RESEARCH

GIPR rs10423928 and bone mineral density in postmenopausal women in Shanghai

Lizhi Zhang[1,2], **Jinwei He**[3], **Xiang Sun**[4], **Dongyue Pang**[2], **Jingjing Hu**[2] and **Bo Feng**[1]

[1]Department of Endocrinology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China
[2]Department of Endocrinology, Jiading Branch of Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[3]Department of Osteoporosis and Bone Disease, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China
[4]Shanghai Institute of Technology, Shanghai, China

Correspondence should be addressed to B Feng: fengbodfyy@tongji.edu.cn

Abstract

We demonstrated previously that there is a correlation between glucagon-like peptide-1 (GLP-1) single-nucleotide polymorphism (SNP) and bone mineral density in postmenopausal women. Both GLP-1 and glucose-dependent insulinotropic peptide are incretins. The glucose-dependent insulinotropic peptide receptor (GIPR) SNP rs10423928 has been extensively studied. However, it is not clear whether *GIPR* gene mutations affect bone metabolism. The aim of this study was to investigate the association between rs10423928 and bone mineral density in postmenopausal women in Shanghai. rs10423928 was detected in 884 postmenopausal women in Shanghai, and the correlation between the GIPR SNP and bone mineral density was assessed. The dominant T/T genotype of rs10423928 was found to be related to the bone mineral density of the femoral neck ($P = 0.035$). Overall, our findings indicate that the dominant T/T genotype of rs10423928 in postmenopausal women is significantly associated with a higher bone mineral density and that the T/T genotype exerts a bone-protective effect.

Key Words

- osteoporosis
- glucose-dependent insulinotropic peptide
- single-nucleotide polymorphism
- polymorphism
- haplotype
- bone mineral density

Endocrine Connections (2022) **11**, **e210583**

Introduction

Postmenopausal osteoporosis is related to aging and has serious health effects. Bone mineral density (BMD) is the most common diagnostic indicator of osteoporosis, and 60–80% of BMD variations are determined by genetic factors (1). Some drugs commonly used to regulate blood sugar, such as glucagon-like peptide-1 (GLP-1) receptor agonists and DPP-4 inhibitors (DPP-4is), can inhibit bone resorption and improve bone formation (2, 3, 4, 5, 6, 7). GLP-1 is a DPP-4 substrate; other substrates of DPP-4, such as glucose-dependent insulinotropic peptide (GIP) and GLP-2, can also affect bone metabolism, promote bone formation, or reduce bone resorption by osteoclasts (8, 9, 10, 11).

Glucose-dependent insulinotropic peptide (GIP) plays a biological role by binding to the corresponding GIP receptor (GIPR) on the cell surface. *GIPR* is located on chromosome 19 q13.3 and comprises 14 exons, having the size of approximately 14 kb (12). GIPR, which is widely expressed in various tissues and organs, is also expressed in extra-pancreatic cells, such as osteoblasts and the small intestine (13, 14). Mutations in *GIPR* may lead to abnormal GIPR expression and function, which may be related to the risk of osteoporosis. Furthermore, phenotypic differences in the human body and susceptibility to drugs or diseases may be related to single-nucleotide polymorphisms (SNPs). There are 13 SNPs in *GIPR*. Among them, rs10423928 has been studied extensively. It involves the replacement of thymine with an adenine base (T/A) (15). Research on rs10423928 mainly focuses on type 2 diabetes and impaired insulin secretion (16, 17). In this study, we screened the CHBS (Genetic Variation Database of Han Nationality Population in Beijing, China) for GIPR SNP rs10423928 using second-stage HapMap data (ftp://ftp.ncbi.nlm.nih.gov/hapmap/).

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0583

Table 1 Basic information of the patients enrolled in this study. Continuous variables with a normal distribution are represented by the mean ± s.d. (x ± s), and data with a non-normal distribution are represented by the median and interquartile range.

