmHg)	131.08 ± 17.30	131.67 ± 15.60	0.421
HBP (mmHg)	82.63 ± 10.29	80.05 ± 8.76	0.130
BMI (kg/m2)	24.61(22.58, 27.31)	23.59(21.41,27.09)	0.834
Diabetes duration (years)	5.0(1.00, 9.80)	9.0(4.72, 14.63)	<0.001
Complications of diabetes, n (%)			
Diabetic peripheral vascular disease	122(63.2)	50(86.2)	<0.001
Diabetic nephropathy	28(14.5)	13(22.4)	0.153
Diabetic retinopathy	59(30.6)	14(24.1)	0.538
Diabetic peripheral neuropathy	26(13.5)	11(19.0)	0.301
Diabetes treatment, n (%)			
Insulin	59(30.6)	21(36.2)	0.154
Metformin	93(48.2)	30(51.7)	0.163
TZD	11(5.6)	5(8.6)	0.425
GLP-1RA	1(0.0)	0(0.0)	0.583
SGLT2i	1(0.0)	0(0.0)	0.583
DPP4i	37(19.2)	13(22.4)	0.588
Sulfonylurea	55(28.5)	26(44.8)	0.020
Glinide	14(7.3)	8(13.8)	0.265
Cardiovascular disease, n (%)	15(7.8)	9(15.5)	0.079
Smoking history, n (%)	30(15.5)	9(15.5)	0.314
Drinking history, n (%)	54(28.0)	10(17.2)	0.100
HbA1c (%)	9.1(7.10, 10.92)	8.0(6.91, 9.62)	0.003
HOMA-IR	2.68(1.62, 4.10)	2.70(1.51, 4.56)	0.166
TC (mmol/L)	4.44(3.88, 5.41)	4.10(3.32, 4.87)	0.007
TG (mmol/L)	1.65(1.04, 2.47)	1.42(1.00, 1.81)	0.039
LDL (mmol/L)	2.65 ± 1.02	2.24 ± 0.88	0.006
HDL (mmol/L)	1.05(0.85, 1.25)	1.17(0.90, 1.36)	0.074
ALT (U/L)	19.00(14.00, 29.00)	20.50(14.00, 28.00)	0.922
AST (U/L)	17.00(14.00, 24.00)	18.00(13.00, 23.00)	0.900
BUN (mmol/L)	5.87 ± 2.29	5.91 ± 2.22	0.910
CREA (μmol/L)	76.54 ± 33.73	72.72 ± 24.34	0.425
eGFR (mL/min/1.73m2)	91.64 ± 20.63	86.38 ± 19.09	0.085
UA (μmol/L)	355.30 ± 98.33	340.69 ± 94.29	0.318
TSH (uIU/mL)	1.90(1.24, 2.83)	2.01(1.19, 2.91)	0.465
FT3 (pmol/L)	4.30(3.90,4.70)	4.1(3.60,4.40)	0.027
FT4 (pmol/L)	17.00 ± 2.72	15.94 ± 2.40	0.009
E2 (pmol/L)	74.60(29.20,111.10)	54.60(18.40,102.30)	0.096
PTH (pg/mL)	34.40(26.80, 42.20)	32.50(26.90, 38.40)	0.152
Ca (mmol/L)	2.32 ± 0.11	2.32 ± 0.12	0.853
P (mmol/L)	1.24 ± 0.18	1.21 ± 0.18	0.212

Abbreviations: SBP, systolic blood pressure; HBP, diastolic blood pressure; BMI, body mass index; TZD, trazodone; GLP-1RA, glucagon-like peptide 1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor; DPP4i, dipeptidyl peptidase 4 inhibitor; AGI, α-glucosidase inhibitor; HbA1c, glycated hemoglobin; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; TC, total cholesterol; TG, triacylglycerol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CREA, blood creatinine; eGFR, estimated glomerular filtration rate; UA, uric acid; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; E2, estradiol; PTH, parathyroid hormone; Ca, blood calcium; P, Blood inorganic phosphorus.

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Table 3 The Comparison of BMD, FRAX Score and Prevalence of Osteoporosis Between AGIs Group and Non-AGIs Group

	Non-AGIs Group (n = 193)	AGIs Group (n = 58)	P
Femoral neck BMD	0.744 ± 0.130	0.698 ± 0.128	0.022
Lumbar spine total BMD	0.961 ± 0.150	0.893 ± 0.191	0.005
FRAX score (Major osteoporotic)	2.2(1.5, 3.5)	2.8(1.7, 3.8)	0.003
FRAX score (Hip Fracture)	0.4(0.1, 1.1)	0.7(0.2, 1.3)	0.009
Osteoporosis, n (%)	31(16.1)	19(32.8)	0.008

a higher risk of severe osteoporotic fracture and hip fracture within 10 years. Meanwhile, the proportion of patients with osteoporosis was obviously higher in the AGIs group than in the Non-AGIs group ($P < 0.05$). Additionally, statistical analysis of bone turnover markers revealed that the β-CTX and P1NP levels in the AGIs group were significantly lower than those in the Non-AGIs group ($P < 0.01$), while no significant difference was observed in 25OHD and OC levels between the two groups (Figure 1), suggesting that the bone transformation rate in AGIs group was lower.

