

· 老年人骨质疏松专栏 ·

老年糖尿病患者骨密度变化和骨代谢指标与胰岛素抵抗关系的初步探讨

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【摘要】目的 探索老年糖尿病患者胰岛素抵抗(IR)对维生素D(vit D)代谢和骨代谢影响。**方法** 纳入2011年01月至2013年12月于本院内分泌科住院的65~89岁的2型糖尿病患者55例。采集病例资料, 进行口服葡萄糖糖耐量试验、胰岛素和C肽释放实验, 检测骨转换指标、进行双光能X线骨密度检查, 分析该组患者葡萄糖代谢、IR对骨代谢的影响。**结果** 血清糖化血红蛋白(HbA1c)水平与血清维生素D₃(VitD₃)呈负相关($r = -0.42$, $P = 0.019$), 与甲状旁腺激素(PTH)呈正相关($r = 0.40$, $P = 0.05$); 空腹C肽(FCP)与PTH呈正相关($r = 0.46$, $P = 0.015$); 恒稳态模型评估(HOMA)- β 也与PTH呈正相关($r = 0.56$, $P = 0.004$); HOMA-C肽(CR)与骨钙素(OCN)呈正相关($r = 0.461$, $P = 0.031$), 也和PTH呈正相关($r = 0.43$, $P = 0.028$)。空腹血糖、HbA1c以及HOMA- β 、HOMA-CR以及骨转换指标和任何部位骨密度T值均无显著相关性。**结论** 在老年糖尿病患者中, 改善IR、及时纠正vit D缺乏或不足对预防骨质疏松具有重要临床意义。

【关键词】 糖尿病, 2型; 胰岛素抵抗; 骨质疏松; 骨密度; 骨质疏松性骨折; 肌肉骨骼生理学现象

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Correlation of bone density and metabolism with insulin resistance in aged diabetic patients

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【Abstract】Objective To determine the effects of insulin resistance (IR) on bone metabolism and vitamin D metabolism in the elderly patients with diabetes mellitus(DM). **Methods** A total of 55 patients with type 2 DM at the age ranging from 65 to 89 years admitted in our department from January 2011 to December 2013 were recruited in this study. All of them were tested for oral glucose tolerance test, insulin release test and C-peptide release test. Serum levels of vitamin D₃ (VitD₃) and parathyroid hormone (PTH), and biomarkers for bone metabolism, including osteocalcin (OCN) and carboxy-terminal β collagen crosslinks (β -CTX) were also detected. Bone mineral density (BMD) was measured by dual energy X-ray absorptiometry. Correlation analysis was performed on the effects of glucose metabolism and IR on bone metabolism. **Results** In the cohort, the serum level of glycosylated hemoglobin (HbA1c) was negatively correlated with that of VitD₃ ($r = -0.42$, $P = 0.019$), but positively with PTH ($r = 0.40$, $P = 0.05$). PTH was also positively related to fasting C peptide (FCP) ($r = 0.40$, $P = 0.015$) and Homeostasis Model Assessment(HOMA- β) ($r = 0.56$, $P = 0.004$). Bone formation marker OCN was in a positive correlation with HOMA-calretinin (HOMA-CR, $r = 0.461$, $P = 0.031$), while PTH was positively related to HOMA-CR either ($r = 0.43$, $P = 0.028$). But no correlation was seen in T values of BMD from every region of the total body with blood glucose, HbA1c, HOMA- β , HOMA-CR and bone metabolic markers. **Conclusion** For aged patients with diabetes, it is of great clinical significance to ameliorate IR and timely treat VitD deficiency or insufficiency in order to prevent osteoporosis.

【Key words】 diabetes mellitus, type 2; insulin resistance; osteoporosis; bone density; osteoporotic fractures; musculoskeletal physiological phenomena

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在世界范围内,骨质疏松(osteoporosis, OS)与糖尿病均是日益严重的健康卫生问题。OS患者在全世界已达2亿人,是中老年人骨折的重要原因,也是致死致残的重要原因^[1,2]。世界卫生组织也在2013年的工作报告中再次强调了糖尿病对人类健康的威胁,患病人数已达3.4亿^[3],而我国2012年卫生统计显示糖尿病患病率已达10.7%^[4]。糖尿病不但和OS有共同的发病基础^[5],也是OS和骨折的危险因素^[6-10],关于糖尿病引起骨代谢异常的机制,目前提出的理论包括胰岛素或胰岛素样生长因子分泌不足、胰岛素抵抗(IR)、维生素D(vitD)代谢异常等^[11-16],这些也在糖尿病患者中得到了证实,但在老年糖尿病患者中,这些因素是否仍是骨代谢异常的原因呢?本研究对此进行初步探讨。