Characteristics	Age < 60 years (n = 224)	Age ≥ 60 years (n = 660)	*P*
Age (years)	54.9 ± 5.8	71.3 ± 7.4	0.00
Height (cm)	156.2 ± 5.2	152.0 ± 5.4	0.00
Weight (kg)	57.6 ± 8.4	55.2 ± 8.5	0.027
BMI (kg/m^2)	23.6 ± 3.3	23.9 ± 3.5	0.497
Blood calcium (mmol/L)	2.34 (2.27–2.40)	2.32 (2.26–2.39)	0.718
Blood phosphorus (mmol/L)	1.14 (1.03–1.23)	1.12 (1.01–1.23)	0.700
Albumin (g/L)	47.00 (46.00–49.00)	46.00 (44.00–48.00)	0.008
Alkaline phosphatase (U/L)	69.00 (56.00–80.00)	72.00 (60.00–90.00)	0.004
Creatinine (μmol/L)	54.00 (49.00–60.75)	59.00 (52.00–66.00)	0.00
25(OH)D (ng/mL)	20.92 (16.28–26.86)	21.36 (15.56–27.97)	0.87
Parathyroid hormone (pmol/L)	40.65 (32.82–53.34)	42.37 (31.63–56.22)	0.128
β-Collagen-specific sequence (ng/L)	403.50 (223.00–5630)	366.00 (216.75–551.00)	0.68
L1–4 BMD (g/cm^2)	0.894 (0.806–0.992)	0.859 (0.773–0.968)	0.008
Neck BMD (g/cm^2)	0.758 (0.708–0.848)	0.692 (0.623–0.761)	0.00
Total BMD (g/cm^2)	0.801 (0.727–0.895)	0.742 (0.662–0.817)	0.00

Both GLP-1 and GIP are incretins. Previously, we demonstrated a correlation between GLP-1 receptor gene (*GLP-1R*) polymorphisms and BMD in postmenopausal women in Shanghai, China (18). Therefore, we aimed at elucidating whether there is a correlation between GIP/GIPR and BMD and whether *GIPR* mutations affect the effects of GIP/GIPR.

Materials and methods

Subjects

The study was approved by the Ethics Committee of the Sixth People's Hospital, Shanghai Jiaotong University (2014-KY-001(K)). Han women who are being treated for osteoporosis at Shanghai Sixth People's Hospital were enrolled in this study. All subjects signed informed consent forms. BMD and other clinical data were analyzed.

The inclusion criteria were as follows: (i) natural menopause for more than 1 year and (ii) no anti-osteoporotic treatment (except for calcium and vitamin D supplementation). The exclusion criteria were any disease that affects bone metabolism and use of medication, except for GLP-1 analogs or DPP4 inhibitors.

We included 907 postmenopausal women in this study; however, in order to minimize selection bias, some subjects were excluded, some samples were contaminated, were of poor quality, or were not successfully typed after one failure. Finally, 884 samples from postmenopausal women (mean age: 67.2 ± 10.0 years) were subjected to SNP detection. The average menopausal age of the 884 postmenopausal women was 47.41 years, and 90% of them had osteopenia/osteoporosis and 307 women had a history of fractures. These 307 women were ruled out of diseases and external factors that affect bone metabolism, accounting for approximately 34.73% of the participants.

SNP detection

Tag SNPs were selected based on the International Human Genome Haplotype Program (International HapMap

Table 2 Information related to SNP sites in the GLP-1R and GIPR genes.

SNPs	Chromosome position	SNP property	Alleles	HWE *P* value	MAF in CHBS	MAF in this study
rs2268657	39020542	Intron 1	C/T	0.1902	0.34	0.326
rs2295006	46182304	Nonsynon_exon2	G/A	0.7755	0.07	0.06
rs3765467	46182304	Nonsynon_exon4	G/A	0.5521	0.23	0.255
rs6923761	39055485	Nonsynon_exon5	G/A	1	0.01	0.01
rs1042044	39041502	Nonsynon_exon7	C/A	1	0.47	0.46
rs2268641	39050266	Intron 12	C/T	0.5249	0.39	0.417
rs4714210	39055485	3′-UTR_exon13	G/A	0.1432	0.29	0.317
rs10423928	46182304	Intron 12	T/A	0.9107	0.20	0.208

CHBS, Genetic Variation Database of Han Nationality Population in Beijing, China; HWE, Hardy–Weinberg equilibrium; MAF, minimum mean allele frequency; Non-synon, non-synonymous.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0583

Project (ftp://ftp.ncbi.nlm.nih.gov/hapmap/), with the following criteria: (i) minimum mean allele frequency (MAF) > 0.01; (ii) coefficient of linkage disequilibrium (LD) $r^2 > 0.8$; and (iii) SNPs reported in a previous genome-wide association study. The GIPR rs10423928 locus was characterized.

