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在线全文

循环炎症蛋白成纤维细胞生长因子21与骨质疏松以及骨折的关系研究*

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【摘要】 **目的** 系统性筛选循环炎症蛋白（circulating inflammatory proteins, CIPs）中影响骨质疏松症（osteoporosis, OP）和骨折的潜在靶点，通过临床样本验证其与骨密度（bone mineral density, BMD）的关联，为骨代谢调控提供新靶点证据。**方法** 利用双向孟德尔随机化分析CIPs与OP和骨折的因果关系。纳入2型糖尿病（type 2 diabetes mellitus, T2DM）和健康人群，收集患者一般资料，检测并比较合并OP的T2DM组（DOP）、无OP的T2DM组（NDOP）及对照组的成纤维细胞生长因子21（fibroblast growth factor 21, FGF21）与骨代谢指标。**结果** EBI GWAS Catalog数据库中获取的共91种CIPs中，逆方差加权（inverse variance weighting, IVW）分析显示FGF21同时与OP和过去5年发生骨折存在潜在因果关系，其水平升高增加OP风险〔比值比（odds ratio, OR）=1.003，95%置信区间（confidence interval, CI）：1.001～1.005；P=0.004〕和过去5年发生骨折风险（OR=1.004，95%CI：1.000～1.008；P=0.038），反向MR显示OP和过去5年发生骨折对正向分析中确定的FGF21在内的8种CIPs没有因果影响。临床研究显示：DOP组血浆FGF21〔396.92（308.98，523.94）pg/mL〕高于NDOP组〔346.88（283.82，466.86）pg/mL〕和对照组〔233.66（169.95，327.78）pg/mL〕（均P<0.05）。在全部样本中，调整年龄、体质量指数、糖化血红蛋白、钙和磷后，FGF21与腰椎（β=－0.003，95%CI：－0.004～－0.002，P<0.000 1）和全髋T值（β=－0.002，95%CI：－0.003～－0.001，P<0.0001）呈负相关，而在T2DM中，FGF21与腰椎（β=－0.003，95%CI：－0.004～－0.0014，P<0.0001）和全髋T值（β=－0.001，95%CI：－0.002 2～－0.000 5，P=0.002）呈负相关，调整上述协变量后，负相关同样存在。**结论** FGF21增加OP和过去5年发生骨折的风险，且存在因果关系，是T2DM骨骼健康受损的潜在危险因素。

【关键词】 成纤维细胞生长因子21 骨密度 骨质疏松症 骨折 孟德尔随机化分析

A Study on the Relationship Between Cyclic Inflammatory Protein Fibroblast Growth Factor 21, Osteoporosis, and Fractures

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[Abstract] Objective Systematically conduct a screening of the potential targets within circulating inflammatory proteins (CIPs) that have an impact on osteoporosis (OP) and fractures. Validate their association with bone mineral density (BMD) via clinical samples, thereby offering novel evidence for the regulation of bone metabolism. **Methods** The study employs bidirectional Mendelian randomization analysis to investigate the causal relationship between CIPs and OP, as well as fractures. Two groups are included: patients with type 2 diabetes mellitus (T2DM) and healthy individuals. General patient data are collected, and fibroblast growth factor 21 (FGF21) and bone metabolism indicators are measured and compared among the T2DM group with OP (DOP), the T2DM group without OP (NDOP), and the control group. **Results** Among the 91 types of CIPs retrieved from the EBI GWAS Catalog database, the inverse variance weighting (IVW) analysis indicated that FGF21 potentially had a causal relationship with both OP and fractures that transpired within the past five years. An elevation in its level augmented the risk of OP (odds ratio [OR] = 1.003, 95% CI: 1.001-1.005; P = 0.004) and the risk of fractures in the past five years (OR = 1.004, 95% CI: 1.000-1.008; P = 0.038). Reverse Mendelian randomization demonstrated that OP and fractures in the past five years had no causal impact on the eight CIPs, including FGF21, identified in the forward analysis. Clinical investigations showed that the plasma FGF21 level in the DOP group (396.92 [308.98, 523.94] pg/mL) was higher than that in the NDOP group (346.88 [283.82, 466.86]

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pg/mL) and the control group (233.66 [169.95, 327.78] pg/mL) (all $P < 0.05$). In all samples, subsequent to adjusting for age, body mass index, glycated hemoglobin, calcium, and phosphorus, FGF21 was negatively correlated with the T-value of the lumbar spine ($\beta = -0.003$, 95% CI: −0.004 to −0.002, $P < 0.0001$) and the T-value of the total hip ($\beta = -0.002$, 95% CI: −0.003 to −0.001, $P < 0.0001$). In T2DM, FGF21 was negatively correlated with the T-value of the lumbar spine ($\beta = -0.003$, 95% CI: −0.004 to −0.0014, $P < 0.0001$) and the T-value of the total hip ($\beta = -0.001$, 95% CI: −0.0022 to −0.0005, $P = 0.002$), and this negative correlation persisted after adjusting for the aforementioned covariates. **Conclusion** FGF21 elevates the risk of OP and fractures that have occurred over the past five years, and a causal relationship exists. It serves as a potential risk factor for impaired bone health in T2DM.

