· 论著 ·

绝经后女性铁蓄积与骨代谢及机体炎症反应的相关性研究

程千[1,2*] 刘起富[3] 金铭[2] 赵国阳[2] 徐又佳[4]
1.上海交通大学医学院附属同仁医院,上海 200050
2.江苏大学附属医院,江苏 镇江 212000
3.山东省青州市人民医院,山东 潍坊 262500
4.苏州大学附属第二医院,江苏 苏州 215000

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摘要: **目的** 研究绝经后女性铁蓄积与骨代谢及机体炎症反应的相关性。**方法** 将 117 名绝经后女性体检者按照骨密度(bone mineral density,BMD)值分成 3 组:骨量正常组(T≥-1)、骨量减少组(-2.5<T<-1)和骨质疏松组(T≤-2.5)。所有体检者均测定:血清生化指标[钙、磷、25(OH)D、血红蛋白、CRP、白细胞、肌酐、尿酸、丙氨酸氨基转移酶、谷草转氨酶、空腹血糖]、铁代谢指标[血清铁蛋白(Fer)、转铁蛋白(TRF)]、骨代谢指标[Ⅰ型胶原代谢产物(β-CTX、PINP)]。**结果** 绝经后女性随着年龄增大,体内血清铁蛋白升高,铁蓄积增加,患骨质疏松症的风险增加,同时伴随 β-CTX、PINP、CRP 升高。其中血清铁蛋白与骨密度呈负相关,与 β-CTX、PINP、CRP 呈正相关。**结论** 绝经后女性体内存在铁蓄积,同时伴有慢性炎症反应,铁蓄积可促进Ⅰ型胶原蛋白降解,加速骨质疏松的进程。

关键词: 铁蓄积;骨代谢;炎症反应;骨质疏松;骨密度

The correlation between iron excess and bone metabolism and inflammation in postmenopausal women

CHENG Qian[1,2*], LIU Qifu[3], JIN Ming[2], ZHAO Guoyang[2], XU Youjia[4]
1.Tongren Hospital Affiliated to Medical College of Shanghai Jiaotong University, Shanghai 200050
2.The Affiliated Hospital of Jiangsu University, Zhenjiang 212000
3.Qingzhou People's Hospital, Weifang 262500
4.The Affiliated Second Hospital of Suzhou University, Suzhou 215000, China
* Corresponding author: CHENG Qian, Email: zggkcq@sina.com

Abstract: **Objective** To study the correlation between iron excess and bone metabolism and inflammatory response in postmenopausal women. **Methods** A total of117 postmenopausal women were divided into normal (T≥-1), bone loss (BL) (-2.5<T<-1) and osteoporosis group (T≤-2.5) according to BMD. Serum biochemical indicators including calcium (Ca), phosphorus (P), 25-hydroxyvitamin D [25(OH)D], white blood cell count (WBC), hemoglobin, glucose, C-reactive protein (CRP), creatinine, uric acid, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were measured in all patients. Iron metabolism indicators, Fer and TRF, as well as serum bone metabolism indicators β-CTX and PINP were determined. **Results** With the age increase of the postmenopausal women, the serum ferritin and iron excess elevated in the body, and the risk of osteoporosis increased along with the increase of β-CTX, PINP, and CRP. The serum ferritin is negatively correlated with BMD, but is positively correlated with β-CTX, PINP, and CRP. **Conclusion** Iron excess in postmenopausal women is accompanied by chronic inflammatory reaction. It promotes the degradation of type I collagen and accelerates the process of osteoporosis.

Key words: iron excess; bone metabolism; inflammatory reaction; osteoporosis; bone mineral density

铁是维持人体生理功能所必需的微量元素之一[1-2],铁的缺乏可导致骨质的流失,进而诱发骨质疏松的发生[3-4]。然而,研究表明[5],体内的高铁负荷对成骨细胞具有毒性作用,过量的铁通过抑制成骨细胞的增殖和分化,促进破骨细胞的生成[6],诱发骨质疏松的形成。实验表明[7],铁蓄积可加重去势动物骨量减少。

绝经后骨质疏松症(postmenopausal osteoporosis,

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* 通信作者:程千,Email:zggkcq@sina.com

