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述评 EDITORIAL

增加钙摄入降低血胆固醇水平的作用机制

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Mechanisms of calcium intake in lowering serum cholesterol levels

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Abstract

Cardiovascular diseases (CVDs), a group of disorders of the heart and blood vessels, are the leading cause of death globally. An estimated 17.1 million people die of CVDs each year, more than 40% of whom die from coronary heart disease (CHD). Hypercholesterolemia is a major risk factor for increasing CHD morbidity and mortality, and serum cholesterol level is a key predictor of CHD development. A number of studies have demonstrated that calcium supplement can lower serum cholesterol levels, which means that calcium might play an important role in preventing the development of CVDs, especially CHD. In this paper, the mechanisms of calcium intake in lowering serum cholesterol levels are summarized, including increasing the excretion of bile acids, interfering with cholesterol absorption, inhibiting the absorption of saturated fatty acids, promoting energy metabolism, regulating plasma $1,25(OH)_2D$ levels, affecting blood insulin sensibility and controlling appetite.

Key Words: Calcium; Cholesterol; Mechanism

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摘要

心血管疾病(cardiovascular diseases, CVDs)已经成为全球危害人类健康生命的头号死因. 平均每年有1710万人因CVDs丧命, 其中,

背景资料
心血管疾病已成为我国居民死亡的首要疾病, 其发病率呈逐年上升的趋势. 冠心病是心血管病的主要死因, 而高胆固醇血症是冠心病发病率和死亡率的主要危险因素, 并且血清胆固醇水平是冠心病事件发病率的主要预测因素. 钙在体内具有维持神经与肌肉活动, 促进体内酶的活性和参与激素分泌等生理功能. 研究显示, 钙摄入量与血浆胆固醇水平密切相关.

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研发前沿

增加钙摄入降低血胆固醇水平是在多方面机制共同作用下实现的. 而钙过量摄入也可增加部分人群心血管病死亡率的风险, 因此, 从有效防治胆固醇水平升高的角度, 亟需探究不同生理状态下人体对钙需求量的适宜范围.

超过40%的人死于冠心病, 而高胆固醇血症是引起冠心病发病率和死亡率上升的主要危险因素, 并且血清胆固醇水平是冠心病发病的主要预测因素. 大量研究证实, 增加钙摄入可以降低或改善血浆胆固醇浓度, 这对预防CVDs, 特别是冠心病的发生和发展具有重大意义. 本文就钙摄入降低血胆固醇水平的作用机制进行综述, 涉及的内容主要包括: 增加胆汁酸的排泄、干扰胆固醇吸收、抑制饱和脂肪酸的吸收、促进能量代谢、调节血1,25(OH)$_2$D水平、影响胰岛素敏感性和控制食欲等.

关键词: 钙; 胆固醇; 机制

核心提示: 高胆固醇血症是引起冠心病发病率和死亡率上升的主要危险因素. 增加钙摄入可以通过增加胆汁酸的排泄、干扰胆固醇吸收、抑制饱和脂肪酸的吸收、促进能量代谢、调节血1,25(OH)$_2$D水平、影响胰岛素敏感性和控制食欲等机制, 降低血浆胆固醇水平, 为高胆固醇血症的防治提供新思路.

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0 引言

随着全球经济的迅速发展和人民生活水平的不断提高, 心血管疾病(cardiovascular diseases, CVDs)已经成为全球危害人类健康生命的头号死因, WHO提供的数据显示, 在2012年约有1750万人死于CVDs, 占全球死亡总数的31%, 其中, 估计740万人死于冠心病[1]. 而高胆固醇血症是引起冠心病发病率和死亡率上升的主要危险因素, 并且血清胆固醇水平是冠心病发病的主要预测因素[2]. 因此, 合理控制和降低血浆胆固醇水平对预防CVDs, 特别是冠心病的发生和发展具有重大意义.

钙是人体含量最丰富的矿物质, 总量超过1000 g. 除了以钙盐的形式沉积于骨骼和牙齿外, 钙在体内还具有维持神经与肌肉活动, 促进体内酶的活性, 参与激素分泌及维持体液酸碱平衡等生理功能. 近些年研究[3-5]发现, 增加膳食钙的摄入可以降低血浆胆固醇浓度或者对高胆固醇血症具有改善作用[6-9], 但对这种现象的机制探讨尚不统一. 本文现将国内外有关钙摄入降低血胆固醇浓度的机制进行归纳, 并加以综述.

