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维生素 D 与肥胖的关系

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[摘要] 维生素D是一种人体必需的脂溶性维生素, 广泛参与到人体多种器官、组织细胞的发育和分化、生长和调节中, 维生素D水平受甲状旁腺激素(parathyroid hormone, PTH)、钙、肠道吸收能力、肝肾功能、皮肤、肌肉等多方面影响。大规模的流行病学数据表明维生素D缺乏在世界范围内普遍流行。肥胖的患病率呈全球性增长趋势。维生素D缺乏与肥胖存在相关性, 肥胖人群血清维生素D水平明显低于正常体重人群, 对肥胖人群进行维生素D的干预治疗有助于改善体重指数(body mass index, BMI)。两者通过环境因素、自身因素及分子水平的变化等相互影响, 肥胖引起维生素D的缺乏或不足。

[关键词] 维生素D; 肥胖; 体重指数; 脂肪组织; 维生素D受体

Vitamin D and obesity

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Abstract Vitamin D is an essential lipid-soluble vitamin in human body, which is extensively involved in the development and differentiation, as well as growth and regulation of numerous human organs and tissues. Vitamin D is subject to multiple factors, including parathyroid hormone (PTH), calcium, intestinal absorbency, hepatic and renal function, skin, and muscle. Large scale epidemiological data suggest that, vitamin D insufficiency is prevalent worldwide. Prevalence of obesity tends to increase on a global scale. Vitamin D insufficiency is correlated with obesity, and the serum vitamin D level in obese population is markedly lower than that in normal weight population. Therefore, vitamin D intervention treatment among the obese population contributes to improving the body mass index (BMI). In this paper, the worldwide epidemiological features of vitamin D and obesity were summarized. Vitamin D and obesity interact mutually through environmental factors, personal factors and changes in molecular levels, so obesity causes insufficiency or deficiency of vitamin D.

Keywords vitamin D; obesity; body mass index; adipose tissue; vitamin D receptor

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维生素D的主要生理作用为调节钙磷代谢和维护骨骼健康,近年来其在肌肉、心血管疾病、糖尿病、癌症、自身免疫和炎症反应等中的作用逐渐受到广泛关注^[1]。流行病学调查^[2-4]发现:维生素D缺乏是一个世界性的健康问题,在我国人群中普遍存在。肥胖是危害公众健康的严重疾病之一,肥胖人群在全球成年人口中占39%^[5]。研究^[6]显示:超重和肥胖与维生素D缺乏风险存在相关性。

1 维生素 D 及其受体

维生素D是一种脂溶性的开环固醇类物质,在特定波长紫外线(290~315 nm)的照射下,人体皮肤中的7-脱氢胆固醇(7-dehydrocholesterol)转变为维生素D₃的前体物质,皮肤能够产生80%~100%机体所需的维生素D。维生素D必须经过肝和肾的两次羟化才能转变为具有生物活性的1,25(OH)₂D₃。人体内的维生素D首先经肝脏25-羟化酶(由CYP2R1或CYP27A1编码)催化而成25-羟基维生素D[25-hydroxyvitamin D₃, 25(OH)D₃] ,是体内维生素D的主要贮存形式,反映体内维生素D的营养状态。25(OH)D₃经肾1 α -羟化酶(由CYP27B1编码)进一步羟化合成1,25(OH)₂D₃(1,25-dihydroxyvitamin D₃) ,该过程主要受甲状旁腺激素(parathyroid hormone, PTH)的严格调节,并受到1,25(OH)₂D₃的自身调节。而24-羟化酶(由CYP24A1编码)可降解25(OH)D₃和1,25(OH)₂D₃。活性维生素D₃的合成酶(25-羟化酶、1 α -羟化酶)和分解酶(24-羟化酶)均属于维生素D代谢酶, CYP2R1, CYP27A1, CYP27B1和CYP24A1均属于细胞色素P450酶(cytochrome P450 enzymes, CYP450)家族。1,25(OH)₂D₃是体内维生素D的主要代谢物,

可与组织中广泛存在的维生素D受体(vitamin D receptor, VDR)结合,发挥激素样作用,又称D激素。VDR除存在于肠道、肾和骨骼外,还存在于许多其他组织。维生素D通过VDR发挥其骨外生理效应。VDR为亲核蛋白,属于类固醇激素/甲状腺激素受体超家族成员^[7],广泛存在于乳腺、前列腺、胰腺、T淋巴细胞等体内多种组织细胞中;此外,某些肿瘤细胞如乳腺癌、结肠癌细胞中也发现有VDR存在^[8]。