[Key words] Fibroblast growth factor 21 Bone mineral density Osteoporosis Fracture Mendelian randomization analysis

骨质疏松症(osteoporosis, OP)是一种以骨密度(bone mineral density, BMD)降低、骨微结构破坏和骨折风险增加为特征的全身性代谢性骨病[1-2], 而在50岁或以上的女性和男性中分别有1/3和1/5会罹患OP相关脆性骨折[3]。随着人口老龄化加剧, OP发病率持续攀升, 已成为重要的公共卫生问题[4]。

研究表明, 骨骼和免疫系统之间存在密切相互作用[5-6]。成骨细胞和破骨细胞活性受免疫细胞分泌的各种炎症蛋白的调节, 包括细胞因子、趋化因子和生长因子[7]。循环炎症蛋白(circulating inflammatory proteins, CIPs)不仅可以通过抑制骨形成、促进骨流失和损害骨再生来诱导OP[8-9], 也可以通过促进成骨细胞分化来抑制OP, 通过多种信号通路诱导成骨[10], 并且参与早期骨折愈合和骨再生[11]。骨骼和CIPs之间的相互作用复杂且存在潜在矛盾, 因此探究CIPs与OP的因果关系显得尤为重要。

成纤维细胞生长因子21(fibroblast growth factor 21, FGF21)是CIPs中的一员, 与糖脂代谢和骨稳态调节密切相关[12-14]。既往研究发现糖尿病(diabetes mellitus, DM)患者的血清FGF21水平显著升高, 这表明血清FGF21可能是代谢紊乱的生物标志物[15-16], 而机体中的代谢紊乱已被证明会加速骨稳态的有害改变, 并导致OP的发生[17-18]。2型糖尿病(type 2 diabetes mellitus, T2DM)和OP经常并存, 尤其是在老年人中[19], 研究证实DM患者发生骨折的风险更高[20-22]。由于FGF21对骨骼健康的具体影响仍存在争议[13], 因此, 本研究利用孟德尔随机化(Mendelian randomization, MR)筛选CIPs中与OP和骨折有潜在因果关系的蛋白, 最终选择与两者均具有因果关系的FGF21蛋白, 在临床样本中验证其血浆水平与BMD的关系。

1 资料与方法

1.1 MR研究设计

选择OP和过去5年发生骨折作为结果变量, 选择91种CIPs显著相关的单核苷酸多态性(single nucleotide polymorphisms, SNPs)作为工具变量(instrumental variables, IVs), 进行双向MR分析, 以识别基因预测与OP风险相关的CIPs, 并检测是否存在任何反向因果关系。对于在双向MR分析中显示对OP有因果影响的CIPs, 进一步分析其与过去5年发生骨折的因果关系。为验证结果的可靠性, 采用异质性检验、多效性分析和敏感性分析排除结果的偏倚。

1.2 MR数据获取

CIPs的汇总数据来自全基因组关联研究(Genome-Wide Association Study, GWAS), 包括14 824名欧洲血统的参与者[23](见网络资源附件附表1)。OP和过去5年发生骨折汇总数据来自IEU OPEN GWAS 项目(https://gwas.MRcieu.ac.uk/; GWAS ID: ukb-b-12141; ukb-b-13346)(见网络资源附件附表2)。

1.3 MR工具变量筛选条件

选择符合以下标准的SNPs作为IVs。首先, 对于CIPs, 相关GWAS样本量相对较小, 显著关联位点数量有限, 采用相对宽松的阈值有助于获得足够且具有生物学意义的遗传工具变量, 从而提高MR分析的统计效能, 因此SNPs全基因组显著性阈值设为小于5×10^{-6}, 而对于OP及骨折表型, GWAS样本量较大、遗传结构复杂, 采用更为严格的阈值可有效降低假阳性风险, 保证因果推断的稳健性, 故设为5×10^{-8}。其次, SNPs无连锁不平衡(LD)($r^2 = 0.001$, 聚类距离为10 000 kb)。第三, F统计量 > 10(其中$F = \beta_exposure^2/SE_exposure^2$)的SNPs被纳入。最后, 所有回文SNPs均剔除。