PMOP)是一种全身性骨代谢疾病,表现为女性绝经后进行性的骨质疏松[8]。以往研究[9]表明,铁仅在雌激素缺乏的情况下影响骨量。然而,笔者研究[10]发现,铁蓄积是绝经后骨质疏松症的一个独立危险因素。本研究对绝经后女性体检者的相关数据进行了回顾性分析,探讨绝经后女性铁蓄积与骨代谢及机体炎症反应之间的相关性。

1 材料和方法

1.1 资料来源

本研究收集了 117 名绝经后女性体检者资料,排除患有继发性骨质疏松症、小肠吸收不良或其他营养缺乏疾病。所有体检者均记录其身高、体重、体质量指数(bone mass index, BMI)、骨密度(bone mineral density, BMD),同时完善相关的血液指标检查。根据世界卫生组织 WHO 诊断标准[21],确定患有骨质疏松症的诊断标准为:T≥-1(骨量正常),-2.5<T<-1(骨量减少),T≤-2.5(骨质疏松症)。该项研究经苏州大学附属二院伦理委员会批准,所有体检者在检查之前均签署知情同意书。

1.2 方法

所有体检者均测定:血清生化指标[钙、磷、25(OH)D、血红蛋白、CRP、白细胞、肌酐、尿酸、丙氨酸氨基转移酶、谷草转氨酶、空腹血糖]、铁代谢指标[血清铁蛋白(Fer)、转铁蛋白(TRF)]、骨代谢指标[I型胶原代谢产物(β-CTX、PINP)]。每位体检者在禁食一夜后(10 h 或更长时间),抽取肘前静脉血,根据检验结果绘制图表。采用电化学发光检测血清 Fer 和 TRF 含量;通过电化学阻抗法检测血常规;其他生化指标采用酶动力学法测定(AU 5400, OLYMPUS, Japan);β-CTX、PINP 也用标准 ELISA 方法评估。

1.3 统计学处理

将 117 名绝经后女性体检者,按照骨密度值分成 3 组,骨量正常组、骨量减少组和骨质疏松组。采用 PCA 进行分组验证,以保证分组的合理性和后续数据的准确性。其中需要考虑的因素有年龄、绝经年限、T 值(股骨颈及 L1~4)、血红蛋白、肌酐、尿酸、甘油三酯、总胆固醇、BMI、Fer、TRF、25(OH)D、β-CTX、PINP、Ca、P、CRP、WBC、AST、ALT、葡萄糖。用 Dunnett's 多重分析检验正常组与骨量减少组、正常组与骨质疏松组的骨代谢指标的相关性。采用回归分析法分析血清铁蛋白、基线特征及骨代谢指标的相关性。

2 结果

2.1 铁蓄积与骨质疏松及机体慢性炎症反应的相关性

按照股骨颈和腰椎(L1~4)部位的 T 值,将 117 名绝经后女性体检者,分成正常组(n=28)、骨量减少组(n=71)和骨质疏松组(n=18)。采用 PCA 进行分组验证(图 1),结果与按照 T 值分组一致,说明分组是准确的,具有统计学意义。就基线特征而言