Amplification was achieved by performing multiplex PCR. Each measurable allele locus-ligation product was obtained after two ligation reactions. The raw data files were analyzed using the GeneMapper 4.1 software (Applied Biosystems). The iMLDR® multiple SNP typing system (Shanghai Tianhao Biotechnology Co., Ltd., Shanghai, China) (19) was used to classify the GIPR rs10423928 SNP site in 884 samples from postmenopausal women.

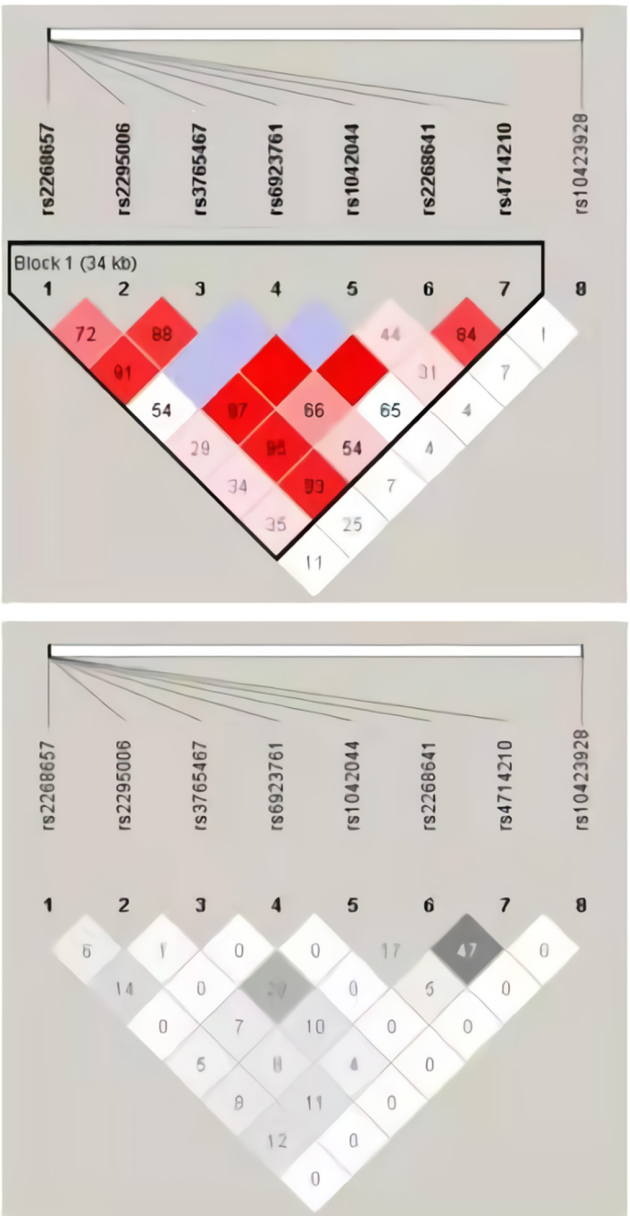

Figure 1
No linkage disequilibrium relationship between GIPR SNP rs10423928 and GLP-1R SNPs.

BMD

The BMD of the lumbar spine 1–4 (L1–4), left femoral neck, and total hip was measured for postmenopausal female subjects, expressed in g/cm^2, using dual-energy x-ray absorptiometry (GE Lunar Prodigy Bone Densitometer, Little Chalfont, UK). Following strict quality-control requirements, the instrument was tested once daily before use with a standard phantom to evaluate the stability of the system. The coefficient of variation of the lumbar spine, left femoral neck, and total hip BMD measurements was 1.39, 2.22, and 0.70%, respectively.

Statistical analysis

Statistical analysis was performed using the SPSS software (version 24.0; SPSS, Inc.). Continuous variables with a normal distribution are expressed as mean ± S.D. ($\bar{x} \pm s$). Continuous variables between groups were compared using the *t*-test. Chi-squared tests were used to compare categorical variables. The Haploview software (version 4.2) was used to calculate the D' value and LD coefficient (r^2) between SNPs. After adjusting for age, linear regression was used to assess the relationship between GIPR SNP and BMD in postmenopausal women. $P < 0.05$ was considered to reflect a statistically significant difference.