1 增加胆汁酸的排泄

正常成年人体内每天可合成1.5 g胆固醇, 其中约有2/5在肝脏内转变成胆汁酸. 胆汁酸随胆汁进入肠道后, 主要参与脂类的消化和吸收. 进入肠道的各种胆汁酸大部分可被重吸收后再利用, 其余部分随粪便排出体外. 可见, 胆固醇在肝细胞中转化生成胆汁酸并排出体外是机体胆固醇代谢的一个重要途径[10].

事实上, 有很多学者在体内、外实验[11,12]结果中发现, 钙可以结合胆汁酸, 同时减弱了其在肠道内消化脂类的活性[13,14], 并促进胆汁酸的排泄[15]. Govers等[16]在早前的研究中就已阐述, 在小肠内, 钙的磷酸盐沉淀物更易于与甘氨酸结合型胆汁酸或非结合型胆汁酸相结合, 从而降低体内的胆汁酸水平. 之后, Xu等[17,18]在研究大豆蛋白对大鼠和人血浆胆固醇浓度的影响时, 提出了非磷酸化学说, 认为肠腔内的钙与磷可以形成不溶性的钙磷复合物, 胆汁酸可同这些复合物以离子交换的方式结合在一起随粪便排出体外.

由于胆汁酸排出量增加, 胆囊体积减小, 作为机体反馈调节的结果, 这就引起肝内胆汁酸合成的限速酶-7α-羟化酶(CYP7A1)的基因表达上调, 使该酶的合成增加, 导致由胆固醇合成胆汁酸的量增加[19]; 当胆固醇的量不能满足胆汁酸合成时, 作为肝脏胆固醇的来源, 一方面肝脏表面低密度脂蛋白受体(low-density lipoprotein receptor, LDL-R)表达上调, LDL-R直接摄取血液循环中LDL-C参与代谢[20], 另一方面, 高钙也可通过减少血中胆固醇酯转移蛋白来增加高密度脂蛋白胆固醇含量[19,21], 将胆固醇逆向转运至肝脏, 最终导致血浆胆固醇浓度的下降.

2 干扰胆固醇的吸收

研究[12]通过给健康成人提供钙强化面包, 每天补充1000 mg钙, 持续4 wk后发现, 钙不仅增加了粪便中胆酸的含量, 也使动物中性胆固醇排出增加. 体外实验中, 在浓度超过3 mmol/L条件下, Ca^{2+}可以和胆汁酸形成体积较大、难溶

的聚合物, 在降低了胆汁酸活性的同时, 也阻止了胆汁中固有的胆固醇向外溶解和吸收[11]. 随着胆汁酸活性的下降, 肠道内食物中的脂类消化程度减弱, 进一步导致食物中未吸收的胆固醇排出增加[12,20], 在这个过程中, 参与胆固醇吸收和转运的肠道胆固醇转运蛋白NPC1L1和微粒体甘油三酯转运蛋白mRNA的表达下调[19]. 可见, 在膳食胆固醇向肝脏转移的过程中, 由于肠道内胆固醇吸收量减少, 致使血中胆固醇含量下降.

然而, Aslanabadi等[20]观察了富含钙(250 mg/L)、镁(48 ppm)和碳酸氢盐(1350 mg/L)的天然矿泉水对患有高脂血症成年人血脂的影响, 1 mo后人群血中胆固醇和LDL含量明显下降, 研究者认为这与另外两个物理因素有关: 一是实验用矿泉水的碱性特性, 由于在相对较低的pH环境下, 来自小肠微团溶液的胆固醇吸收率较高[22], 而矿泉水提升了肠内的pH, 导致胆固醇吸收减少; 二是矿泉水的高渗特性, 高渗作用可以刺激胆汁流入十二指肠, 并产生类似可溶性纤维的功能, 减少了胆固醇的吸收, 干扰了胆汁酸的肝肠循环[20]. 但在此过程中, 钙元素本身的贡献有多大尚需探讨.