1.4 MR因果分析

逆方差加权(inverse variance weighting, IVW)作为主要分析方法用于评估暴露与结局的因果关系, 并通过加权中位数法(weighted median)、加权众数法(weighted mode)、简单众数法(simple mode)和MR-Egger回归验证IVW结果的可靠性。通过Cochran's Q检验评估异质性。采用留一法敏感性分析逐次剔除单个SNP以观察其对整

体估计的影响。使用MR-PRESSO全局检验分析水平多效性。统计学显著性设定为错误发现率(FDR)< 0.05。

1.5 临床研究对象

共纳入191例研究对象, 分为3组: 64例合并T2DM的OP(DOP)组患者和65例无OP的T2DM(NDOP)组患者, 均来自四川大学华西医院内分泌与代谢科, 以及62例年龄匹配的健康志愿者。T2DM的诊断标准采用中国2型糖尿病防治指南(2020年版)[24], OP的诊断标准采用2022年版《原发性骨质疏松症诊疗指南》[25]。排除标准: ①肝肾疾病、库欣综合征、甲亢、甲状旁腺功能亢进、风湿病、骨转移性肿瘤及严重心血管和脑血管疾病、器官衰竭; ②既往使用皮质类固醇、免疫抑制剂、钙剂、维生素D、双膦酸盐、选择性雌激素受体调节剂、降钙素、雌激素治疗、抗骨吸收治疗、噻嗪类利尿剂。本研究获得四川大学华西医院生物医学伦理审查委员会批准(2022年审738号)。

1.6 临床指标检测

糖化血红蛋白(glycolated hemoglobin, HbA1c)采用高效液相色谱法测定(G8, 东曹)。Ⅰ型胶原羧基端肽(C-terminal telopeptide of type Ⅰ collagen, CTX)采用酶联免疫吸附试验(ELISA)(Immunodiagnostic Systems Ltd., 英国)检测; 骨钙素(osteocalcin, OC)采用ELISA(R&D Systems, 美国)检测; 钙(Ca)和磷(P)采用cobas701平台及配套试剂(罗氏, 瑞士)测定。血浆FGF21浓度采用ELISA法(BioVendor, 英国)检测, 批内和批间变异系数分别为3.0% ~ 4.1%和3.0% ~ 3.6%。ELISA所用抗体专用于人FGF21, 未观察到与人FGF19和人FGF23的交叉反应。BMD采用双能X线吸收测定法(DMS公司, 法国)进行测量。受试者测量腰椎(L1-L4)前后位及髋部的BMD。测量精度为0.5% ~ 0.8%。BMD检查由一名具有5年以上经验且不知晓本研究目的的技术人员进行, 以避免测量偏倚。

1.7 统计学方法

统计分析采用R软件(版本4.4.1)进行。连续变量的正态性检验采用Kolmogorov-Smirnov检验。所有连续变量均以中位数(四分位数间距)表示。组间比较中, 符合正态分布的连续变量采用单因素方差分析(one-way analysis of variance, ANOVA), 并使用Tukey法进行两两比较; 不符合正态分布的连续变量采用Kruskal–Wallis *H*检验, 并进行两两Wilcoxon秩和检验, 采用Holm方法进行多重比较校正。采用多因素回归分析FGF21与BMD、CTX、OC、年龄及体质量指数(body mass index, BMI)之间的相关性。进一步调整BMI、年龄、HbA1c、Ca和P等因素后, 评估FGF21与腰椎及全髋T值之间的关联性。P< 0.05(双侧检验)为差异有统计学意义。