Results

To determine the effect of aging on osteoporosis in elderly women, the subjects were divided into different age groups according to a recognized age classification system (<60 and ≥60 years) (20). Table 1 shows the baseline characteristics of these subjects. No significant difference was detected in the serum calcium and phosphorus levels between the groups. Alkaline phosphatase (AKP) was significantly higher in the group aged ≥60 years than in the group aged <60 years ($P = 0.004$). The BMD in the group aged ≥60 years was lower than that in the group aged <60 years ($P < 0.001$).

Table 3 Clinical data corresponding to GIPR rs10423928 SNP locus in postmenopausal women.

rs10423928 genotype	*n*	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	L1–4 BMD (g/cm^2)	Femoral neck BMD (g/cm^2)	Total hip BMD (g/cm^2)
T/T	556	67.1 ± 10.1	152.7 ± 5.5	55.5 ± 8.9	23.8 ± 3.6	0.877 ± 0.161	0.708 ± 0.120	0.755 ± 0.132
A/T	289	67.6 ± 9.8	153.7 ± 5.7	56.1 ± 8.2	23.7 ± 3.3	0.896 ± 0.155	0.728 ± 0.119	0.769 ± 0.130
A/A	39	65.4 ± 9.7	152.0 ± 5.8	56.5 ± 6.1	24.5 ± 3.0	0.882 ± 0.148	0.719 ± 0.124	0.773 ± 0.143

Allele frequencies

The GIPR rs10423928 locus was analyzed. The genotype distribution met the Hardy–Weinberg equilibrium. The MAF of rs10423928 in the CHBS (representing the national database) is 20%, and in the present study, it was 20.8% (Table 2). There was no linkage disequilibrium relationship between rs10423928 and GLP-1R SNPs ($0.908 < D' < 1$) (Fig. 1).

Table 3 shows the clinical data corresponding to rs10423928 in postmenopausal women. The rs10423928 locus has three genotypes: T/T, A/T, and A/A. Among them, the T/T genotype was detected in 556 patients (62.9%), the A/T genotype was detected in 289 patients (32.7%), and the A/A genotype was detected in 39 patients (4.4%).

Based on the linear regression analysis, the rs10423928 locus was unrelated to age, height, weight, BMI, Ca, P, PTH, AKP, ALB, and Scr ($P > 0.05$; Table 4). A close correlation was noted between the rs10423928 locus and BMD. The T/T genotype positively correlated with the femoral neck BMD and Ward's triangle area BMD in postmenopausal women ($P < 0.05$; Table 5).

Discussion

Genome-wide association analysis has confirmed that BMD is associated with multiple genetic-susceptibility regions (21, 22). Correlations between vitamin D receptor gene polymorphisms and osteoporosis were discovered in 1994 (23). Subsequently, >100 gene polymorphisms related to bone metabolism regulation have been identified.

Currently, there are no relevant data from clinical research showing that *GIPR* polymorphism is related to bone metabolism. In our previous research, we found that GLP-1R SNP is related to bone metabolism. Both GIP and GLP-1 are incretins, and both of them are related to glucose and lipid metabolism. The purpose of our research was to determine whether there is a correlation between GIPR SNP and bone metabolism.

Some clinical and animal studies have shown that GIPR has a relationship with bone metabolism. Patients with type 2 diabetes express low levels of GIPR or have defective GIPR (24, 25). In GIPR knockout mice, the cortical bone becomes thinner, the number of endosteal osteoclasts increases, and BMD decreases, indicating that there is a decrease in bone strength and bone quality (11). GIPR knockout mice exhibited an increased plasma calcium concentration after feeding, indicating that GIP may play a role in calcium homeostasis (26). GIP can guide the absorption of skeletal nutrients through the gut–bone axis and regulate bone turnover. There is a close relationship between bone turnover and intestinal hormones (27, 28, 29).

GIP can affect bone metabolism directly and indirectly (30, 31, 32, 33, 34), and it plays a biological role by binding

Table 4 Linear-regression analysis of correlations between the GIPR gene rs10423928 locus and ordinary index in postmenopausal women.

Mark	Dominant		Recessive		Addictive	
	β	*P*	β	*P*	β	*P*
Age	0.220	0.753	−1.806	0.271	−0.075	0.898
Height	0.842	0.176	−1.038	0.449	0.431	0.403
Weight	0.597	0.527	0.795	0.702	0.522	0.504
BMI	0.009	0.982	0.747	0.377	0.112	0.725
Ca	−0.012	0.443	−0.000	0.998	−0.009	0.514
P	0.024	0.376	0.049	0.102	0.023	0.192
PTH	−1.870	0.208	−7.173	0.312	−2.228	0.076
AKP	−0.619	0.158	−0.564	0.594	−0.511	0.168
ALB	−0.448	0.839	−2.703	0.620	−0.647	0.731
Scr	0.090	0.939	−2.095	0.424	−0.023	0.817

β, regression coefficient.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0583

Table 5 Linear-regression analysis of correlations between the GIPR gene rs10423928 locus and BMD in postmenopausal women.