1 对象与方法

1.1 研究对象

采集2011年1月至2013年12月在郑州大学第一附属医院内分泌科住院的老年糖尿病患者,年龄>65岁;2型糖尿病的诊断采用2010年美国糖尿病联合会(American Diabetes Association, ADA)的糖尿病诊断标准:(1)糖化血红蛋白(glycosylated hemoglobin, HbA1c)≥6.6%;(2)空腹血糖(fasting blood-glucose, FBG)≥7.0mmol/L;(3)口服糖耐量试验餐后2h血糖≥11.1mmol/L;(4)伴有明显的高血糖症状时,随机血糖≥11.1mmol/L。排除下列情况者:饮酒≥48g/d,吸烟≥20支/d,糖皮质激素服用≥3个月,放化疗史,自身免疫性疾病(狼疮、类风湿性关节炎等),慢性腹泻(≥2个月),库欣病,甲状腺疾病,甲状旁腺疾病,恶病质等。

1.2 研究方法

检测并记录所有患者一般情况,包括年龄(岁)、性别、身高(cm)、体质量(kg),糖尿病病史(年)。所有患者均进行口服葡萄糖耐量试验以及胰岛素-C肽释放试验,血糖采用葡萄糖氧化酶法测定;HbA1c用高效液相色谱法测定;血清胰岛素和C肽采用电化学发光法。血脂、血肌酐、尿素氮、尿酸、血钙磷、肝功能、血常规等常规生化检测由郑州大学第一附属医院检验科执行。用空腹C肽(fasting C peptide, FCP)代替胰岛素的改良稳态模型评估(Homeostasis Model Assessment, HOMA)公式评价IR和胰岛β细胞功能: $HOMA-\beta = 270 \times FCP / 0.333 [FBG - 3.5]$, $HOMA-CR = 1.5 + FBG \times FCP / (2.8 \times 0.333)$, FCP单位为μg/L, FBG单位为mmol/L。

所有患者均接受骨密度检查,所用仪器为Norland

双光能X线骨密度仪,检测部位包括腰椎(L₂₋₄)、股骨颈、Ward区、大转子区。所检测的骨代谢相关指标包括骨钙素(osteocalcin, OCN, 电化学发光法),甲状旁腺激素(parathyroid hormone, PTH, 酶联免疫法),I型胶原C端交联肽(carboxy-terminal β collagen crosslinks, β-CTX),I型前胶原N端前肽(procollagen type I N-terminal propeptide, P I NP),维生素D₃(Vitamin D₃, VitD₃)。

1.3 统计学处理

应用SPSS16.0软件包进行分析,数据以 $\bar{x} \pm s$ 表示,采用Pearson相关分析。以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 一般情况

符合入组标准的患者共55例,其中男31例,女24例。年龄范围65~89岁,男性(69.9 ± 8.7)岁,女性(70.2 ± 9.1)岁,体质量指数(25.1 ± 3.3)kg/m²,糖尿病病史(7.9 ± 3.8)年,FBG(8.1 ± 1.5)mmol/L, HbA1c(8.7 ± 2.3)%(图1)。

2.2 葡萄糖代谢与骨代谢指标的相关分析

骨代谢相关指标分别为OCN(16.65 ± 8.14)ng/L, PTH(33.38 ± 15.92)μg/L, CTX(0.33 ± 0.22)μg/L, P I NP(50.93 ± 23.71)ng/L, VitD₃(15.54 ± 6.67)μg/L。HOMA-β, HOMA-CR, HbA1c与血清VitD₃呈负相关($r = -0.42$, $P = 0.019$;图1A);HbA1c与PTH呈正相关($r = 0.40$, $P = 0.05$;图1B);FCP与PTH呈正相关($r = 0.46$, $P = 0.015$;图1C);HOMA-β也与PTH呈正相关($r = 0.56$, $P = 0.004$);HOMA-CR与OCN呈正相关($r = 0.46$, $P = 0.031$;图1D),也与PTH呈正相关($r = 0.43$, $P = 0.028$)。

2.3 糖代谢相关指标与骨密度的相关分析

腰椎部位骨密度(L₂₋₄)T值为 -0.54 ± 2.25 ,股骨颈部位骨密度T值为 -0.07 ± 2.28 ,大转子部位骨密度T值 -0.29 ± 1.84 ,Ward三角区骨密度T值 -1.98 ± 1.41 (图2)。55例研究对象中发生OS者14例,骨量减少者25例。FGB、HbA1c与腰椎、股骨颈、大转子、Ward三角区骨密度T值均无显著相关性;以及HOMA-β、HOMA-CR和各个部位的骨密度T值也均无显著相关性(骨密度扫描范围定义见图3)。