2 结果

2.1 MR工具变量的选取

使用双向MR分析探究91种CIPs与OP的因果关系, 共纳入961例符合筛选标准的IVs, 所有F统计量均超过10, 见网络资源附件附表3。

2.2 正向MR分析CIPs对OP的因果影响

在91种CIPs中, 经FDR多重比较校正后, 所有蛋白与OP之间的关联均未达到统计学显著性, 然而, 在IVW分析中观察到8种蛋白与OP之间存在有统计学意义的关联(P< 0.05), 提示潜在的因果信号(图1)。其中有4种CIPs高水平会降低OP的发生风险, 包括趋化因子配体19(C-C motif chemokine ligand 19, CCL19)〔比值比(odds ratio, OR)= 0.998, 95%置信区间(confidence interval, CI): 0.995 ~ 1.000; P= 0.047〕, 趋化因子配体4(CCL4)(OR= 0.999, 95%CI: 0.998 ~ 1.000; P= 0.028), γ干扰素(interferon gamma, IFN-γ)(OR= 0.996, 95%CI: 0.992 ~ 1.000; P= 0.043), 白介素-2受体β(interleukin 2 receptor subunit beta, IL-2Rβ)(OR= 0.996, 95%CI: 0.993 ~ 1.000; P= 0.021), 4种CIPs高水平会升高OP的发生风险, 包括分化簇6(cluster of differentiation 6, CD6)(OR= 1.002, 95%CI: 1.001 ~ 1.003; P< 0.001), 胱抑素D(cystatin D, CST5)(OR= 1.001, 95%CI: 1.000 ~ 1.002; P= 0.036), FGF21(OR= 1.003, 95%CI: 1.001 ~ 1.005; P= 0.004), 白血病抑制因子(leukemia inhibitory factor, LIF)(OR= 1.005, 95%CI: 1.000 ~ 1.009; P= 0.034)。此外, 在敏感性分析中没有观察到异质性或水平多效性的证据, 见网络资源附件附表4。

2.3 反向MR分析OP对CIPs的因果影响

反向MR显示OP对正向分析中确定的8种CIPs均未表现出潜在的因果效应(见网络资源附件附图1)。值得注意的是, 图中加粗的P值仅表示在单一MR方法(MR Egger)下达到统计学意义(P< 0.05), 该关联未在其他敏感性分析方法中得到重复, 因此IL-2Rβ的分析结果需要谨慎解读。此外, 敏感性分析未观察到其他蛋白存在异质性或水平多效性的证据, 见网络资源附件附表5。

2.4 CIPs与骨折风险间的因果研究

对于双向MR分析中与OP提示潜在相关的8种CIPs, 进一步探究了其与过去5年发生骨折的因果关系。总共纳入123个IVs(F> 10), 详见网络资源附件附表6。正向MR分析中, 经 FDR 多重比较校正后, 8种CIPs与过去5年发生骨折之间的关联均未达到统计学显著性, 然而, 在

Exposure	Outcome	nSNP	Method	*P*	OR (95% CI)
CCL19	Osteoporosis	11	MR Egger	0.106	0.996 (0.991 to 1.000)
		11	Weighted median	**0.029**	0.997 (0.994 to 1.000)
		11	Inverse variance weighted	**0.047**	0.998 (0.995 to 1.000)
		11	Simple mode	0.172	0.997 (0.992 to 1.001)
		11	Weighted mode	0.054	0.997 (0.994 to 1.000)
CCL4	Osteoporosis	9	MR Egger	**0.033**	0.998 (0.996 to 0.999)
		9	Weighted median	**0.021**	0.999 (0.997 to 1.000)
		9	Inverse variance weighted	**0.028**	0.999 (0.998 to 1.000)
		9	Simple mode	0.395	0.999 (0.996 to 1.001)
		9	Weighted mode	**0.039**	0.999 (0.997 to 1.000)
IFN-γ	Osteoporosis	4	MR Egger	0.672	1.004 (0.988 to 1.020)
		4	Weighted median	0.050	0.995 (0.991 to 1.000)
		4	Inverse variance weighted	**0.043**	0.996 (0.992 to 1.000)
		4	Simple mode	0.196	0.994 (0.987 to 1.001)
		4	Weighted mode	0.175	0.994 (0.987 to 1.001)
IL-2Rβ	Osteoporosis	6	MR Egger	0.929	1.001 (0.987 to 1.015)
		6	Weighted median	**0.046**	0.996 (0.992 to 1.000)
		6	Inverse variance weighted	**0.021**	0.996 (0.993 to 0.999)
		6	Simple mode	0.194	0.996 (0.990 to 1.001)
		6	Weighted mode	0.196	0.996 (0.990 to 1.001)
CD6	Osteoporosis	9	MR Egger	0.171	1.001 (1.000 to 1.002)
		9	Weighted median	**0.006**	1.001 (1.000 to 1.002)
		9	Inverse variance weighted	**<0.001**	1.002 (1.001 to 1.003)
		9	Simple mode	0.288	1.002 (0.999 to 1.004)
		9	Weighted mode	**0.026**	1.001 (1.000 to 1.002)
CST5	Osteoporosis	27	MR Egger	**0.040**	1.001 (1.000 to 1.003)
		27	Weighted median	**0.016**	1.001 (1.000 to 1.002)
		27	Inverse variance weighted	**0.036**	1.001 (1.000 to 1.002)
		27	Simple mode	0.089	1.003 (1.000 to 1.007)
		27	Weighted mode	**0.018**	1.001 (1.000 to 1.002)
FGF21	Osteoporosis	9	MR Egger	0.122	1.005 (0.999 to 1.010)
		9	Weighted median	**0.044**	1.003 (1.000 to 1.005)
		9	Inverse variance weighted	**0.004**	1.003 (1.001 to 1.005)
		9	Simple mode	0.626	0.999 (0.994 to 1.003)
		9	Weighted mode	0.189	1.003 (0.999 to 1.006)
LIF	Osteoporosis	5	MR Egger	0.312	1.012 (0.993 to 1.032)
		5	Weighted median	0.149	1.004 (0.999 to 1.009)
		5	Inverse variance weighted	**0.034**	1.005 (1.000 to 1.009)
		5	Simple mode	0.346	1.003 (0.997 to 1.009)
		5	Weighted mode	0.351	1.003 (0.997 to 1.009)

