

## · 论著 ·

# 老年2型糖尿病患者血清骨钙素水平与认知功能障碍的相关性研究

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**摘要:** 目的 探讨老年2型糖尿病(type 2 diabetes mellitus, T2DM)患者血清骨钙素水平与认知功能障碍的关系,为老年T2DM合并认知功能损害患者早期诊断、早期干预提供依据。方法 选取2017年6月至2018年6月于安徽省立医院就诊的98例患者作为研究对象,其中2型糖尿病组45例,正常对照组53例,比较两组受试者血清骨钙素水平和一般生化指标以及认知功能评分情况,并分析影响认知功能的危险因素以及与骨钙素之间的关系。结果 老年T2DM患者血清骨钙素水平低于对照组( $P<0.01$ ),且认知功能评分低于对照组( $P=0.025$ ),而胰岛素抵抗指数(homeostatic model assessment of insulin resistance, HOMA-IR)高于对照组( $P=0.041$ )。在老年T2DM患者中,简易精神量表(mini-mental state examination, MMSE)分值与骨钙素水平呈正相关( $r=0.364, P=0.014$ ),与HOMA-IR呈负相关( $r=-0.426, P=0.004$ ),骨钙素水平与分项得分中记忆力、注意力和计算力、执行能力呈正相关,与画钟试验(clock drawing test, CDT)呈正相关;多元回归分析发现血清骨钙素水平与MMSE呈独立相关( $P<0.05$ )。结论 老年T2DM患者认知功能损害可能与骨钙素水平相关。

**关键词:** 骨钙素;2型糖尿病;认知功能;胰岛素抵抗

## Correlation between serum osteocalcin level and cognitive dysfunction in elderly patients with type 2 diabetes mellitus

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**Abstract:** **Objective** To investigate the relationship between serum osteocalcin level and cognitive dysfunction in elderly patients with type 2 diabetes mellitus (T2DM), and to provide evidence for early diagnosis and early intervention in elderly patients with T2DM and cognitive impairment. **Methods** A total of 98 patients who were admitted to Anhui Provincial Hospital from June 2017 to June 2018 were enrolled, including 45 patients with type 2 diabetes and 53 patients with normal control. The serum osteocalcin level and general biochemical indicators as well as cognitive function scores were compared between the two groups, and relevant factors affecting cognitive function were also analyzed. Finally, we also analyzed the relationship between osteocalcin and cognitive function. **Results** Serum osteocalcin level in elderly T2DM patients was lower than that in the control group ( $P<0.01$ ), and the cognitive function score was lower than that in the control group ( $P=0.025$ ), while the HOMA-IR (homeostatic model assessment of insulin resistance) was higher than that in the control group ( $P=0.041$ ). In elderly patients with T2DM, MMSE score was positively correlated with serum osteocalcin level ( $r=0.364, P=0.014$ ), while it was negatively correlated with the HOMA-IR ( $r=-0.426, P=0.004$ ). There was a positive correlation between serum osteocalcin level and memory, attention and calculative ability, as well as executive ability in the score, respectively. In addition, serum osteocalcin level was positively correlated with the clock drawing test (CDT), as well as independently correlated with MMSE score ( $P<0.05$ ). **Conclusion** Cognitive impairment in elderly T2DM patients may be associated with serum osteocalcin level.

**Key words:** osteocalcin; T2DM; cognitive function; insulin resistance

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随着老龄化社会的不断进展,老年糖尿病(diabetes mellitus,DM)与老年痴呆的患病率在世界范围内逐年增加。研究表明,老年糖尿病可以导致认知功能的下降,老年糖尿病患者中约10.8%~17.5%会转向认知缺陷,表现为轻度至中度认知功能障碍和学习和或记忆力下降,其中这些患者约10%~15%会发展成痴呆<sup>[1]</sup>。而骨钙素(osteocalcin,OC)作为一种内分泌激素,除具有调节全身代谢功能外,还参与大脑神经递质的合成并影响认知功能<sup>[2]</sup>。多项基础实验和临床研究均发现血清OC与认知功能关系密切<sup>[3-5]</sup>,Fang等<sup>[6]</sup>对2型糖尿病男性患者的研究表明血清OC水平下降,其认知功能水平也下降。这提示低OC水平可能为认知功能损害的一个危险因子。目前老年糖尿病与认知功能障碍之间的研究较多<sup>[7]</sup>,而关于骨代谢标志物—OC与认知功能之间的直接影响作用,临床报道仍较少。因此本研究旨在通过检测老年T2DM患者中血清OC水平,并对该人群进行认知功能评估,探讨OC与老年T2DM患者认知功能之间的相关性。