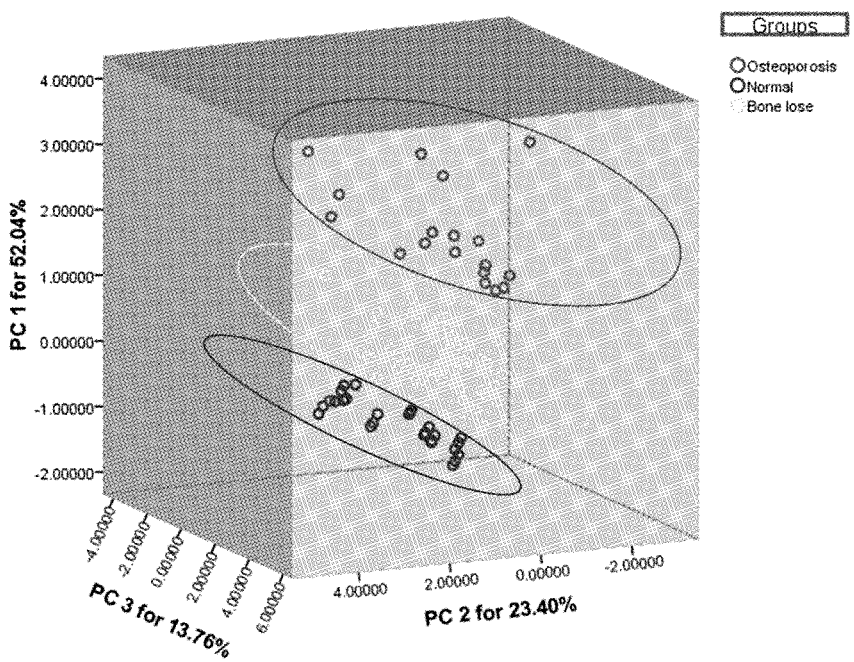

图 1 PCA 分组验证

Fig.1 Verification of grouping by principal component analysis

(表 1),从正常组到骨质疏松组,BMI 呈下降趋势,女性随着年龄和绝经年限增加,体内出现铁蓄积,患骨质疏松症的风险增加,血清铁蛋白水平与 BMD 呈显著负相关($P<0.01$),见图 2;骨质疏松组在年龄、绝经年限、BMI、CRP 等方面与正常组相比,有统计学意义($P<0.05$);血清铁蛋白不仅与绝经年限呈正相关($P<0.01$),同时与 CRP 水平呈正相关($P<0.05$),见图 3。

表 1 正常组、骨量减少组和骨质疏松组的基线特征比较

Table 1 Baseline characteristics in normal, bone loss, and osteoporosis group

特征	骨量正常组($n=28$)	骨量减少组($n=71$)	骨质疏松组($n=18$)
年龄/岁	66.89±11.54	70.61±9.11▲	77.61±10.43*
股骨颈 T 值	−0.39±0.88	−1.75±0.75	−3.22±0.53
L1~4 T 值	−0.36±0.62	−1.87±0.88	−3.53±0.53
25(OH)D/(mmol/L)	43.59±9.13	43.05±19.36	44.07±22.71
身高/cm	158.33±5.89	158.55±3.71	154.94±4.48
体重/kg	57.89±9.43	59.03±8.96	49.94±9.61
BMI/(kg/m^2)	23.12±3.76	23.38±3.10	20.74±3.61*
Ca/(mmol/L)	2.25±0.10	2.24±0.14	2.18±0.13
P/(mmol/L)	1.06±0.18	1.10±0.19	1.11±0.24
绝经年限/年	15.89±9.71	19.99±8.63	27.33±11.79**
血红蛋白/(g/L)	113.33±16.05	117.66±19.73	105.11±16.02
CRP/(mg/L)	8.47±4.37	8.77±4.56▲	9.74±4.98*
WBC/(10^9/L)	6.92±2.00	6.80±2.16	6.83±1.51
N/%	70.56±10.55	69.66±9.84	71.35±9.29
Total CO_2/(mmol/L)	26.66±2.21	25.27±2.20	25.22±6.01
肌酐/(U/L)	53.22±8.47	56.45±20.05	58.06±13.14
尿酸/(μmol/L)	213.56±36.37	268.35±74.62	232.33±79.38
甘油三酯/(mmol/L)	0.87±0.33	1.25±0.71	1.33±1.52
总胆固醇/(mmol/L)	4.54±1.14	4.91±1.02	4.67±0.97
AST/(U/L)	21.00±5.59	25.34±19.13	24.56±11.42
ALT/(U/L)	17.56±7.76	20.03±20.88	19.28±12.82
葡萄糖/(mmol/L)	6.28±0.89	5.71±1.06	5.83±0.98