Correlation Between AGIs Application and BMD Level in T2DM Patients

In order to further explore the correlation between AGIs application and BMD in T2DM patients, a multiple linear regression analysis was conducted with BMD value as the dependent variable. Table 4 indicated a distinguish negative correlation between AGIs application and lumbar spine total BMD after adjusting for potential confounding variables (β = −0.053, 95% CI −0.100~-0.006, P = 0.029). However, there was no significant correlation between AGIs application and femoral neck BMD.

Discussion

With the increasingly serious aging of China's population, the prevalence of osteoporosis, as an age-related disease, is also ascending. It is worth noting that T2DM patients are more prone to fractures than non-T2DM patients, even at the same BMD levels.[2,3,22,23] Therefore, in the whole process of diabetes management, it is necessary to carefully evaluate the potential factors that promote the decline of bone mass in T2DM patients, especially those that can be avoided or changed, such as medication choice. This study used DXA to measure BMD levels in patients and the FRAX score to assess bone strength and the risk of fractures within 10 years. The findings revealed that BMD levels in T2DM patients were negatively correlated with the application of AGIs. Compared with the patients without AGIs use, patients with AGIs use had lower BMD values, higher incidence of osteoporosis, and higher FRAX scores, accompanied by the reduction of both bone turnover markers P1NP and β-CTX levels. Furthermore, AGIs application was identified as an independent risk factor for a decrease in lumbar BMD.

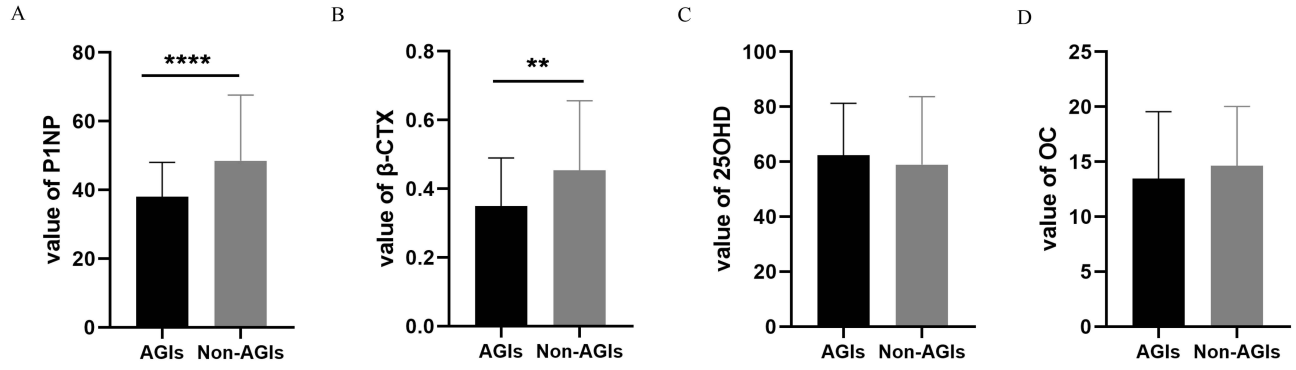

Figure 1 Bone turnover markers between AGIs group and Non-AGIs group.
Notes: (**A**) type I procollagen amino-terminal peptide (P1NP); (**B**) carboxy-terminal β-crosslinking telopeptide of type I collagen (β-CTX); (**C**) osteocalcin (OC); (**D**) 25-hydroxy vitamin D3 (25OHD). **P < 0.01, ****P < 0.0001.

Table 4 Multiple Linear Regression Analysis Evaluated the Association Between AGIs Application and BMD in T2DM Patients

	Lumbar Spine Total BMD		Femoral Neck BMD	
	β (95% CI)	P	β (95% CI)	P
Model-1 (n = 251)	−0.055(−0.101, −0.008)	0.023	−0.009(−0.045, 0.028)	0.646
Model-2 (n = 251)	−0.055(−0.100, −0.010)	0.016	−0.017(−0.051, 0.018)	0.341
Model-3 (n = 246)	−0.053(−0.100, −0.006)	0.029	−0.009(−0.045, 0.027)	0.636

Notes: Model 1 variables: age, gender, AGIs application. Model 2 variables: BMI, smoking history, alcohol consumption history, FT3, FT4, E2 and sulfonylurea application were adjusted on the basis of model 1. Model 3 variables: diabetes duration, diabetes-related complications, HOMA-IR and HbA1c were adjusted on the basis of model 2.