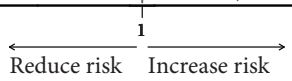

图 1 8种CIPs与OP的正向MR分析结果

Fig 1 Results of the forward MR analysis of eight CIPs and OP

CCL19: C–C motif chemokine ligand 19; CCL4: C–C motif chemokine ligand 4; IFN-γ: interferon gamma; IL-2Rβ: interleukin-2 receptor subunit beta; CD6: cluster of differentiation 6; CST5: cystatin D; FGF21: fibroblast growth factor 21; LIF: leukemia inhibitory factor; nSNP: number of single nucleotide polymorphism; OR: odds ratio. $P < 0.05$ are shown in bold, indicating statistical significance.

IVW分析中观察到FGF21会增加过去5年发生骨折的风险(OR= 1.004, 95%CI: 1.000 ~ 1.008; P= 0.038),具体结果见图2。反向MR分析无任何反向因果关系(见网络资源附件附图2)。此外,在敏感性分析中没有观察到异质性或水平多效性的证据,见网络资源附件附表7和附表8。

2.5 临床基线特征

由于91种CIPs中IVW分析提示只有FGF21同时与OP和过去5年发生骨折存在因果关系,故本研究收集了191例研究对象,在临床血液样本中验证其与骨代谢指标的关系。在性别和年龄匹配的组别中,Ca和P水平无明显差异(P> 0.05)。如预期,DOP组和NDOP组的HbA1c水平高于对照组(P< 0.05);DOP组患者的腰椎和全髋T值低于NDOP组和对照组(P< 0.05)。OT在DOP组中的水平高于对照组(P< 0.05)。见表1。

Exposure	Outcome	nSNP	Method	*P*	OR (95% CI)
CCL19	Fractures over the past five years	17	MR Egger	0.599	0.998 (0.992 to 1.005)
		17	Weighted median	0.385	1.002 (0.997 to 1.008)
		17	Inverse variance weighted	0.314	1.002 (0.998 to 1.006)
		17	Simple mode	0.591	1.003 (0.993 to 1.012)
		17	Weighted mode	0.641	1.002 (0.995 to 1.008)
CCL4	Fractured/broken bones in last 5 years	17	MR Egger	0.786	1.000 (0.996 to 1.003)
		17	Weighted median	0.485	0.999 (0.996 to 1.002)
		17	Inverse variance weighted	0.412	0.999 (0.997 to 1.001)
		17	Simple mode	0.828	1.001 (0.994 to 1.007)
		17	Weighted mode	0.499	0.999 (0.996 to 1.002)
IFN-γ	Fractured/broken bones in last 5 years	9	MR Egger	0.845	1.001 (0.990 to 1.013)
		9	Weighted median	0.911	1.000 (0.992 to 1.009)
		9	Inverse variance weighted	0.832	1.001 (0.995 to 1.007)
		9	Simple mode	0.354	1.006 (0.994 to 1.019)
		9	Weighted mode	0.658	0.997 (0.985 to 1.009)
IL-2Rβ	Fractured/broken bones in last 5 years	11	MR Egger	0.515	1.004 (0.992 to 1.017)
		11	Weighted median	0.454	0.997 (0.989 to 1.005)
		11	Inverse variance weighted	0.125	0.996 (0.990 to 1.001)
		11	Simple mode	0.660	0.997 (0.984 to 1.010)
		11	Weighted mode	0.632	0.997 (0.984 to 1.010)
CD6	Fractured/broken bones in last 5 years	13	MR Egger	0.986	1.000 (0.996 to 1.004)
		13	Weighted median	0.850	1.000 (0.998 to 1.002)
		13	Inverse variance weighted	0.647	1.001 (0.998 to 1.004)
		13	Simple mode	0.081	0.992 (0.984 to 1.000)
		13	Weighted mode	0.895	1.000 (0.998 to 1.002)
CST5	Fractured/broken bones in last 5 years	30	MR Egger	0.183	1.002 (0.999 to 1.005)
		30	Weighted median	0.187	1.002 (0.999 to 1.004)
		30	Inverse variance weighted	0.112	1.002 (1.000 to 1.004)
		30	Simple mode	0.540	1.002 (0.995 to 1.009)
		30	Weighted mode	0.180	1.002 (0.999 to 1.004)
FGF21	Fractured/broken bones in last 5 years	13	MR Egger	0.383	0.996 (0.986 to 1.005)
		13	Weighted median	0.489	1.002 (0.996 to 1.007)
		13	Inverse variance weighted	**0.038**	1.004 (1.000 to 1.008)
		13	Simple mode	0.683	1.002 (0.993 to 1.010)
		13	Weighted mode	0.583	1.002 (0.996 to 1.007)
LIF	Fractured/broken bones in last 5 years	10	MR Egger	0.536	1.006 (0.987 to 1.026)
		10	Weighted median	0.908	0.999 (0.991 to 1.008)
		10	Inverse variance weighted	0.499	1.003 (0.994 to 1.012)
		10	Simple mode	0.913	0.999 (0.985 to 1.014)
		10	Weighted mode	0.909	0.999 (0.986 to 1.013)