BMD	Dominant		Recessive		Addictive	
	β	*P*	β	*P*	β	*P*
L1	0.014	0.180	−0.004	0.860	0.010	0.289
L2	0.017	0.150	0.002	0.930	0.012	0.216
L3	0.021	0.123	0.000	0.988	0.015	0.194
L4	0.026	0.053	0.015	0.639	0.020	0.073
L1–2	−0.019	0.296	0.018	0.671	−0.011	0.468
L1–3	−0.023	0.271	0.039	0.426	−0.011	0.522
L1–4	−0.021	0.331	0.050	0.331	−0.009	0.639
L2–3	−0.010	0.603	0.038	0.407	−0.002	0.888
L2–4	−0.010	0.611	0.050	0.297	−0.001	0.956
L3–4	0.010	0.581	0.044	0.293	0.013	0.402
Neck	0.018	0.035[a]	0.007	0.737	0.013	0.059
Ward's	0.019	0.033[a]	0.016	0.466	0.016	0.040[a]
Troch	0.009	0.278	0.005	0.802	0.007	0.317
Inter	0.017	0.140	0.032	0.234	0.016	0.096
Total	0.014	0.118	0.017	0.427	0.012	0.111

[a]$P \leq 0.05$.
β, regression coefficient.

to the corresponding GIPR on the cell surface. GIPR SNP rs10423928 has been studied frequently. It consists of the major allele T and the minor allele A. Individuals with the T/T genotype who consume a high-carbohydrate/low-fat diet have a lower risk of type 2 diabetes (16). The minor allele A is associated with an impaired insulin secretion stimulated by glucose and GIP and a decreased BMI, lean body mass, and waist circumference (17). In the present study, we found that the BMD in the group aged ≥60 years was lower than that in the group aged <60 years ($P < 0.001$). This indicates that with age, the bone mass of women decreases (35, 36). We neither find that the genotypes of rs10423928 are associated with BMI and body weight nor did we find an association of each genotype with Ca, P, PTH, and AKP.

Studies have found that there is a strong linkage disequilibrium between the SNPs rs10423928 and rs1800437 (Glu 354Gln located in exon 10, E354Q) of the *GIPR* locus ($r^2 = 0.99$). rs1800437 can reduce the expression of GIPR in carriers (37, 38). In the Danish Osteoporosis Prevention Study (39), rs1800437 was associated with BMD and fracture risk. Compared with those with the major allele G, the femoral neck BMD and total hip bone BMD of women with the minor allele C were significantly reduced. Women who are homozygous for the variant C allele have an increased risk of non-vertebral fractures. Our study revealed that the dominant T/T genotype of rs10423928 in postmenopausal women was significantly associated with a higher BMD of the femoral neck. This indicated that the T/T genotype of GIP has a protective effect against osteoporosis.

Our study was not a prospective study but a cross-sectional cohort study. We found that the dominant T/T genotype of rs10423928 was significantly associated with a higher BMD, unlike the other genotypes in postmenopausal women. This does not indicate that this genotype can prevent or warn of osteoporosis. The T/T genotype seems to have a bone-protective effect, but the mechanism needs to be further explored.

Taken together, our study showed that the dominant T/T genotype of rs10423928 in postmenopausal women is significantly associated with a higher BMD and that the T/T genotype seems to have a bone-protective effect.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This work was supported by the Pudong New Area Health and Family Planning Commission Fund Project (grant number PWZzk2017-12).

Ethical statement
The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethics Committee of the Sixth People's Hospital, Shanghai Jiaotong University (2014-KY-001(K)).