3 讨论

在糖尿病患者中,OS的发生率高于一般人群,但其发病机制仍不明确,其中胰岛素和胰岛素样生长

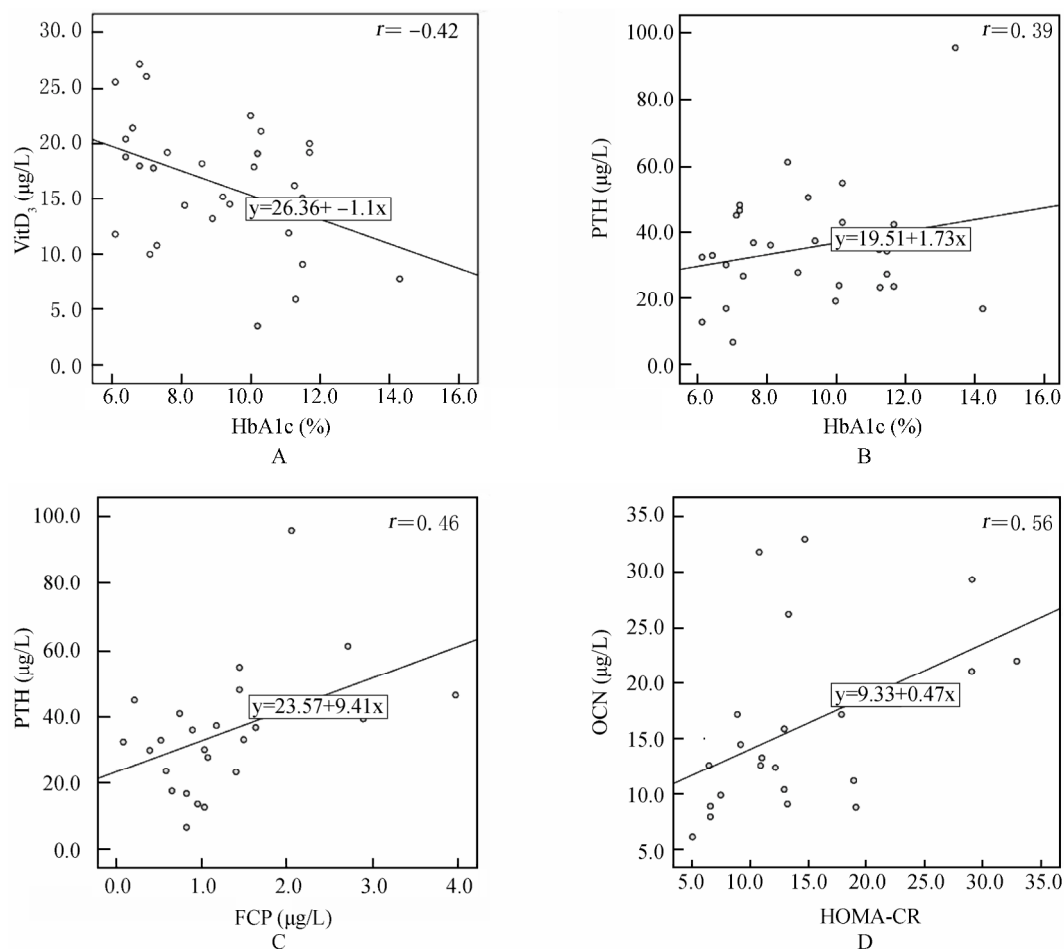


图1 骨代谢与糖代谢指标的相关性分析

Figure 1 Correlation analysis between biomarkers of bone metabolism and glycometabolism

VitD₃: vitamin D₃; HbA1c: glycosylated hemoglobin A1c; PTH: parathyroid hormone; FCP: fasting C-peptide; OCN: osteocalcin; HOMA-CR: Homeostasis Model ModelAssessment-calretinin