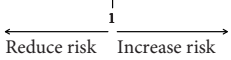

图 2　8种CIPs与过去5年骨折的正向MR分析结果

Fig 2　Positive MR analysis results of 8 CIPs and fractures that occurred in the past 5 years

Abbreviations are the same as in Fig 1. $P < 0.05$ are shown in bold, indicating statistical significance.

2.6　DOP、NDOP和对照组血浆FGF21水平

由表1可见，DOP组的血浆FGF21水平高于NDOP组和对照组（$P<0.05$），且NDOP组血浆FGF21水平亦高于对照组（$P<0.05$）。校正BMI和分组因素后，FGF21水平与年龄呈正相关（$\beta=3.41$，95%CI：0.004 ~ 6.811，$P=0.0497$）。

2.7　FGF21与BMD

结果见表2。在总样本中，FGF21与腰椎（$\beta=-0.003$，95%CI：−0.004 ~ −0.002，$P<0.000\ 1$）和全髋T值（$\beta=-0.002$，95%CI：−0.003 ~ −0.001，$P<0.000\ 1$）呈负相关，当调整年龄、BMI、HbA1c、Ca和P后，负相关仍存在，在女性中，观察到类似情况。而在男性中，FGF21仅与腰椎（$\beta=-0.002$，95%CI：−0.004 ~ 0，$P=0.039$）呈负相关，在调整年龄、BMI、HbA1c、Ca和P后，负相关仍存在。

在T2DM样本中，FGF21与腰椎（$\beta=-0.003$，95%CI：−0.004 ~ −0.001 4，$P<0.000\ 1$）和全髋T值（$\beta=-0.001$，95%CI：−0.002 2 ~ −0.000 5，$P=0.002$）呈负相关，调整年龄、BMI、HbA1c、Ca和P后，负相关同样存在。进一步按性别分层显示：T2DM男性中，FGF21与腰椎（调整后$\beta=-0.003$，95%CI：−0.006 ~ −0.000 6，$P=0.015$）及全髋T值（调整后$\beta=-0.002$，95%CI：−0.004 ~ −0.000 4，$P=0.019$）均呈显著负相关。T2DM女性中，FGF21与腰椎T值相关性仍显著（调整后$\beta=-0.002$，95%CI：−0.004 ~ −0.000 3，$P=0.025$），而与全髋T值的相关性不显著（调整后$P=0.803$）。