Author contribution statement
(i) Conception and design: L Zhang, B Feng; (ii) Administrative support: B Feng; (iii) Provision of study materials or patients: J He; (iv) Collection and assembly of data: J He, L Zhang, X Sun; (v) Data analysis and interpretation:

X Sun, W He, Dongyue Pang, Jingjing Hu. All authors contributed to writing the manuscript and approving the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1 Peacock M, Turner CH, Econs MJ & Foroud T. Genetics of osteoporosis. *Endocrine Reviews* 2002 **23** 303–326. (https://doi.org/10.1210/edrv.23.3.0464)

2 Josse RG, Majumdar SR, Zheng Y, Adler A, Bethel MA, Buse JB, Green JB, Kaufman KD, Rodbard HW, Tankova T, *et al.* Sitagliptin and risk of fractures in type 2 diabetes: results from the TECOS trial. *Diabetes, Obesity and Metabolism* 2017 **19** 78–86. (https://doi.org/10.1111/dom.12786)

3 Ma X, Meng J, Jia M, Bi L, Zhou Y, Wang Y, Hu J, He G & Luo X. Exendin-4, a glucagon-like peptide-1 receptor agonist, prevents osteopenia by promoting bone formation and suppressing bone resorption in aged ovariectomized rats. *Journal of Bone and Mineral Research* 2013 **28** 1641–1652. (https://doi.org/10.1002/jbmr.1898)

4 Meng J, Ma X, Wang N, Jia M, Bi L, Wang Y, Li M, Zhang H, Xue X, Hou Z, *et al.* Activation of GLP-1 receptor promotes bone marrow stromal cell osteogenic differentiation through β-catenin. *Stem Cell Reports* 2016 **6** 579–591. (https://doi.org/10.1016/j.stemcr.2016.02.002)

5 Monami M, Dicembrini I, Antenore A & Mannucci E. Dipeptidyl peptidase-4 inhibitors and bone fractures: a meta-analysis of randomized clinical trials. *Diabetes Care* 2011 **34** 2474–2476. (https://doi.org/10.2337/dc11-1099)

6 Trujillo JM & Nuffer W. GLP-1 receptor agonists for type 2 diabetes mellitus: recent developments and emerging agents. *Pharmacotherapy* 2014 **34** 1174–1186. (https://doi.org/10.1002/phar.1507)

7 Yamada C, Yamada Y, Tsukiyama K, Yamada K, Udagawa N, Takahashi N, Tanaka K, Drucker DJ, Seino Y & Inagaki N. The murine glucagon-like peptide-1 receptor is essential for control of bone resorption. *Endocrinology* 2008 **149** 574–579. (https://doi.org/10.1210/en.2007-1292)

8 Glorie L, D'Haese PC & Verhulst A. Boning up on DPP4, DPP4 substrates, and DPP4-adipokine interactions: logical reasoning and known facts about bone related effects of DPP4 inhibitors. *Bone* 2016 **92** 37–49. (https://doi.org/10.1016/j.bone.2016.08.009)

9 Mabilleau G. Incretins and bone: friend or foe? *Current Opinion in Pharmacology* 2015 **22** 72–78. (https://doi.org/10.1016/j.coph.2015.03.007)

10 Mabilleau G, Perrot R, Mieczkowska A, Boni S, Flatt PR, Irwin N & Chappard D. Glucose-dependent insulinotropic polypeptide (GIP) dose-dependently reduces osteoclast differentiation and resorption. *Bone* 2016 **91** 102–112. (https://doi.org/10.1016/j.bone.2016.07.014)

11 Mieczkowska A, Irwin N, Flatt PR, Chappard D & Mabilleau G. Glucose-dependent insulinotropic polypeptide (GIP) receptor deletion leads to reduced bone strength and quality. *Bone* 2013 **56** 337–342. (https://doi.org/10.1016/j.bone.2013.07.003)

12 Yamada Y, Hayami T, Nakamura K, Kaisaki PJ, Someya Y, Wang CZ, Seino S & Seino Y. Human gastric inhibitory polypeptide receptor: cloning of the gene (GIPR) and cDNA. *Genomics* 1995 **29** 773–776. (https://doi.org/10.1006/geno.1995.9937)

13 Fujita Y, Wideman RD, Asadi A, Yang GK, Baker R, Webber T, Zhang T, Wang R, Ao Z, Warnock GL, *et al.* Glucose-dependent insulinotropic polypeptide is expressed in pancreatic islet alpha-cells and promotes insulin secretion. *Gastroenterology* 2010 **138** 1966–1975. (https://doi.org/10.1053/j.gastro.2010.01.049)

14 Baggio LL & Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology* 2007 **132** 2131–2157. (https://doi.org/10.1053/j.gastro.2007.03.054)