## 1 材料和方法

### 1.1 研究人群

从中国科学技术大学附属第一医院安徽省立医院门诊和住院部患者中筛选60岁以上老年人98例,其中45例为T2DM患者,另外53例患者为正常人群,所有受试者均无已知认知功能障碍病史,近3月无胃肠动力药物及精神药物服用史。排除应用胰岛素的糖尿病患者;继发性血糖升高的因素;既往或者目前正在服用性激素、糖皮质激素、噻唑烷二酮类、双膦酸盐、钙剂、维生素K、华法林、维生素D等影响骨代谢的药物;既往有骨折病史;既往有脑血管病史或头颅影像有脑血管表现;既往有严重低血糖、酮症昏迷史;既往有甲状腺功能减退症病史;既往有颅脑肿瘤、头颅外伤等疾病史;既往有抑郁症或其他精神疾病导致的认知障碍者;合并视听及肢体障碍者;有酗酒及滥用精神类药物史。

### 1.2 研究方法

收集两组受试者人体测量学的一般资料,包括受检者性别、年龄、职业、文化程度、身高、体重和血压等,计算体质质量指数(BMI=体重kg/身高m<sup>2</sup>)。同时检测两组受试者一般生化指标:空腹血糖(fasting blood glucose, FPG)、糖化血红蛋白(hemoglobin alc, Hb A1c)、空腹胰岛素(fasting insulin, FINS)、空腹血脂[总胆固醇(total

cholesterol, TC)、三酰甘油(triglyceride, TG)、低密度脂蛋白胆固醇(low density lipoprotein cholesterol, LDL-C)、高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)]等。并根据空腹血糖及胰岛素水平计算胰岛素抵抗(HOMA-IR=FPG×FINS/22.5)。另外采集每位受试者空腹血标本,离心后将血清样本保存在-80℃冰箱中,统一采用放射免疫分析法(radio-immunoassay, RIA)检测血清OC水平。

最新美国糖尿病指南<sup>[8]</sup>和中国痴呆与认知障碍诊疗指南<sup>[9]</sup>均推荐应用认知功能评估量表对糖尿病合并认知功能损害的患者进行认知功能评估,主要包括简易精神量表(mini-mental state examination, MMSE),临床痴呆评定量表(clinical dementia rating, CDR)等,而MMSE用于痴呆的筛查(A级推荐),CDR用于痴呆严重程度的分级评定和随访(B级推荐)。因画钟试验(clock drawing task, CDT)用于早期痴呆的筛查,可以弥补MMSE的不足。故针对本研究中每位受试者的认知功能评估均采用认知功能量表(MMSE评分)(包括定向力、记忆力、注意力和计算力、回忆能力、语言能力、执行能力和命名能力)以及画钟试验(CDT),并记录每项得分。

### 1.3 统计学处理

应用SPSS 22.0软件进行数据的统计分析。数据用 $\bar{x}\pm s$ 表示,用两独立样本t检验比较两组间骨钙素水平及生化指标,用Pearson相关分析检验老年T2DM患者中认知功能评分与各代谢指标之间的相关性,并采用多元逐步回归分析骨钙素与MMSE的相关性。检验均为双侧, $P<0.05$ 表示差异有统计学意义。

## 2 结果

### 2.1 两组基本资料比较

两组间年龄、文化程度以及血脂水平比较,差异无统计学意义( $P>0.05$ )。与对照组比较,老年2型糖尿病组中患者BMI、FPG、HbA1C、HOMA-IR水平升高,差异有统计学意义( $P<0.05$ ),而骨钙素水平较对照组下降,差异有统计学意义( $P<0.01$ )。见表1。