3　讨论

本研究利用CIPs的最新版GWAS数据，通过双向MR确定了8种与OP之间存在因果关系的CIPs，其中，

表 1 临床样本的基线特征

Table 1 Baseline characteristics of clinical samples

Clinical characteristic	DOP group (n = 64)	NDOP group (n = 65)	Control group (n = 62)
Age/yr., median (P_{25}, P_{75})	65.00 (59.00, 71.25)	62.00 (54.00, 74.00)	62.00 (57.25, 69.00)
Sex (male/female)/case	11/53	37/28	32/30
BMI/(kg/m^2), median (P_{25}, P_{75})	23.81 (21.23, 27.48)	24.52 (22.49, 25.71)	26.78 (23.32, 27.8)
HbA1c/%, median (P_{25}, P_{75})	7.55 (6.80, 9.00)*	7.60 (7.10, 9.20)*	5.40 (5.20, 5.60)
CTX/(ng/mL), median (P_{25}, P_{75})	0.25 (0.22, 0.28)	0.26 (0.23, 0.27)	0.25 (0.21, 0.27)
OT/(ng/mL), median (P_{25}, P_{75})	15.52 (12.93, 16.65)*	14.72 (11.74, 15.29)	12.94 (10.42, 15.10)
Ca/(mmol/L), median (P_{25}, P_{75})	2.21 (2.07, 2.26)	2.20 (2.13, 2.24)	2.20 (2.09, 2.28)
P/(mmol/L), median (P_{25}, P_{75})	1.15 (0.95, 1.24)	1.08 (0.98, 1.16)	1.12 (0.93, 1.23)
Lumbar T score (median [P_{25}, P_{75}])	−3.10 (−3.40, −2.55)$^{\#,*}$	0.10 (−0.30, 1.20)	0.80 (−0.55, 1.95)
Total Hip T score (median [P_{25}, P_{75}])	−2.70 (−3.12, −2.50)$^{\#,*}$	−0.77 (−0.90, −0.10)*	−0.10 (−0.80, 0.58)
FGF21/(pg/mL), median (P_{25}, P_{75})	396.92 (308.98, 523.94)$^{\#,*}$	346.88 (283.82, 466.86)*	233.66 (169.95, 327.78)

BMI: body mass index; HbA1c: glycolated hemoglobin; CTX: C-terminal telopeptide of type Ⅰ collagen; OC: osteocalcin; FGF21: fibroblast growth factor 21; Ca: calcium; P: phosphorus. DOP, T2DM patients with OP; NDOP, T2DM patients without OP. $^{\#}$ P < 0.05, vs. NDOP group; * P < 0.05, vs. control group.

表 2 FGF21与BMD之间的相关性

Table 2 The correlation between FGF21 and BMD

Subject		Lumbar T score			Total Hip T score		
		β	95% CI	P	β	95% CI	P
Total (all)	Unadjusted	−0.003	−0.004 to −0.002	< 0.000 1	−0.002	−0.003 to −0.001	< 0.000 1
	Adjusted	−0.004	−0.005 to −0.002	< 0.000 1	−0.002	−0.003 to −0.001	< 0.000 1
Male	Unadjusted	−0.002	−0.004 to 0	0.039	−0.001	−0.003 to 0	0.167
	Adjusted	−0.002	−0.004 to −0.000 3	0.021	−0.001	−0.002 to 0.000 2	0.115
Female	Unadjusted	−0.003	−0.004 to −0.002	< 0.000 1	−0.002	−0.003 to −0.001	< 0.000 1
	Adjusted	−0.003	−0.004 to −0.002	< 0.000 1	−0.001	−0.002 to −0.000 3	0.008
T2DM (all)	Unadjusted	−0.003	−0.004 to −0.001 4	< 0.000 1	−0.001	−0.002 2 to −0.000 5	0.002
	Adjusted	−0.003	−0.004 9 to −0.001 4	0.004	−0.002	−0.002 7 to −0.000 4	0.008
Male	Unadjusted	−0.002	−0.005 to 0.000 7	0.143	−0.001	−0.003 to 0.001 7	0.626
	Adjusted	−0.003	−0.006 to −0.000 6	0.015	−0.002	−0.004 to −0.000 4	0.019
Female	Unadjusted	−0.002	−0.003 to −0.000 9	0.001	−0.001	−0.002 to −0.000 4	0.004
	Adjusted	−0.002	−0.004 to −0.000 3	0.025	−0.000 1	−0.001 3 to 0.001	0.803

Adjusted indicates results after adjustment for age, body mass index (BMI), glycated hemoglobin (HbA1c), calcium (Ca), and phosphorus (P).

CD6、FGF21、CST5和LIF会增加OP的风险，CCL4、CCL19、IFN-γ和IL-2Rβ会降低OP的风险，值得注意的是，FGF21还会增加过去5年发生骨折的风险，尽管上述关联在FDR校正后未达到统计学显著性，但FGF21在多种敏感性分析中表现出一致的效应方向，且既往研究提示其在骨代谢及炎症调控中具有一定的生物学作用。因此，该结果更倾向于提示一种潜在的因果关联。在此基础上，本研究进一步在合并或未合并OP的T2DM患者及健康对照人群中，验证了FGF21与BMD水平之间的关系，发现DOP患者的血浆FGF21水平明显高于NDOP患者和健康人群，且NDOP组的FGF21水平也明显高于健康人群；无论在全部受试者还是T2DM患者中，FGF21均与腰椎和全髋T值呈负相关。