2 维生素 D 与肥胖

2.1 维生素 D 与肥胖的相关性

研究^[9]表明:在成年人中低水平维生素D与肥胖的发生有关。虽大多数横断面研究受到实验设计的限制,但一些临床研究^[10]支持肥胖是造成维生素D水平低下的危险因素(图1)。肥胖人群的血清25(OH)D₃水平与体重、体重指数(body mass index, BMI)和脂肪数量成反比^[11],其血清25(OH)D₃水平比正常体重者低20%^[12]。在肥胖人群中,25(OH)D₃缺乏的患病率为40%~80%,明显高于正常体重人群^[13]。Guasch等^[14]研究表明:与高BMI的个体相比,低BMI的个体血清25(OH)D₃水平较高;高BMI的肥胖个体发生维生素D缺乏的风险更高。事实上,不同的流行病学调查都普遍显示低水平的维生素D对应着更高的BMI,且独立于体力活动多少及维生素D的摄入的变化。研究^[15]表明: BMI每上升1 kg/m²,则维生素D的浓度下降1.15% ($P=6.52610227$);且高BMI容易导致低血清25(OH)D₃水平,而低血清25(OH)D₃水平对BMI的影响却非常小,提示低水平维生素D很有可能是肥胖的结果,而非肥胖的原因。

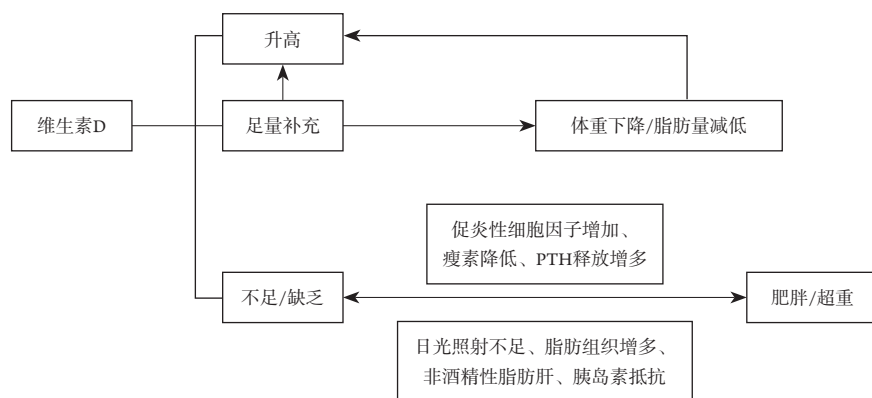


图1 维生素D与肥胖的关系

Figure 1 Relationship between vitamin D and obesity

2.2 维生素D与脂肪组织

了解维生素D对脂肪细胞功能的影响可以帮助确定肥胖和维生素D之间的因果关系。脂肪组织是脂溶性维生素D的储存位置^[16], 在肥胖者的脂肪组织中可发现高水平的维生素D^[17]。研究^[18-20]表明: 脂肪组织表达VDR以及维生素D代谢的酶, 故脂肪能够参与部分维生素D的合成与分解, 并成为维生素D的直接靶器官; 特别是维生素D可独立于PTH的作用抑制脂肪生成, 在脂肪代谢中的起到关键作用。一项基于动物模型3T3-L1小鼠前脂肪细胞的研究^[21]结果表明维生素D具有抗脂肪形成的作用。

维生素D产生和分解代谢的细胞色素P450酶(CYP2R1, CYP27A1, CYP27B1, CYP24A1)存在于脂肪组织中^[18]。Wamberg等^[22]研究了20位肥胖者与20位消瘦者血清25(OH)D₃水平与皮下脂肪(subcutaneously adipose tissue, SAT)和内脏脂肪(visceral adipose tissue, VAT)中维生素D代谢酶的表达水平之间的关系, 结果表明: 与SAT相比, 25-羟化酶CYP27A1在VAT中的表达水平更高; 另一种25羟化酶CYP2J2与1 α -羟化酶CYP27B1的表达水平在偏瘦个体的SAT中最高, 这些数据表明在肥胖者的SAT中CYP2J2和CYP27B1的表达较低, 故25(OH)D₃和1,25(OH)₂D₃的产生可能下降。24-羟化酶CYP24A1在脂肪组织部位或组间的表达没有差异, 表明对于脂肪组织的影响主要与维生素D的产生有关, 而非其分解代谢。Nimitphong等^[23]的体外人脂肪细胞培养实验结果支持了Wamberg等^[22]的结论。与低BMI人群相比, 高BMI人群皮下脂肪及内脏脂肪的25-羟化酶及1 α -羟化酶表达下调, 使维生素D生物转化下降^[22]。