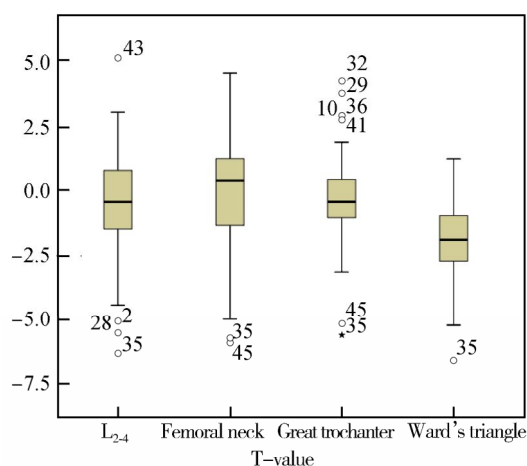


图2 研究对象的各个部位骨密度平均值

Figure 2 T values of bone mineral density for all subjects
L₂₋₄: lumbar 2-4

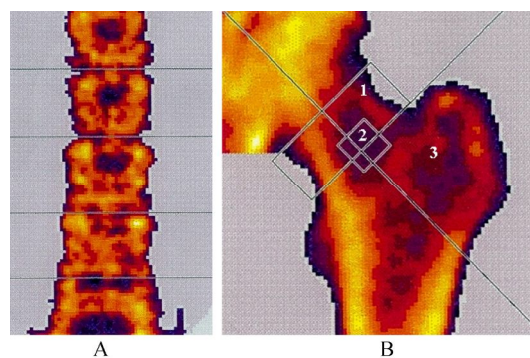


图3 骨密度检测扫描范围

Figure3 Scanning coverage for bone mineral density in subjects
A: scanning coverage of L₂₋₄; B: 1, scanning coverage of femoral neck; 2, scanning coverage of Ward's triangle; 3, scanning coverage of great trochanter; L₂₋₄: lumbar 2-4

因子缺乏是目前公认的机制之一,本研究初步探索了老年糖尿病患者的胰岛功能及IR对骨代谢及骨密度的影响。

在本研究中未发现糖代谢指标与骨密度之间的相关性,其在非老年糖尿病患者研究中的结果。分析导致这种结果的原因可能是血糖相关

指标与骨密度变化的时效差异。静脉血糖反映即时血糖, HbA1c反映近3个月的血糖水平, 而骨密度是骨代谢长期变化的结果。并且在老年患者中, 影响骨代谢的因素更趋复杂。杜雪梅等^[17]比较了老年糖尿病患者合并OS与未合并OS患者的FBG和HbA1c水平, 结果显示两组之间无显著差异。提示在老年2型糖尿病患者中, 严格的血糖控制对OS的预防作用有限, 因而应注意避免低血糖发生, 以减

少跌倒和骨折的风险。

在本研究组的老年糖尿病患者中, VitD₃缺乏普遍, 平均值仅为15.54μg/L。且血清VitD₃水平与HbA_{1c}存在负相关关系, 提示血糖控制不佳者血清VitD₃水平更低。VitD₃是影响骨代谢的一个重要类固醇激素, VitD₃不足或缺乏也是导致OS的原因之一, 并在糖尿病患者中已经得到了证实。国外研究也发现了VitD₃水平与HbA_{1c}存在负相关^[18,19], 且McGill等^[18]的研究结果再次证明了VitD缺乏对胰岛素功能的影响以及对糖代谢的影响, 体外研究也表明VitD水平与胰岛素抵抗的相关性。反之, 补充VitD可以改善糖尿病患者IR也得到了多项研究的证实^[20], 另有研究表明补充VitD可有效增加糖尿病患者血清骨保护素(osteoprotegerin)水平^[21]。因此, 对于血糖控制欠佳的老年糖尿病患者应注意监测并及时补充VitD₃, 接受充足的阳光照射, 以防或减少OS的发生。

OCN是由成骨细胞合成并分泌的多肽, 主要沉积于骨基质中以维持骨骼的正常矿化, 是反映骨形成的良好指标, 也是临床上的常用指标。OCN由49~50个氨基酸残基组成, 也称γ-羟基谷氨酸。本研究结果显示在老年糖尿病患者中, HOMA-CR与OCN呈正相关, 也与PTH呈正相关, 提示在老年糖尿病患者中IR越严重骨转换越快。虽然胰岛素具有促进骨形成的作用, 但不少研究表明IR者骨密度降低^[14,16]。国内外的相关研究也表明老年男性糖尿病患者中IR加速骨转换^[12,13]。另外, 四川医科大学童南伟教授研究小组在绝经后的糖尿病妇女中也有类似的发现^[22]。这表明IR可能是加速老年糖尿病患者骨量流失的原因之一, 但尚需大样本研究进一步证实, 其具体机制也值得深入探索。但至少该结果提示对于老年糖尿病患者的治疗, 在关注改善胰岛素分泌不足的同时, 改善IR治疗同样重要, 不仅利于血糖控制, 而且有益于改善快速骨转换。

4 结 论

在老年糖尿病患者中, IR可能是加速骨量流失的原因之一, 改善IR对预防OS可能具有双重的作用; 另外长期良好的血糖控制有助于预防及改善VitD缺乏, 减少骨量流失; 对于老年糖尿病患者也应注意测定VitD水平, 及时纠正VitD缺乏或不足。

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