3 抑制饱和脂肪酸的吸收

膳食中的饱和脂肪酸是升高血浆总胆固醇(total cholesterol, TC)含量的主要物质之一, 而且这种升高现象主要发生在LDL-C部分[23]. 因此, 降低膳食中总脂肪尤其是饱和脂肪酸的含量可以更好的降低血浆中TC和LDL-C的水平[24]. Denke等[25]以13名伴有中度高胆固醇血症男性为研究对象, 每天给予总量为2200 mg的钙, 发现膳食高钙受试者每天的粪便饱和脂肪酸排泄量由6%增加到13%, 同时血浆TC与LDL-C浓度均明显下降. 而对这一现象的科学解释为, Ca^{2+}可在肠道内同脂肪酸结合形成难溶的、不易吸收的钙皂[14,26], 最终减少了饱和脂肪酸的吸收. 此外, 上文已提到, 高钙引起的胆汁酸活性降低, 致使消化膳食脂肪的能力减弱, 部分未被消化的膳食脂肪就随粪便排出体外[13,14].

作为机体胆固醇合成的原材料之一, 饱和脂肪酸来源不足, 可使肝脏内合成胆固醇的限速酶-羟甲戊二酸单酰辅酶A还原酶(HMGCoAR)的基因表达下调[27], HMGCoAR合成减少, 进而, 减少了肝脏内源性胆固醇的生成[28]; 另外, 饱和脂肪酸还可抑制肝细胞表面LDL-R, 从而减少了肝脏对血液中LDL的清除[29,30]. 因此, 高钙膳食模式下, 饱和脂肪酸的吸收抑制最终导致血浆TC及LDL-C浓度的下降.

4 促进能量代谢

研究[31]显示, 生长发育期低钙摄入可引起肥胖, 而且这种作用能持续至成年期, 同时, 肥胖患者常伴有高胆固醇血症, 发病情况高于超重人群, 并且体态指标与血胆固醇指标的变化存在显著性相关[32]. 部分原因是由于肥胖可使脂解激素与抗脂解激素分泌失调, 脂肪的合成与分解代谢均显著增多, 最终造成了包括胆固醇在内脂质代谢紊乱[33]. 动物和人群实验[34-37]结果均显示, 适量增加钙摄入, 受试对象在体脂质量减轻的同时血脂状况也发生不同程度的改善. 可见, 高钙可通过减少体内脂肪含量调整机体脂类代谢紊乱状态, 从而进一步改善血中胆固醇水平. 究其原因, 可能与血$1,25(OH)_2$维生素D[$1,25(OH)_2D$]水平息息相关.

此外, 当用钙元素含量为2.8%的高脂饲料喂养♂昆明小鼠4 wk后, 组织细胞中脂肪合成和维生素D受体基因表达下调, 而脂肪分解的基因表达上调, 同时, 在脂肪前体细胞中还伴有p38 MAPK信号通路上游基因*MKK6*和下游基因*MAPKAPK2*表达增强[38]. 可见, 钙还可通过调节脂肪细胞p38 MAPK信号通路和钙结合蛋白S100A16的出核[39], 抑制脂肪合成和/或加速脂肪分解.

5 调节血$1,25(OH)_2D$水平

人体可根据膳食中钙的摄入量, 通过维生素D调节钙的代谢, 以保持钙在体内的正常分布与平衡. 学者将85例高血压患者按照每天膳食钙摄入量进行分组, 发现低钙摄入(<800 mg/d)能引起肥胖[40], 通过进一步分析认为, 一方面, 由于低钙状态下血中$1,25(OH)_2D$水平增高, 而维生素D可通过细胞膜维生素受体(1,25D MARRS)加速脂肪细胞钙内流, 细胞内钙含量增加, 不仅促进脂肪酸合成, 同时还抑制脂肪酶生成[41,42]; 另一方面, $1,25(OH)_2D$亦可利用脂

创新盘点

本文重点综述了增加钙摄入在降低血胆固醇水平过程中的作用及机制的最新进展. 研究显示, 可通过调整膳食结构或有针对性的补充钙剂, 实现高胆固醇血症的防治.

应用要点
避免或减少药物应用, 调整膳食钙的摄入量将在高胆固醇血症防治方面具有重要意义.

肪细胞核维生素D受体抑制解偶联蛋白2的表达, 减少热能产出[43]. 由此, 学者反向推测[44], 高钙摄入减少体脂的机制很可能与脂肪细胞内低浓度的钙离子[45]激活的脂肪分解[40,46]密切相关.