AGIs delay the digestion of starch and sucrose in the intestines by reversibly and competitively inhibiting pancreatic α-amylase and membrane-bound intestinal α-glucosidase, flattening the postprandial blood glucose excursions,[24] with high safety and no drug interaction. Current research on oral AGIs and bone health is limited. In 2021, a meta-analysis compared the fracture risks associated with various hypoglycemic drugs and found that voglibose reduced the risk of fractures in diabetic patients and was significantly beneficial than insulin, sodium-glucose cotransporter 2 inhibitors (SGLT2i), dipeptidyl peptidase 4 inhibitors (DPP4i), and some glucagon-like peptide 1 receptor agonists (GLP-1RAs) in terms of fracture.[25] In the same year, a double-blind, randomized clinical trial indicated that attenuating postprandial glycemic indices, with an AGI, markedly decreased postprandial bone resorption and could be explained by the rise in serum GLP-1,[26] suggesting that AGI may have bone-protective effects. However, a nationwide observational study in Japanese elderly with diabetes found AGI was related to increased hip fracture risk compared with metformin.[27] Additionally, a small sample clinical control study in 2023 demonstrated that treatment with acarbose reduced postprandial suppression of bone resorption in patients with T2DM.[28] Overall, the current evidence is inconclusive and conflicting regarding the effects of AGIs on bone metabolism and risk of fractures.

Based on the statistical results of 251 T2DM patients included in this study, we found that the use of AGIs was negatively correlated with the level of lumbar spine BMD and may increase the risk of osteoporosis and fracture. This result may be partially due to the longer duration of diabetes and more diabetic peripheral vascular lesions in the patients in AGIs-group, since previous studies had shown that T2DM complications were associated with a higher risk of fracture.[29] In a Danish case-control study, diabetic retinopathy (OR 2.1), kidney disease (OR 2.0), neuropathy (OR 1.9), and macrovascular complications (OR 1.9) were all associated with an increased risk of fracture30. Fracture events were also more common when T2DM persisted over 10 years.[30] In addition, the levels of HbA1c, FT3 and FT4 in AGIs group were significantly lower than those in Non-AGIs group, hinting that the reduction of BMD was not caused by worse blood glucose control,[31] hyperthyroidism,[32] and other adverse factors for bone. Although the proportion of female in AGIs group was higher than that in the Non-AGIs group, there was no significant difference between the two groups in age and E2 level. It should be noted that in terms of the types of hypoglycemic drugs, only one of the 251 patients used GLP-1RA because it was not widespread at that time. The use of sulfonylureas was higher in the AGIs group than in the Non-AGIs group, but the impact of sulfonylureas on bone mass remains unclarified. Previous studies showed a reduced incidence of fractures in patients treated with sulfonylureas,[33,34] while paradoxically, other studies suggested that sulfonylureas may increase the risk of falls and fractures by increasing hypoglycemia.[8,35]

To further clarify the bone conversion after AGIs use, we analyzed the levels of bone turnover markers and found that the levels of P1NP and β-CTX were significantly declined in the AGIs group, suggesting a lower bone transformation rate.

Existing researches have shown that in T2DM patients, AGIs regulate postprandial glucose and bone resorption by stimulating GLP-1 secretion and inhibiting DPP-4 to improve circulating GLP-1 levels,[36–38] and acarbose was found to have a positive effect on the intestinal microbiota.[39] Therefore, it is speculated that the alteration of intestinal microbiota and intestinal insulin may be related to the mechanism by which AGIs affect bone metabolism, but the above conclusions have not been fully verified and recognized.

More interestingly, we found that AGIs application was an independent risk factor for lumbar spine BMD reduction in T2DM patients, but there was no significant correlation with femoral neck BMD. It was speculated that this may be related to the different metabolic and bone composition characteristics of different skeletal sites. The lumbar spine is cancellous bone, which may be more prone to bone loss.

So far, there is insufficient research on the impacts of commonly used hypoglycemic drugs AGIs on bone metabolism. Our study provides more evidence for the effects of AGIs on bone mass in T2DM. We found that in clinically severe diabetic patients, the use of AGIs was associated with a decrease in BMD and potentially an increased the risk of osteoporosis and fractures, which may suggest caution in the use of AGIs among patients with T2DM patients and poor BMD. However, as a cross-sectional study, this study has several limitations: 1. The sample size is small; 2. As a single-center study, there is a selection bias; 3. There is a lack of data on the duration and dosage of AGIs used by patients, which limits further analysis, thus reducing its value. The effects and mechanisms of AGIs on bone metabolism require further large-sample and scientifically designed studies for validation.

Conclusion

This study indicates that the use of AGIs in patients with T2DM is significantly associated with an increased risk of reduced BMD, osteoporosis, and fracture.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author or the first author upon reasonable request.

Ethical Approval

This research was approved by the Ethics Committee of Xiamen Hospital, Zhongshan Hospital Affiliated to Fudan University on February 29, 2024 (No. B2024-014). All patients in this study provided informed written consent for inclusion. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration and its later amendments or comparable ethical standards.

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Author Contributions

Xiumei Luo: data curation, formal analysis, funding acquisition, investigation, resources, writing – original draft, writing – review and editing. Shangjian Li: data curation, formal analysis, investigation, validation, methodology, writing – original draft. Ning Chen: conceptualization, methodology, project administration, supervision, validation, writing – review and editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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