注:与正常组相比,▲* $P<0.05$;与正常组相比,** $P<0.01$。

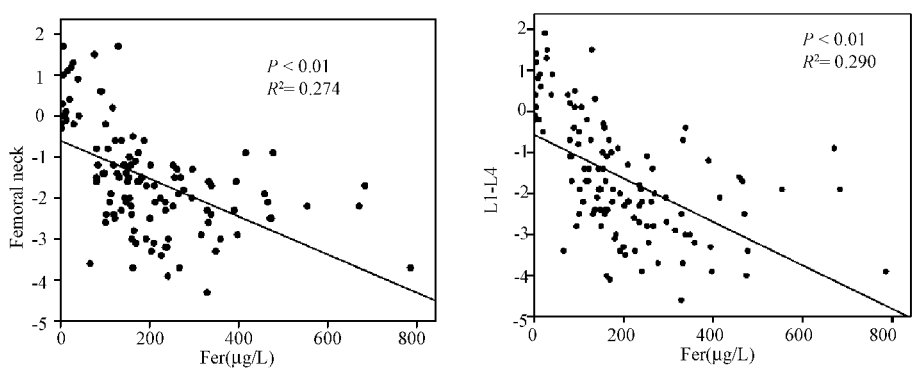

图 2 血清铁蛋白与 BMD 的相关性

Fig.2 The correlation between serum iron and BMD

注:与正常组相比,▲* $P<0.05$;与正常组相比,** $P<0.01$。

2.2 铁蓄积与骨代谢指标的相关性

正常组、骨量减少组和骨质疏松组的血清铁蛋白平均值分别为(120.96±43.18)、(223.37±130.27)、(307.50±161.48)μg/L,转铁蛋白平均值分别为(2±0.22)、(1.95±0.36)、(1.62±0.29)g/L。由图 4 可见,与正常组相比,骨量减少组和骨质疏松组的血清铁蛋白值显著升高($P<0.05$),转铁蛋白值下降($P<0.05$);骨质疏松组 β-CTX 平均值[(667.90±316.55)ng/L]高于正常组[(406.06±112.12)ng/L],$P<0.05$;PINP 平均值[(78.03±37.31)μg/L]明显高于正常组[(37.60±13.17)μg/L],$P<0.01$。血清铁蛋白与骨代谢指标Ⅰ型胶原代谢产物 β-CTX、PINP 呈显著正相关($P<0.01$,图 5)。

