·综述·

镁与骨质疏松

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摘要: 镁离子是人体内重要的阳离子,参与多种生理活动。。镁缺乏易导致骨质疏松,适当补充镁可以增强骨密度,改善骨组织形态,缓解骨质疏松等症状。此外,可降解金属镁及其镁合金因其在骨折和骨缺损治疗中的潜在优势,有望在未来的骨外科治疗中得到广泛应用。然而镁离子促进成骨细胞增殖和分化,促进骨骼生长作用机制仍待深入研究。本文综述了镁在骨代谢中的作用及相关分子机制的最新研究进展。

关键词: 镁;骨质疏松症;成骨细胞;TRPM7

Magnesium and osteoporosis Magnesium and osteoporosis

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Abstract: Magnesium is the major intracellular divalent cation and is involved in many physiological processes. Magnesium deficiency may lead to osteoporosis. However, magnesium supplementation may promote bone growth and prevent osteoporosis. This paper reviews the progress on the mechanism of magnesium-stimulated bone growth and bone metabolism.

Key words: Magnesium; Osteoporosis; Osteoblasts; TRPM7

镁离子是人体内重要的二价阳离子,参与体内几乎所有代谢活动[1],具有调节葡萄糖代谢、胰岛素敏感、血管平滑肌节律以及影响血压稳定等作用[2]。镁离子的摄入和平衡是一个动态过程,包括肠道吸收、骨骼的存储交换和肾脏的排泄[3]。成人每天需要摄入 300 ~ 400 mg/kg 镁,使血清内的镁浓度维持在 0. 75 ~ 1. 00 mmol/L 范围内,若血清镁低于 0. 75 mmol/L 即为低镁血症,而高于 1. 0 mmol/L 即为高镁血症。体内镁的含量约为 22. 6 g,其中大约 65% 储存在骨骼中[4],骨骼中 1/3 的镁以磷酸盐形式存在,2/3 吸附在矿物质元素结构表面,由此可见,镁对骨骼健康非常重要[3]。镁缺乏易引发骨质疏松,导致骨脆性增加[5,6],而适量补充镁制剂则促进骨生长,缓解骨质疏松。本文综述了镁与骨质疏松的最新研究进展。

1 镁缺乏与骨质疏松

镁缺乏易引发骨质疏松[5,6]。骨质疏松症是一种全身性骨代谢障碍疾病,其显著特征是骨组织显微结构受损,骨矿成分和骨基质等比例不断减少,骨质变薄,骨小梁数量降低,表现为骨脆性增加和骨折危险度升高。

1.1 镁缺乏导致骨质疏松

正常人群中,男性镁的最低需要量为 420 mg/天,女性为 320 mg/天,调查发现,大多数人的日常镁摄入量均低于上述指标[7]。Robert K. Rude 等在动物模型和人类流行病学观察中均发现:镁缺乏导致骨质疏松[8]。流行病学研究发现:人类饮食中镁的摄入量与骨密度具有正相关性[5]。Kanazawa 等研究了一例 82 岁的骨质疏松女患者,由于长期营养不良而患有低血镁症,而镁缺乏导致其体内 PTH 分泌和肾脏维生素 D 的合成受到抑制[9],骨密度降低。Khazdooz 等人研究了 60 例绝经后骨质疏松症患者,发现这些患者的平均日镁摄取量为 120 mg/天,仅为建议摄取量的 37%,而患者平均血清镁含量仅为 0. 7 ± 0. 01 mmol/L,低于正常水平[10]。Ersin 等人在 77 例绝经后骨质疏松症患者体内也发现:患者体内红细胞中的镁含量(51. 51 μg/mL)明

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显低于正常的绝经后妇女(54.54 μg/mL),这些结果表明骨质疏松可能与镁离子进入细胞的转运机制有关[11]。

此外,动物模型研究进一步证明镁缺乏导致骨质疏松[5]。Rude[12]等人用含镁量仅为 0.002% 的饮食喂养小鼠(正常饮食中镁含量为 0.05%),发现所有小鼠均表现为低镁血症,并且骨组织镁含量也明显减少;幼鼠生长板的宽度减小 33%,软骨细胞柱的数量和强度下降,同时,小鼠胫骨干骺端的骨小梁体积减少,破骨细胞的数量增加了 135%,成骨细胞的数量明显减少,这表明镁缺乏能够明显抑制骨生长。通过建立不同程度的镁缺乏模型鼠,分别为饮食中镁含量为 0.005%[13]、0.0125%[14] 和 0.025%[15] 的大鼠,研究人员发现,与正常饮食(含镁 0.05%)大鼠相比,摄入含镁 0.005% 和 0.0125% 饮食的大鼠表现为低血镁症,血清中 PTH 含量减少,而摄入含镁 0.025% 饮食的大鼠血清中的镁含量和 PTH 含量均正常,但所有大鼠体内的 1,25(OH)$_2$-维生素 D 含量均下降[13-15];骨组织形态学研究表明镁缺乏大鼠体内的骨小梁体积均明显减小,摄入含镁 0.005% 和 0.025% 饮食的大鼠体内检测到破骨细胞的数量明显增加[13, 15]。由此可见,体内镁缺乏将导致成骨细胞和破骨细胞的数量和功能的异常,从而导致骨质疏松。