增加OP风险的炎症蛋白中：LIF属于白介素6家族，在骨骼中抑制成熟的成骨细胞功能。它还负责增强前列腺素诱导的骨吸收[26]。CD6主要在T细胞表面表达，通过CD6-白细胞黏附分子信号转导促进破骨细胞形成和骨破坏基因的转录[27]。CST5属于胱抑素家族，值得注意的是，研究表明上调的CST5通过阻断NF-κB通路抑制OP大鼠模型中的骨吸收和破骨细胞的激活[28]，这与本研究结果相反，但是关于CST5对骨骼影响的研究较少，还需要进一步探索其作用机制。虽然FGF21对骨骼健康的具体影响尚不明确[13]，然而已有研究表明*FGF21*转基因小鼠及药理性FGF21治疗均导致明显骨量丢失，敲除*FGF21*基因的小鼠则表现为高骨量表型，其机制是FGF21通过增强过氧化物酶体增殖物激活受体γ(PPAR-γ)活性，抑制间充质干细胞的成骨分化并促进脂肪细胞分化[29]。

降低OP风险的炎症蛋白中：CCL4和CCL19均会促进破骨细胞的活力和迁移能力[30-31]，破骨细胞可以吸收骨组织并释放转化生长因子-β，转化生长因子-β会募集成骨前

细胞重塑骨骼并增强整体成骨细胞生态位状况[32]。IL-2可以通过IL-2Rβ和γ形成的二聚体传导信号，诱导细胞增殖和分化[33]，因此IL-2Rβ水平的降低可能导致细胞增殖的抑制。IFN-γ不仅通过诱导runt相关转录因子2通路刺激成骨细胞分化从而促进骨矿化，而且还通过抑制破骨细胞活性来减少骨流失[34]。

由于FGF21在调节糖脂代谢中发挥重要作用，显示出治疗代谢性疾病的潜力[12]，故FGF21有望成为治疗DM和肥胖症的新药，目前正处于临床试验阶段。鉴于DM本身与骨折风险增加相关，且噻唑烷二酮类药物（如罗格列酮）作为PPAR-γ激动剂可导致骨质流失甚至OP[35]，提示在开发降糖药物时需关注骨安全性 。本研究发现FGF21会增加OP和过去5年发生骨折的风险，且与BMD负相关。因此，作为由肝脏、脂肪等组织表达的内分泌因子，FGF21与骨骼这一内分泌器官之间可能存在互作。当FGF21用于代谢性疾病治疗时，应警惕其对骨的作用。

本研究的创新性主要体现在，采用MR方法，对91种CIPs进行全面地系统筛选，识别与OP及骨折风险具有潜在因果关系的关键蛋白，并在临床样本中验证FGF21血浆水平与BMD之间的相关性。与既往研究相比，本研究从整体层面对多种CIPs与骨折及骨质疏松结局的因果关系进行了系统评估，并结合临床样本验证，从而增强了研究结论的可靠性[36-37]。此外，本研究发现FGF21对骨密度的影响存在性别差异。女性中其与腰椎及髋部BMD均呈显著负相关，而男性中相关性主要限于腰椎部位。这可能与雌激素可调节FGF21的分泌与信号通路有关。女性在绝经后内分泌变化可能强化FGF21对骨代谢的不利效应，而男性体内相对稳定的雄激素水平可能部分抵消这一作用。因此，性激素可能通过影响FGF21介导的能量代谢与骨稳态通路，造成性别间差异。这一发现提示未来研究应关注不同性别中FGF21信号通路的调节网络和分子机制。同时，本研究亦存在以下局限性：①MR分析主要基于欧洲人群的遗传学数据，而临床样本分析则来源于中国人群。由于不同人群在遗传背景、等位基因频率、连锁不平衡结构以及疾病易感性等方面可能存在显著差异，这种人群来源的不一致性可能对研究结果的外推性和一致性产生一定影响。②由于数据库中仅针对普通OP患者和骨折患者，未包含糖尿病患者，而临床研究却包含T2DM患者，代谢紊乱可能影响FGF21与BMD的关联。③临床研究只检测了部分血清生化指标和骨代谢标志物，未能获取患者骨折事件的前瞻性数据，这使得本研究无法直接评估循环中FGF21水平与骨折风险的关联强度。④上述关联在FDR校正后未达到统计学显著性，仍需在独立人群数据及后续功能实验中进一步验证。

综上所述，本研究通过双向MR分析鉴定出8种与OP存在因果关系的CIPs，其中FGF21同时会增加过去5年骨折风险。此外，本研究还揭示了FGF21与T2DM患者BMD之间存在负相关关系，且与年龄、BMI、HbA1c、Ca和P无关，为FGF21在骨代谢中的作用提供了新的见解。值得注意的是，FGF21对骨密度的影响在男性和女性中可能存在差异。未来研究可重点探讨性激素在其中发挥的调节作用，以及不同部位骨组成差异对上述关联的影响机制。

*　　*　　*

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