随着研究的深入[47,48], 1,25(OH)$_2$D被发现能刺激脂肪组织表达11β羟化类固醇脱氢酶-1, 此酶可催化皮质酮转化生成皮质醇, 皮质醇又参与了脂肪酸的合成和UCP表达的抑制. 而高钙膳食伴随的机体低水平1,25(OH)$_2$D, 最终减少了由脂肪细胞分泌的皮质醇的生成[48].

6 影响胰岛素敏感性

流行病学研究[49,50]结果发现, 高钙膳食有益于高危人群2型糖尿病的预防, 而且钙摄入量与机体对胰岛素的敏感性呈正相关[51,52]. 所以, 钙摄入不足时, 机体对胰岛素的敏感性下降, 抵抗增强[31], 血中胰岛素水平升高, 诱导HMGCoAR的基因表达上调[53], HMGCoAR合成增多, 进而增加了内源性胆固醇的生成.

在胰岛素应答组织里, Ca^{2+}对胰岛素参与的细胞内过程至关重要, 高钙条件下, 血中1,25(OH)$_2$D水平下降[54], 细胞内Ca^{2+}浓度降低, 这就防止了由于细胞内Ca^{2+}浓度增高导致的胰岛素信号转导过程的损害[55], 胰岛素敏感性增强[39], 伴有血糖[56]和胰岛素[33]降低, 血胆固醇含量下降.

7 控制食欲

在一项长达6 mo限制能量摄入的人体试验中, Gilbert等[57]发现, 与安慰剂组对比, 每天摄入1000 mg来自牛奶中的钙, 明显减小了受试者食欲和饥饿感的增幅; Jones等[58]也得出相似的结果, 而且实验组摄入的膳食脂肪量明显下降, 并伴有高水平的血浆酪酪肽(peptide tyrosine tyrosine, PYY). PYY为肠内分泌细胞释放的一种激素, 作为中枢系统肽类信号因子可直接作用于下丘脑和脑干的饱食中枢, 引起食欲降低, 摄食减少[59].

在动物研究[60,61]中, 高钙(1.5%)饲料大鼠血浆神经肽Y(neuropeptide Y, NPY)含量明显降低, 而与PYY相反, NPY是调节促进食欲的主要肽类信号因子[62], 所以, 高钙膳食降低了实验动物体内NPY水平, 也就导致了实验动物食欲降低, 摄食减少.

因此推测, 高钙摄入至少通过调节PYY和NPY两种信号因子, 来控制机体食欲, 减少摄食, 最终降低血胆固醇水平, 改善血脂状况.

8 存在问题

虽然多数体内、外实验均已证实, 适量钙摄入对控制血浆胆固醇水平有积极作用, 但仍有部分研究显示出相反的结果. 在一项长达2年的双盲随机对照试验中, Li等[63]给伴有血脂紊乱的绝经妇女每天补充800 mg钙元素, 该人群血浆胆固醇含量显著增高, 但这种现象在补钙的未绝经妇女中并未发生. 该作者通过动物和体外实验对该现象进行了解释[64]: 在雌激素缺乏状态下, 长期钙补充可通过细胞膜瞬时受体电位通道蛋白1(TRPC1)增加肝细胞内Ca^{2+}浓度, 激活了磷酸二酯酶, 继而降低胞内环磷酸腺苷水平, 从而导致肝脏CYP7A1减少, 胆固醇代谢障碍, 最终引起血浆胆固醇含量增高; 当雌激素存在时, 可与肝细胞膜G蛋白偶联雌激素受体结合, 抑制TRPC1, 进而干扰了上述过程.

在另一项大型临床试验[65]中, 3.6万名绝经期妇女在膳食钙为1100 mg/d的基础上, 随机补充钙1 g/d和400 IU维生素D或安慰剂共9年, 补钙和维生素D者亦轻微增加心肌梗塞和中风的风险(13%和22%).

这些结果提示我们, 雌激素也可参与钙对胆固醇代谢的调节过程. 由此进一步分析, 在性别、年龄及特殊生理条件下, 由于人群生理状态的差异, 机体对钙的生理需要量也不尽相同, 因此, 从有效防治高胆固醇血症的角度, 亟待明确处于不同生理条件下(未成年人、孕产妇及老年人等)人体对钙需要量的适宜范围.