2.3 减重对于维生素D的影响

最近研究^[16,24]表明: 肥胖个体中维生素D的总存储量更高, 预计这些存储将在体重减轻过程中释放并可能增加25(OH)D₃水平。Palacios等^[25]在对98名超重或肥胖的人群进行研究时发现: 脂肪的集聚影响血清25(OH)D₃的水平, 体脂含量与血清25(OH)D₃呈负相关。383名超重或肥胖妇女参加为期2年的减肥计划, 结果显示: 比基础体重减轻5%~10%的人, 血清维生素D增长为2.7 ng/mL; 比基础体重减轻超过10%的人, 血清维生素D增加为5.0 ng/mL($P=0.014$)^[26], 表明体重减轻与血清维生素D浓度升高有关。研究结束后, 维生素D缺乏的人较研究初始时减少13%, 这可能与身体脂肪的减少相关。Sulistyoningrum等^[27]研究指出内脏脂肪对血清25(OH)D₃水平影响更大。

3 肥胖引起维生素D不足或缺乏的机制

3.1 环境因素与自身因素

紫外线促使7-脱氢胆固醇(7-dehydrocholesterol), 也就是维生素D₃的前体, 合成维生素D₃^[28]。虽然肥胖者较正常体重者具有更大的体表面积, 但由于肥胖者户外活动减少, 衣着保守, 致使皮肤接受紫外线照射时间缩短, 故内源性维生素D的合成明显下降^[29]。越来越多的证据^[30]证实: 空气污染是肥胖和低维生素D水平发生的独立危险因素, 并与不健康的饮食和生活习惯有关。

尽管肥胖者的血清维生素D的水平被认为是低的, 但其脂肪组织中有高水平的维生素D^[26]。脂溶性的维生素D储存在脂肪组织中^[25]。Sulistyoningrum等^[27]相关研究显示肥胖人群低血清25(OH)D₃水平可能是由大量的维生素D溶解于脂肪组织造成的。Wacker等^[28]研究发现: 肥胖妇女较正常体重妇女其皮下脂肪中25(OH)D₃含量升高, 且25(OH)D₃为亲脂性分子, 更易储存于脂肪组织中, 故肥胖人群维生素D含量下降可能系脂肪组织含量增多, 从而摄取大量血循环维生素D进入脂肪组织, 致使维生素D生物利用度显著下降。研究^[29]报道: 食物中摄取的维生素D, 有17%储存在脂肪中。另一种理论是肥胖人群和消瘦人群中的维生素D浓度与身体尺寸呈负相关, 25(OH)D₃分布于血清、脂肪、肝、肌肉等许多其他组织器官中, 因肥胖者器官组织体积增大, 故有更大的体积来分布25(OH)D₃, 血清25(OH)D₃的水平相应降低^[30]。

非酒精性脂肪肝病(non-alcoholic fatty liver disease, NAFLD)与维生素D的关系已被充分认识, 即维生素D的水平与NAFLD的严重程度呈负相关^[31]。NAFLD包括单纯性脂肪肝、非酒精性脂肪肝失代偿期、肝硬化、肝细胞癌^[32]。NAFLD会影响维生素D的活性和功能^[33]。最近的一项荟萃分析报道^[33]指出NAFLD患者维生素D降低发生率比健康普通人高26%。然而非酒精性脂肪肝与维生素D的相关性也可能是由于肥胖及脂肪肝本身的危险因素而形成的结果, 比如久坐不动的生活方式及不合理的膳食等, 目前还未充分证明肝维生素D羟化能力的下降是由于NAFLD, 关于二者关系需要更多文献及循证证据来证明。

皮下脂肪^[34]与内脏脂肪^[35]都可能是胰岛素抵抗(insulin resistance, IR)等代谢综合征起病的因素。肥胖患者的低维生素D水平似乎对IR和血糖稳态有负面影响^[36]。有研究^[37-38]证实了低维生素D状

态与IR之间的负相关性。一项体外研究^[39]表明伴有IR性肥胖人群的脂肪细胞释放维生素D的功能可能已经受损。

3.2 分子水平的变化

瘦素是一种由脂肪细胞分泌的激素, 可通过调节能量代谢来保持体脂相对稳定。脂肪细胞分泌的瘦素与体脂含量呈正相关, 并反映出机体的能量状况^[40]。瘦素通过与VDR相互作用, 通过自分泌、旁分泌对脂肪细胞有脂解作用, 从而调控脂质代谢^[41]。最近有研究^[42]在小鼠脂肪组织中发现 $1,25(\text{OH})_2\text{D}_3$ 能够直接刺激mRNA表达和分泌瘦素。因此, 维生素D的减少可能使瘦素的表达降低, 从而使食欲增加、消耗减少, 可能与肥胖的发生有关^[23]。