1.2 镁缺乏诱发骨质疏松的原因

近年来的研究表明:镁缺乏引起体内钙离子平衡的紊乱,同时引起甲状旁腺激素(PTH)和 1,25(OH)$_2$-维生素 D 的分泌减少[5],造成骨形成减少,骨矿化异常。最新研究发现:低浓度的镁离子还抑制成骨细胞的增殖与分化[16-18],Leidi 等人发现:低镁状态下,成骨细胞上调诱导型一氧化氮合酶(iNOS)的表达,增加一氧化氮的释放,减少骨形成[18]。NO 对成骨细胞的影响具有剂量效应,适量低浓度的 NO 能够促进成骨细胞的增殖,而随着 NO 浓度的提高,成骨细胞的增殖受到明显抑制[19]。JNK 在低镁介导的 iNOS 激活过程中起到重要作用,缺镁状态下 JNK 的抑制剂能够恢复成骨细胞的正常增殖,并且能够抑制 iNOS 表达的上调[18]。

另外,镁缺乏致使血清中护骨素(OPG)水平降低,RANKL(receptor activator of nuclear factor-κ B ligand)水平增加,从而引起破骨细胞的数量增加,活性增强,促进骨吸收[20]。而成骨细胞在低镁状态下诱导 iNOS 表达的上调,诱导合成的 NO 能够介导炎性细胞因子的释放,促进破骨细胞聚集并增加其骨吸收作用[19]。此外,镁缺乏时,骨组织中 TNFα 与 P 物质的表达上调,引起小鼠在缺镁状态下活性破骨细胞增加[13],敲除 TNFα 受体基因能够缓解由于镁缺乏引起的骨损伤[21]。

2 镁与骨骼生长

2.1 补充镁缓解骨质疏松

研究发现,口服补充醋酸镁(1830 mg/天)[22]或静脉注射硫酸镁(720 mg/12 h)[9],可抑制绝经后骨质疏松病人的骨转换,使椎骨和股骨的骨密度明显增加,骨质疏松得到缓解。Yasuhiro[23] 和 Yun[24] 等在动物模型中也发现:饮食中补充镁能够缓解卵巢切除后大鼠的骨质疏松症状。Yasuhiro 等人用卵巢切除的大鼠来模拟绝经后骨质疏松病人的症状,高镁饮食(含镁 0.15%)处理大鼠,6 周以后,与正常饮食(含镁 0.05%)的大鼠相比,高镁饮食大鼠的尿液中脱氧吡啶诺林(骨吸收的指标)的含量明显减少,血清中 PTH 水平降低,骨钙素的水平明显提高;大鼠股骨的强度和韧性得到显著恢复[23]。Matsuzaki 等人[25]的研究表明,高镁饮食能够降低大鼠血清中 PTH 的水平,缓解由高磷饮食引起的大鼠体内增强的骨吸收作用;当用正常饮食、高磷饮食和高磷高镁饮食诱导大鼠,2 周以后,高磷组和高磷高镁组大鼠血清中的骨钙素和 CTx(骨吸收指标)水平均明显高于正常饮食组,但与高磷饮食组相比,高磷高镁组大鼠血清 PTH 和 CTx 水平明显降低。Bae 等人还发现,饮食中补充镁能够明显改善大鼠体内的骨转换率,通过调节骨质疏松大鼠血清中 OPG/RANKL 的比例,从而减少骨吸收作用[20]。我们的研究[26]也发现金属镁植入糖尿病性骨质疏松大鼠的股骨,随着金属镁的降解,大鼠的骨密度得到显著恢复,血清中骨钙素水平明显提高。

2.2 镁与镁合金治疗骨折和骨缺损

金属镁及其镁合金在骨折和骨缺损治疗中具有潜在的优势,镁的密度(1.7 g/cm^3)接近人骨密度(1.75 g/cm^3),其弹性模量(45 GPa)也与人骨(20 GPa)接近,其良好的生物相容性和可降解性使成为近年来生物医用金属材料的一个研究热点[27]。