### 2.2 两组认知功能及分项得分比较

与对照组比较,老年2型糖尿病组中患者MMSE评分及分项得分和画钟试验得分均下降,其中MMSE总分及定向力、注意力和计算力下降较为

明显,差异有统计学意义( $P<0.05$ )。见表2。

**表1** 老年T2DM组与正常对照组一般资料及骨钙素水平比较

**Table 1** Comparison of general data and serum osteocalcin level between elderly T2DM group and normal control group

指标	糖尿病组(n=45)	对照组(n=53)	t值	P值
男性/女性/n	29/16	33/20	0.496	0.067
年龄/岁	74.57±9.954	72.69±11.561	-0.853	0.389
文化程度/年	8.98±4.986	8.09±5.587	-0.818	0.415
BMI/(kg/m <sup>2</sup> )	24.23±2.590	22.87±3.486	-2.157*	0.034
FPG/(mmol/L)	6.91±2.811	4.87±0.767	-5.104**	<0.001
FINS/(mIU/L)	3.69±2.434	3.55±2.299	-0.209	0.514
HbA1C/%	6.90±1.472	5.63±0.843	-5.212**	<0.001
HOMA-IR	1.14±0.887	0.78±0.584	-2.027*	0.041
TC/(mmol/L)	4.19±1.068	4.03±1.044	0.502	0.603
TG/(mmol/L)	1.61±1.221	1.38±0.672	-1.156	0.251
HDLC/(mmol/L)	1.08±0.375	1.09±0.249	0.702	0.655
LDLC/(mmol/L)	7.29±33.827	2.79±5.137	-0.966	0.336
骨钙素/(ng/mL)	6.11±3.359	9.77±6.092	3.766**	<0.001

注: \*  $P<0.05$ , \*\*  $P<0.01$ 。

**表2** 老年T2DM组与正常对照组认知功能及分项得分比较

**Table 2** Comparison of cognitive function and sub-item scores between elderly T2DM group and normal control group

指标	糖尿病组 (n=45)	对照组 (n=53)	t值	P值
MMSE评分	19.78±8.626	23.52±7.188	2.379*	0.025
画钟试验	1.02±1.865	1.40±1.978	0.708	0.375
定向力	6.78±3.336	7.97±3.003	2.362*	0.036
记忆力	2.18±1.093	2.55±0.913	1.243	0.076
注意力和计算力	2.69±1.987	3.67±1.826	2.659*	0.014
回忆能力	1.36±1.348	1.85±1.188	1.904	0.060
语言能力	1.20±0.734	1.28±0.811	0.484	0.644
执行能力	3.75±1.542	4.12±1.315	1.609	0.054
命名	1.73±0.624	1.82±0.473	1.089	0.280

注: \*  $P<0.05$ 。

**2.3** 老年T2DM组中MMSE评分与一般资料相关性分析

单因素相关分析发现,在老年2型糖尿病人群中,MMSE评分与年龄、空腹胰岛素水平及胰岛素抵抗HOMA-IR呈负相关,差异有统计学意义( $P<0.05$ ),与骨钙素水平呈正相关( $P<0.05$ ),与血脂水平无明显相关( $P>0.05$ )。见表3。

**2.4** 老年T2DM组中骨钙素水平与认知功能及分项得分相关性分析

单因素相关分析发现,骨钙素水平与MMSE评分、画钟试验以及记忆力、注意力和计算力、执行能力均呈正相关,差异有统计学意义( $P<0.05$ )。见表4。经多元逐步回归分析校正年龄、文化程度、血糖、血脂、BMI等影响后,骨钙素水平仍与MMSE呈独

立相关( $P<0.05$ )。见表5。

**表3** 老年T2DM组中MMSE评分与一般资料相关性分析

**Table 3** Correlation analysis between MMSE score and general data in elderly T2DM group

因素	r值	P值
年龄/岁	-0.322*	0.031
文化程度/年	0.183	0.228
FPG/(mmol/L)	-0.273	0.069
FINS/(mIU/L)	-0.302*	0.044
HbA1C/%	-0.108	0.480
HOMA-IR	-0.426**	0.004
TC/(mmol/L)	0.141	0.355
TG/(mmol/L)	-0.117	0.446
HDLC/(mmol/L)	0.043	0.777
LDLC/(mmol/L)	-0.250	0.098
骨钙素/(ng/mL)	0.364*	0.014

注: \*  $P<0.05$ , \*\*  $P<0.01$ 。

**表4** 老年T2DM组中骨钙素水平与认知功能及分项得分相关性分析

**Table 4** Correlation analysis between serum osteocalcin level and MMSE score as well as sub-scores in elderly T2DM group

因素	r值	P值
MMSE评分	0.364*	0.014
画钟试验	0.462**	0.001
定向力	0.195	0.199
记忆力	0.325*	0.029
注意力和计算力	0.470**	0.001
回忆能力	0.209	0.169
语言能力	0.049	0.752
执行能力	0.392**	0.008
命名能力	0.242	0.109