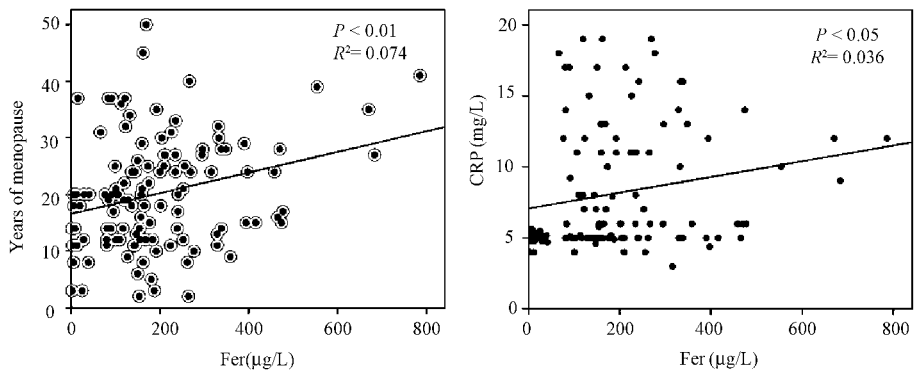

图 3 血清铁蛋白与绝经年限、CRP 的相关性

Fig.3 Correlative analysis between serum iron and years of menopause and CRP

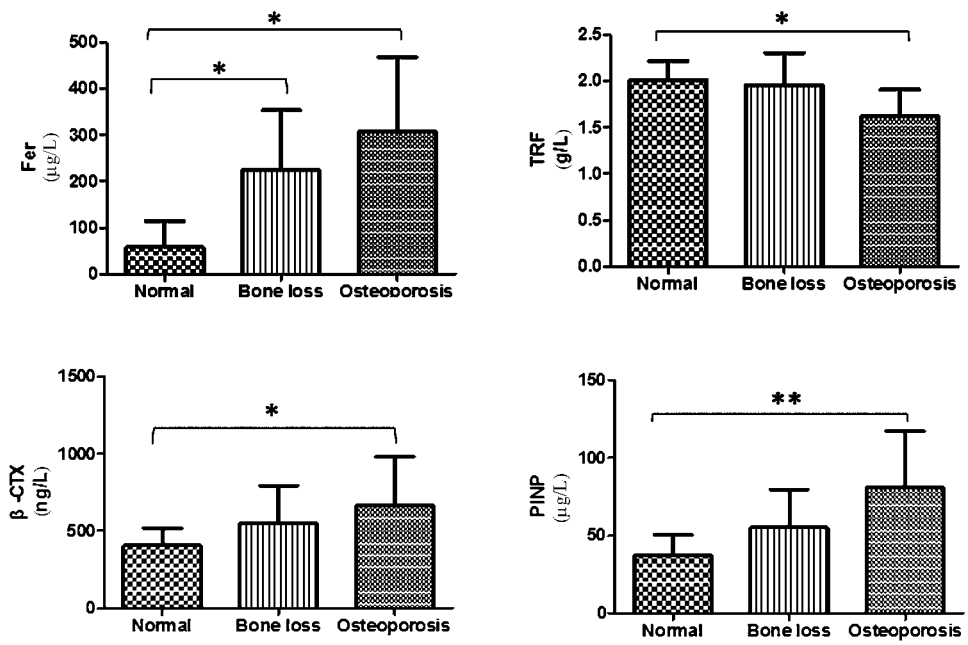

图 4 正常组、骨量减少组与骨质疏松组的血清铁蛋白、转铁蛋白、β-CTX、PINP 的相关性

Fig.4 Correlation among serum iron, β-CTX, and PINP in different groups

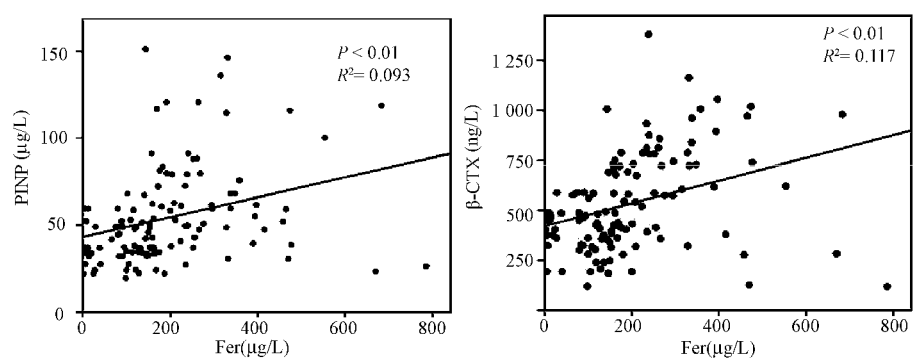

图 5 血清铁蛋白与 PINP、β-CTX 的相关性

Fig.5 Correlation between serum iron and β-CTX and PINP

3 讨论

骨组织中 17%~20%的成分为胶原蛋白[11]，其中最常见的为 I 型胶原蛋白。胶原蛋白的存在提高了骨的韧性，降低了骨的脆性，致使骨强度增加[12]。大约 30%的胶原蛋白是由成骨细胞分泌的[13]，其成分的改变加速了疾病的进展[14]。I 型胶原蛋白由 I 型胶原氨基端延长肽（PINP）与 I 型胶原羧基端肽（CTX）组成[15]，它们是 I 型胶原蛋白的降解产物[16-17]，是骨基质合成的生物标志物。其中 PINP 在血清中以两种形式存在，一种是与前胶原蛋白的天然分离产物相对应的完整的三聚肽，另一种是前胶原蛋白的降解产物单体肽[18]。I 型胶原蛋白在骨吸收时释放 CTX 到血液中[19]，包括 α-CTX 和异构化的 β-CTX，前者只能在尿液中测出[20]。笔者首次报道了铁蓄积对胶原蛋白降解的影响，其通过促进 I 型胶原降解来增加骨吸收。统计结果显示，血清铁蛋白与 PINP、β-CTX 呈正相关。通过 PubMed 检索相关文献发现，金属离子的确能够促进或抑制胶原蛋白的降解，如 Osorio 等[21]发现体内锌过载，可抑制基质金属蛋白酶介导的胶原蛋白降解。

BMD 是临床中诊断骨质疏松症的最重要的指标[22]。然而，单纯依靠 BMD 的 T 值进行分组，尚不能准确的描述样本的总体信息。如果样本分组错误，组与组之间的比较就会不准确，结果可能是错误的。PCA 是一个多变量的数据分析，可以用来比较复杂的样本之间的相似点和不同点[23-25]。因此，笔者依据 BMD 的 T 值分组后，再使用 PCA 进行分组验证，如果得出的结果不一致，就要重新调整样本分组。但是通过结果观察到，经过 PCA 验证，各组之间并没交叉，进一步证实了根据 T 值分成 3 组的合理性和可行性。因此，后续对各组之间的指标进行比较，就具有统计学意义。

我国女性的绝经年龄一般在 50 岁左右[26]，通常年龄越大，绝经年限越长，体内的雌激素水平就越低。女性绝经后，随着年龄的增大，骨量逐渐减少，继而发生骨质疏松。骨质疏松症患者的身高和体重呈显著下降趋势，最终导致 BMI 明显降低。研究表明[27]，铁盐能抑制羟磷灰石晶体的生长，说明了铁对骨形成有直接抑制作用。骨质疏松症患者的血清铁蛋白升高，BMD 显著下降，绝经年限越长，铁蓄积越严重。