肥胖者体内脂肪组织增生肥大, 致使供血相对不足, 进而引发组织缺氧、炎症反应及巨噬细胞聚集^[43]。维生素D可调节免疫系统功能, 且可抑制脂肪组织释放促炎性细胞因子, 从而减轻其慢性炎症反应; 维生素D3通过减少脂肪细胞的趋化因子和细胞因子释放以及单核细胞的趋化性而对脂肪细胞发挥抗炎作用^[39,44-45]。循环 $25(\text{OH})\text{D}_3$ 的增加可致炎症标志物C型反应性蛋白(CRP), 肿瘤坏死因子 α (TNF- α)和白介素6(IL-6)明显降低^[46]。

维生素D缺乏或不足可引起PTH释放增多。Song等^[47]研究认为: PTH增加可能通过诱发血钙浓度升高, 从而促进脂肪细胞 Ca^{2+} 内流, 激活脂肪酶, 最终抑制脂肪分解。对于维生素D缺乏患者, 为使 $25(\text{OH})\text{D}_3$ 水平的正常化, 其 $1,25(\text{OH})_2\text{D}_3$ 生成及PTH水平可能会反应性减低, 从而预防体重增加^[48]。

4 补充维生素D对肥胖的影响

由于肥胖者维生素D水平及维生素D生物利用度均明显降低, 故需补充更高剂量维生素D才可满足机体所需。一项超过12 000名成年人的研究^[49]显示高BMI与维生素D的补充反应成反比。另一项研究^[50]显示: 补充维生素D后, 超重或肥胖女性的血清 $25(\text{OH})\text{D}_3$ 水平升高水平低于正常BMI的女性; 与 $\text{BMI}<25\text{ kg/m}^2$ 的组别相比, 肥胖组的血清 $25(\text{OH})\text{D}_3$ 水平低了7 ng/mL, 说明对于维生素D补充的反应与体重有关。依靠短期的低剂量的补充维生素D提高 $25(\text{OH})\text{D}_3$ 的水平来影响脂肪组织是不够的。对于成人来说, 维生素D的最小推荐剂量为

400~2 000 U/d^[51]。在肥胖患者中, 需要更高的剂量(2~3倍, 至少6 000~10 000 U/d)的维生素D来治疗维生素D缺乏, 并维持 $25(\text{OH})\text{D}_3>30\text{ ng/mL}$, 随后维持治疗3 000~6 000 U/d^[52]。

Christakos等^[8]研究发现: 补充维生素D和钙能够减少饮食性肥胖个体的BMI和脂肪总量。另一项研究^[53]让77例肥胖妇女每日接受维生素D 1 000 U或安慰剂的补充, 12周后, 维生素D补充组体脂肪量显著降低, 且血清中的维生素D的浓度升高, 然而两组受试者的体重和腰围均无显著变化。一项包括171名超重和肥胖成年人随机对照双盲实验^[54]发现: 与安慰剂相比, 每日补充钙1 050 mg和维生素D 300 U, 16周后, 内脏脂肪显著下降($P=0.039$)。另一项研究^[55]显示: 接受能量摄入限制的肥胖大学生, 每日补充钙600 mg和维生素D 125 U, 12周后, 尽管组间体重变化没有差异, 但补充组内脏脂肪量和脂肪面积的明显减少。

根据既往研究^[56], 地中海饮食被认为是健康的饮食模式, 应使肥胖患者增加地中海饮食的知识, 并倡导地中海饮食习惯。尽管适度的阳光照射仍然是最方便和最安全的方式来获得维生素D, 食品强化计划仍是解决全球维生素D缺乏症这一问题的合理途径。

5 结语

肥胖与维生素D缺乏在世界范围内普遍流行, 血清维生素D水平下降与肥胖关系密切, 二者相互影响, 但具体机制有待进一步阐明, 建立大样本的流行病学调查以及相应的细胞学机制实验十分必要。此外, 肠道菌群的结构改变与肥胖、IR、非酒精性脂肪肝、轻度炎症状态等的发生密切相关, 已成为近年来的研究热点。肠道菌群的结构改变是否能够引起维生素D水平的改变尚不明确, 有待进一步探究。肥胖患者由于其维生素D生物利用度降低, 对维生素D的需求量明显升高, 但给予肥胖者外源性维生素D是否有利于其体脂含量及体脂分布的改善尚需更多的研究证实。

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