9 结论

中国居民营养与健康状况调查结果[66]显示, 我国居民每标准人日钙摄入量为388.8 mg, 按照中国居民膳食营养素参考摄入量计算[18-49岁人群的推荐摄入量(recommended nutrient intake, RNI)为800 mg/d; 50岁以上人群的RNI为1000 mg/d][67], 还不足成年人钙RNI的一半, 而且这种低钙营养状况在儿童、孕妇和老年人中尤为明显, 可见, 我国居民膳食钙摄入量明显不足. 钙广泛存在于天然食物中, 是维持生命极

为重要的营养素. 因此, 通过调整膳食结构或有针对性的补充钙剂, 增加钙的适宜摄入, 即可预防钙缺乏性骨病, 又能防止血浆胆固醇浓度升高, 或降低血浆胆固醇浓度, 进而降低我国居民心血管疾病的发病率和死亡率, 促进人体健康.

总之, 增加钙摄入可以通过增加胆汁酸的排泄、抑制胆固醇和饱和脂肪酸的吸收、促进能量代谢、调节血1,25(OH)$_2$D水平、影响胰岛素敏感性和控制食欲等机制, 降低血浆胆固醇水平. 因此, 结合我国实际情况, 适量增加钙摄入可同时预防钙缺乏性骨病和血胆固醇含量升高.

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同行评价

本文对钙营养状况对胆固醇代谢影响的机制进行了系统综述, 对于改善我国居民钙营养状况、预防高胆固醇血症具有积极的指导意义.

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• 消息 •

《世界华人消化杂志》正文要求

本刊讯 本刊正文标题层次为 0引言; 1 材料和方法, 1.1 材料, 1.2 方法; 2 结果; 3 讨论; 4 参考文献. 序号一律左顶格写, 后空1格写标题; 2级标题后空1格接正文. 以下逐条陈述: (1)引言 应包括该研究的目的和该研究与其他相关研究的关系. (2)材料和方法 应尽量简短, 但应让其他有经验的研究者能够重复该实验. 对新的方法应该详细描述, 以前发表过的方法引用参考文献即可, 有关文献中或试剂手册中的方法的改进仅描述改进之处即可. (3)结果 实验结果应合理采用图表和文字表示, 在结果中应避免讨论. (4)讨论 要简明, 应集中对所得的结果做出解释而不是重复叙述, 也不应是大量文献的回顾. 图表的数量要精选. 表应有表序和表题, 并有足够具有自明性的信息, 使读者不查阅正文即可理解该表的内容. 表内每一栏均应有表头, 表内非公知通用缩写应在表注中说明, 表格一律使用三线表(不用竖线), 在正文中该出现的地方应注出. 图应有图序、图题和图注, 以使其容易被读者理解, 所有的图应在正文中该出现的地方注出. 同一个主题内容的彩色图、黑白图、线条图, 统一用一个注解分别叙述. 如: 图1 萎缩性胃炎治疗前后病理变化. A: …; B: …; C: …; D: …; E: …; F: …; G: …. 曲线图可按●、○、■、□、▲、△顺序使用标准的符号. 统计学显著性用: ^{a}P<0.05, ^{b}P<0.01(P>0.05不注). 如同一表中另有一套P值, 则^{c}P<0.05, ^{d}P<0.01; 第3套为^{e}P<0.05, ^{f}P<0.01. P值后注明何种检验及其具体数字, 如P<0.01, t = 4.56 *vs* 对照组等, 注在表的左下方. 表内采用阿拉伯数字, 共同的计量单位符号应注在表的右上方, 表内个位数、小数点、±、-应上下对齐. “空白”表示无此项或未测, “-”代表阴性未发现, 不能用同左、同上等. 表图勿与正文内容重复. 表图的标目尽量用t/min, c/(mol/L), p/kPa, V/mL, t/℃表达. 黑白图请附黑白照片, 并拷入光盘内; 彩色图请提供冲洗的彩色照片, 请不要提供计算机打印的照片. 彩色图片大小7.5 cm×4.5 cm, 必须使用双面胶条黏贴在正文内, 不能使用浆糊黏贴. (5)志谢 后加冒号, 排在讨论后及参考文献前, 左齐.

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