研究表明[28-29]，小鼠体内铁蓄积与血清铁蛋白升高、Runx2 mRNA 水平降低、成骨间质干细胞分化的抑制密切相关。根据临床相关数据分析，随着女性绝经年限的增加，其体内血清铁蛋白水平显著升高，铁蓄积促进 I 型胶原蛋白的降解，诱导体内炎症反应，同时增强破骨细胞活力，导致骨吸收增加，继而加速骨质疏松进程。所有这些过程均表现为身高的降低，体重下降，BMI 及 BMD 下降，最终导致骨质疏松症（图 6）。

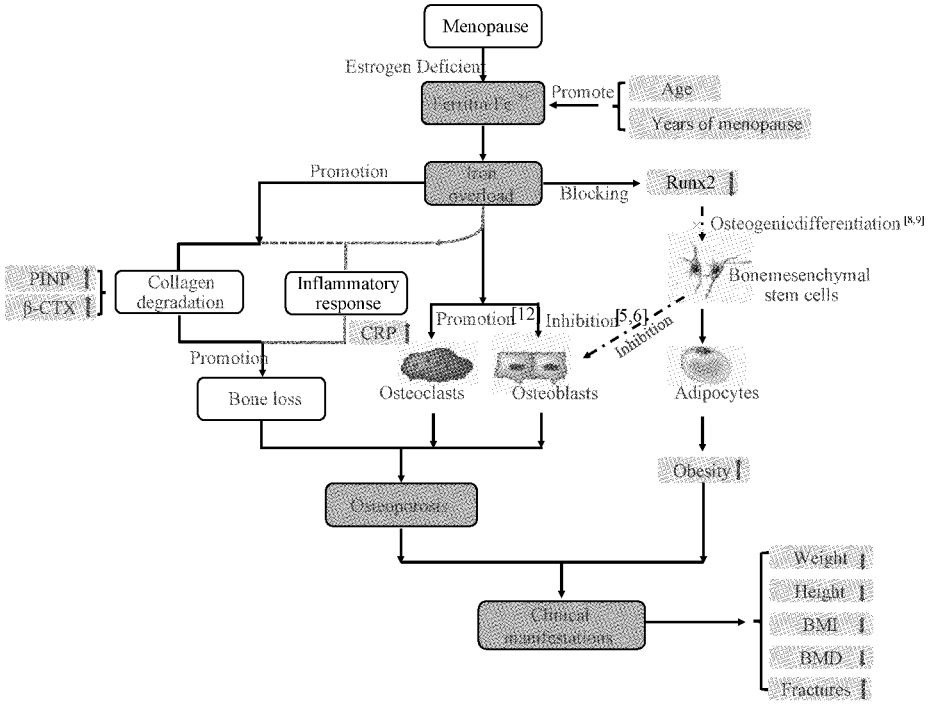

图 6 PMOP 铁蓄积机制

Fig.6 Mechanism of iron overload on PMOP

CRP 是体现机体炎症反应的重要指标，本实验发现，CRP 值在骨量减少组和骨质疏松组明显升高，表明此时机体存在慢性炎症反应[30]。多项临床对照研究[31]表明，骨量减少与机体的慢性炎症状态有一定的相关性。女性绝经后，体内出现铁蓄积，机体处于慢性低度炎症状态，继而出现骨质疏松症，CRP 随着血清铁蛋白的增加而升高，二者呈正相关。因此，研究炎症与骨质疏松症的相关性，或许会成为治疗骨质疏松症的新方法。

随着女性年龄的增大，血清铁蛋白逐渐升高，骨密度逐渐下降，二者之间存在显著相关性。血清铁蛋白升高时，骨量减少、骨质疏松的发生率增大，同时机体伴随着慢性炎症反应，加速 I 型胶原蛋白的降解，继而促进骨质疏松的进程。然而铁蓄积促进 I 型胶原蛋白降解的机制，炎症反应与骨质疏松症的相关机制仍不明确。后续笔者将继续研究胶原蛋白降解调控酶、炎症反应与血清铁蛋白具体调控酶之间的相互作用，为临床治疗骨质疏松提供新的思路。

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