注: \*  $P<0.05$ , \*\*  $P<0.01$ 。

**表5 老年T2DM组中骨钙素水平与MMSE相关性分析**  
**Table 5 Correlation analysis between serum osteocalcin level and MMSE score in elderly T2DM group**

指标	<i>r</i> 值	<i>P</i> 值	多元逐步回归		
			$\beta$	SE	<i>P</i> 值
骨钙素	0.364	0.014	1.258	0.338	0.001

### 3 讨论

2型糖尿病(T2DM)和阿尔茨海默病(AD)是全球最常见的两种衰老性疾病,越来越多的证据表明,老年T2DM与认知功能障碍和痴呆有关,大量流行病学研究发现,老年T2DM患者患AD的风险明显增高<sup>[10-11]</sup>。有研究对824例受试患者随访5年,在校正了年龄、性别、受教育程度等因素后,发现患糖尿病的受试者比非糖尿病受试者发生认知功能障碍的风险高65%,风险比1.65,且糖尿病受试者在随访期间的认知能力减退程度比非糖尿病受试者明显增快<sup>[12]</sup>。另外,最近以台湾地区人口为基础的两项大型研究,并进行大约10年的随访,结果提示糖尿病患者发生AD的风险几乎是同龄非糖尿病患者的两倍<sup>[12-13]</sup>。本研究结果显示,老年T2DM组MMSE评分较对照组明显降低(*P*=0.025),尤其在定向力、注意力和计算力方面差异具有统计学意义(*P*=0.036, *P*=0.014),这与既往研究一致,表明糖尿病患者更易发生认知功能障碍。目前一些基础研究认为糖尿病脑病和认知功能障碍存在胰岛素信号转导通路的共同病理机制,即胰岛素抵抗引起糖脂代谢紊乱造成神经突触的可塑性和学习记忆改变,甚至导致神经元线粒体功能紊乱而引起大脑退行性疾病<sup>[14-16]</sup>。该研究中糖尿病组体重明显高于对照组(*P*=0.034),胰岛素抵抗(HOMA-IR)更明显(*P*=0.041),且胰岛素抵抗与认知功能呈负相关(*r*=-0.426, *P*=0.004),表明糖尿病患者的胰岛素抵抗除参与肥胖形成机制外,还影响认知功能。

骨钙素(osteocalcin, OC)是由成骨细胞特异分泌的,一种维生素K依赖性的非胶原蛋白,研究表明OC参与大脑调节神经递质的合成并影响认知功能<sup>[17-18]</sup>。2013年,Oury等<sup>[19]</sup>首次在动物实验中发现OC可以穿过血脑屏障作用于脑干、中脑和海马来影响几种与学习和记忆形成有关的神经传导物质( $\gamma$ -氨基丁酸、5-羟色胺等)的合成<sup>[20]</sup>,本课题组前期在2型糖尿病动物模型的研究中也发现低OC水平与认知功能损害密切相关<sup>[21]</sup>,另外多项临床研究表明2型糖尿病患者中血清OC水平降低,其认知

功能也下降,并发现OC水平偏低时,即时记忆、延时回忆、注意力及言语功能均下降<sup>[6]</sup>。本研究发现老年T2DM患者中OC水平降低(*P*<0.01),且经单因素分析发现OC水平与画钟试验、记忆力、注意力和计算力以及执行能力呈正相关(*P*<0.05),在校正糖尿病患者的年龄、文化程度、血糖、血脂、BMI等因素影响后,OC仍与MMSE评分相关,表明糖尿病人群高OC水平为认知功能的保护因素,且OC主要影响空间学习和执行能力相关的认知功能。由于最近的一项研究发现血清OC水平降低与大脑微结构改变和认知能力下降之间存在联系<sup>[22]</sup>,由此可推测OC通过潜在的神经调节机制影响大脑微结构,继而改变认知能力。

综合既往实验结果及本研究发现,OC可能通过胰岛素抵抗间接影响神经突触功能或直接作用于大脑微结构来影响认知功能,而高OC水平为认知功能的保护因素,这为骨骼内分泌循环与神经系统的联系提供了临床依据,或许能够为老年2型糖尿病合并认知功能障碍患者寻求新的治疗方法带来福音。由于本实验中观察样本病例数少,周期短,在后期研究中,还需加大样本量和随访时间,进行跨地区研究,为血清骨钙素在老年T2DM患者合并认知功能损害的早期诊断提供更多科学依据。

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