15 Wang GJ, Yang P & Xie HG. Gene variants in noncoding regions and their possible consequences. *Pharmacogenomics* 2006 **7** 203–209. (https://doi.org/10.2217/14622416.7.2.203)

16 Sonestedt E, Lyssenko V, Ericson U, Gullberg B, Wirfalt E, Groop L & Orho-Melander M. Genetic variation in the glucose-dependent insulinotropic polypeptide receptor modifies the association between carbohydrate and fat intake and risk of type 2 diabetes in the Malmo Diet and Cancer Cohort. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** E810–E818. (https://doi.org/10.1210/jc.2011-2444)

17 Lyssenko V, Eliasson L, Kotova O, Pilgaard K, Wierup N, Salehi A, Wendt A, Jonsson A, De Marinis YZ, Berglund LM, *et al.* Pleiotropic effects of GIP on islet function involve osteopontin. *Diabetes* 2011 **60** 2424–2433. (https://doi.org/10.2337/db10-1532)

18 Zhang L, He J, Sun X, Luo X, Zeng J, He W, Liu X & Feng B. Relationship between glucagon-like peptide-1 receptor gene polymorphism and bone mineral density in postmenopausal women in Shanghai. *Annals of Palliative Medicine* 2020 **9** 1732–1741. (https://doi.org/10.21037/apm-19-396)

19 Zhang XY, He JW, Fu WZ, Liu YJ & Zhang ZL. Associations of serum osteocalcin and polymorphisms of the osteocalcin gene with bone mineral density in postmenopausal and elderly Chinese women. *Journal of Nutrigenetics and Nutrigenomics* 2016 **9** 231–242. (https://doi.org/10.1159/000452130)

20 Chou KL & Chi I. Successful aging among the young-old, old-old, and oldest-old Chinese. *International Journal of Aging and Human Development* 2002 **54** 1–14. (https://doi.org/10.2190/9K7T-6KXM-C0C6-3D64)

21 Rivadeneira F, Styrkársdottir U, Estrada K, Halldórsson BV, Hsu YH, Richards JB, Zillikens MC, Kavvoura FK, Amin N, Aulchenko YS, *et al.* Twenty bone-mineral-density loci identified by large-scale meta-analysis of genome-wide association studies. *Nature Genetics* 2009 **41** 1199–1206. (https://doi.org/10.1038/ng.446)

22 Styrkarsdottir U, Halldorsson BV, Gretarsdottir S, Gudbjartsson DF, Walters GB, Ingvarsson T, Jonsdottir T, Saemundsdottir J, Center JR, Nguyen TV, *et al.* Multiple genetic loci for bone mineral density and fractures. *New England Journal of Medicine* 2008 **358** 2355–2365. (https://doi.org/10.1056/NEJMoa0801197)

23 Morrison NA, Qi JC, Tokita A, Kelly PJ, Crofts L, Nguyen TV, Sambrook PN & Eisman JA. Prediction of bone density from vitamin D receptor alleles. *Nature* 1994 **367** 284–287. (https://doi.org/10.1038/367284a0)

24 Holst JJ, Gromada J & Nauck MA. The pathogenesis of NIDDM involves a defective expression of the GIP receptor. *Diabetologia* 1997 **40** 984–986. (https://doi.org/10.1007/s001250050779)

25 Meier JJ, Hücking K, Holst JJ, Deacon CF, Schmiegel WH & Nauck MA. Reduced insulinotropic effect of gastric inhibitory polypeptide in first-degree relatives of patients with type 2 diabetes. *Diabetes* 2001 **50** 2497–2504. (https://doi.org/10.2337/diabetes.50.11.2497)

26 Tsukiyama K, Yamada Y, Yamada C, Harada N, Kawasaki Y, Ogura M, Bessho K, Li M, Amizuka N, Sato M, *et al.* Gastric inhibitory polypeptide as an endogenous factor promoting new bone formation after food ingestion. *Molecular Endocrinology* 2006 **20** 1644–1651. (https://doi.org/10.1210/me.2005-0187)

27 Xie D, Zhong Q, Ding KH, Cheng H, Williams S, Correa D, Bollag WB, Bollag RJ, Insogna K, Troiano N, *et al.* Glucose-dependent insulinotropic peptide-overexpressing transgenic mice have increased bone mass. *Bone* 2007 **40** 1352–1360. (https://doi.org/10.1016/j.bone.2007.01.007)