Li 等[28] 和 Zhang 等[29] 分别报道了 Mg-Ca 和 Mg-Zn 合金植入大白兔股骨内表现出的良好生物相容性、可降解性,并促使植入物周围形成新骨。研究表明,镁合金与小鼠成骨细胞具有良好的生物相容性及骨传导特性[30],在修复实验动物下颌骨表面不同形态骨缺损时具有骨诱导作用[31];植入 SD 大鼠

股骨干内的镁合金具有良好的可降解性、成骨性及组织相容性,其降解过程与新骨成骨过程具有良好的同步性[30]。Weng 等发现而纳米镁材料表现出更好的生物相容性[32]。研究发现,植入体内的镁合金,其主要氧化产物 $Mg(OH)_2$ 能够短暂地刺激成骨细胞的活性,并且减少破骨细胞的数量抑制骨吸收[33]。

2.3 镁促进骨生长的作用机制

体外实验表明,镁离子能够促进成骨细胞的增殖与粘附,促进成骨细胞的成骨活性[34-36]。镁合金材料在体内降解的过程中会释放高浓度的镁离子,Yang[37]等人发现纯金属镁浸出液中镁离子的浓度为 10.286 mM,镁合金 NZ30K 浸出液含镁 5.9028 mM,AZ91D 浸出液中含镁 3.3998 mM;他们用镁合金浸出液处理人间充质干细胞,结果表明:镁离子(≤10 mM)能促进间充质干细胞的粘附与生长,并且促进其向成骨方向分化。然而,也有研究发现高于 5mM 的镁离子能够明显抑制成骨细胞的增殖与分化[34]。

2.3.1 TRPM7 通道蛋白:成骨细胞表面表达钙镁离子的通道蛋白 TRPM7(melastatin-like transient receptor potential 7),它是一种组成型活性阳离子通道并受到胞内 Mg^{2+}/Mg^{2+}-ATP 调节,其胞内区的 C 末端具有 α-激酶的活性[38]。TRPM7 能够通过感知外界镁离子水平而调控细胞的生理活动,其 α-激酶的活性受也到胞内镁离子浓度的调节[39],能自磷酸化并磷酸化下游的靶蛋白。TRPM7 通道蛋白在维持细胞水平的镁离子平衡中起到重要的作用,TRPM7 基因沉默的成骨细胞细胞表现为细胞内镁缺乏[40, 41]。同时,TRPM7 参与了成骨细胞的增殖与分化,沉默 TRPM7 基因,细胞增殖受到明显抑制[40, 41],并且成骨细胞的矿化能力也明显降低[17]。PDGF 能够通过 TRPM7 升高胞内镁离子浓度,促进成骨细胞增殖[40]。

2.3.2 信号通路:研究表明,镁离子能够作为细胞内的第二信使[42]。多种细胞在受到外界刺激时,细胞内的游离镁离子均会有所升高[43]。“膜-镁-有丝分裂”模式(membrane magnesium mitosis model)提出,在有丝分裂信号的刺激下,胞内镁离子浓度会迅速升高,并且通过激活 PI3K 通路促进细胞的有丝分裂[44]。Lozano 等发现,镁离子能够上调与成骨细胞 MC3T3-E1 分化相关的蛋白表达,如 calreticulin、Prolyl4-hydrolase beta polypeptide 以及 Annexin A5[36]。Jeon. S. H 等研究揭示,Taurine 通过激活 ERK1/2 通路引起胞内游离镁离子的含量升高,刺激成骨细胞的增殖[45]。由此可见,胞内镁离子浓度变化对细胞的生长和分化有着重要的作用。

综上所述,镁缺乏易导致骨质疏松,适当补充镁可以增强骨密度,改善骨组织形态,缓解骨质疏松等症状。此外,可降解金属镁及其镁合金因其在骨折和骨缺损治疗中的潜在优势,有望在未来的骨外科治疗中得到广泛应用。然而镁离子促进成骨细胞增殖和分化,促进骨骼生长作用机制仍待深入研究。TRPM7 通道蛋白对维持细胞内镁离子平衡具有重要作用,TRMP7 可以自磷酸化激活并通过磷酸化下游靶蛋白,如 myosin IIA 和 Annexin I,激活其下游的信号传导通路[46, 47]。然而镁离子通过激活 TRPM7 调控成骨细胞分化的信号转导通路仍需进一步研究。因此,阐明镁离子促进成骨细胞生长和分化的作用机制,为治疗骨质疏松和骨折等骨疾病开拓新思路和发现新靶点。

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