28 Bollag RJ, Zhong Q, Ding KH, Phillips P, Zhong L, Qin F, Cranford J, Mulloy AL, Cameron R & Isales CM. Glucose-dependent insulinotropic peptide is an integrative hormone with osteotropic effects. *Molecular and Cellular Endocrinology* 2001 **177** 35–41. (https://doi.org/10.1016/s0303-7207(01)00405-1)

29 Xie D, Cheng H, Hamrick M, Zhong Q, Ding KH, Correa D, Williams S, Mulloy A, Bollag W, Bollag RJ, *et al.* Glucose-dependent insulinotropic polypeptide receptor knockout mice have altered bone turnover. *Bone* 2005 **37** 759–769. (https://doi.org/10.1016/j.bone.2005.06.021)

30 Bollag RJ, Zhong Q, Phillips P, Min L, Zhong L, Cameron R, Mulloy AL, Rasmussen H, Qin F, Ding KH, *et al.* Osteoblast-derived cells express functional glucose-dependent insulinotropic peptide receptors. *Endocrinology* 2000 **141** 1228–1235. (https://doi.org/10.1210/endo.141.3.7366)
31 Zhong Q, Itokawa T, Sridhar S, Ding KH, Xie D, Kang B, Bollag WB, Bollag RJ, Hamrick M, Insogna K, *et al.* Effects of glucose-dependent insulinotropic peptide on osteoclast function. *American Journal of Physiology: Endocrinology and Metabolism* 2007 **292** E543–E548. (https://doi.org/10.1152/ajpendo.00364.2006)
32 Zaidi M, Shankar VS, Huang CL, Pazianas M & Bloom SR. Amylin in bone conservation current evidence and hypothetical considerations. *Trends in Endocrinology and Metabolism* 1993 **4** 255–259. (https://doi.org/10.1016/1043-2760(93)90095-v)
33 Saxena R, Hivert MF, Langenberg C, Tanaka T, Pankow JS, Vollenweider P, Lyssenko V, Bouatia-Naji N, Dupuis J, Jackson AU, *et al.* Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge. *Nature Genetics* 2010 **42** 142–148. (https://doi.org/10.1038/ng.521)
34 Ding KH, Zhong Q, Xu J & Isales CM. Glucose-dependent insulinotropic peptide: differential effects on hepatic artery vs. portal vein endothelial cells. *American Journal of Physiology: Endocrinology and Metabolism* 2004 **286** E773–E779. (https://doi.org/10.1152/ajpendo.00507.2003)
35 Cheng XG, Yang DZ, Zhou Q, Zhuo TJ, Zhang HC, Xiang J, Wang HF, Ou PZ, Liu JL, Xu L, *et al.* Age-related bone mineral density, bone loss rate, prevalence of osteoporosis, and reference database of women at multiple centers in China. *Journal of Clinical Densitometry* 2007 **10** 276–284. (https://doi.org/10.1016/j.jocd.2007.05.004)
36 Chan GK & Duque G. Age-related bone loss: old bone, new facts. *Gerontology* 2002 **48** 62–71. (https://doi.org/10.1159/000048929)
37 Fortin JP, Schroeder JC, Zhu Y, Beinborn M & Kopin AS. Pharmacological characterization of human incretin receptor missense variants. *Journal of Pharmacology and Experimental Therapeutics* 2010 **332** 274–280. (https://doi.org/10.1124/jpet.109.160531)
38 Mohammad S, Patel RT, Bruno J, Panhwar MS, Wen J & McGraw TE. A naturally occurring GIP receptor variant undergoes enhanced agonist-induced desensitization, which impairs GIP control of adipose insulin sensitivity. *Molecular and Cellular Biology* 2014 **34** 3618–3629. (https://doi.org/10.1128/MCB.00256-14)
39 Torekov SS, Harslof T, Rejnmark L, Eiken P, Jensen JB, Herman AP, Hansen T, Pedersen O, Holst JJ & Langdahl BL. A functional amino acid substitution in the glucose-dependent insulinotropic polypeptide receptor (GIPR) gene is associated with lower bone mineral density and increased fracture risk. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** E729–E733. (https://doi.org/10.1210/jc.2013-3766)

Received in final form 22 December 2021
Accepted 14 January 2022
Accepted Manuscript published online 14 January 2022