

乳脂肪球对婴幼儿健康的临床意义

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摘要: 母乳是最适合婴儿消化、代谢能力, 满足婴儿全面营养需求的天然食物。对母乳成分的高度关注和研究, 促进了婴儿配方奶粉的改进。母乳脂肪球的结构被认为是母乳生态系统中的重要部分。临床试验表明, 含有模拟母乳脂肪球结构的新型配方奶粉具有良好的安全性和耐受性, 新型配方奶粉喂养儿的体质量指数发展轨迹更贴近于母乳喂养婴儿; 在粪便样本中的平均粪便脂肪含量、磷和钙的含量以及脂肪酸的总和优于传统配方奶粉, 并调节婴儿肠道菌群; 通过促进 ω -3 长链多不饱和脂肪酸吸收促进婴儿认知发育。

关键词: 母乳; 配方奶粉; 乳脂肪球; 生长发育; 婴儿

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Clinical significance of milk fat globules for infant health

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Abstract: Breast milk is the natural food best suited to infants' digestive and metabolic capabilities, fulfilling their comprehensive nutritional needs. Heightened attention and research on the components of breast milk have facilitated improvements in infant formula. The structure of breast milk fat globules is recognized as an important part of the breast milk biosystem. Clinical trials indicate that novel formulas containing structures mimicking breast milk fat globules exhibit safety and well tolerance, with body mass index development trajectories closer to those of breastfed infants. These formulas surpass traditional infant formulas in terms of average fecal fat content, phosphorus and calcium levels, and total fatty acids in stool samples, while also modulating infant gut microbiota. They promote infant cognitive development by enhancing the absorption of ω -3 long-chain polyunsaturated fatty acids.

Keywords: breast milk; formula milk; milk fat globule; growth and development; infants

母乳是最适合婴儿消化、代谢, 满足婴儿全面营养需求的天然食物, 没有之一。母乳中含有近 2 000 多种生物活性物质, 它们共同协同, 完成对婴幼儿的营养供给。在 0~3 岁婴幼儿身体发育最关键的阶段, 当母乳喂养不足时, 配方奶粉便成为其部分或全部营养来源。乳脂肪球(milk fat globule, MFGs)由乳腺的泌乳细胞表达和分泌, 其含有不同类型的脂肪酸、磷脂、脂溶性维生素和复合脂质等成分, 是婴儿最重要的营养来源之一。通过婴幼儿配方奶粉生产工艺改进, 运用精准控制工艺, 可制备出模拟母乳脂肪球结构、由乳脂肪球膜成分完整包裹的大粒径脂肪球(Nuturis 脂球), 其是否能够具有接近母乳脂肪球的作用, 是母乳成分研究中被高度关注的热点。本文将含有模拟母乳脂肪球结构的新型配方奶粉(new infant milk formula, nIMF)的研究进行归纳综合, 就

nIMF 在临床试验中显示的安全性与耐受性, 以及在降低远期肥胖风险、调控乳脂消化吸收、改善婴儿认知发育等方面进行综述。

1 母乳和天然乳汁中脂肪的存在形式

母乳中脂肪以乳脂肪球的形式存在。乳脂是母乳中含量仅次于乳糖、排名第二的物质, 约占干物质总重的 30%, 并为婴儿提供了约 50% 的能量、必需脂肪酸以及脂溶性维生素。

乳脂肪球是母乳、牛乳等天然乳中脂肪的存在形式, 球内的甘油三酯内核粒径为 3~5 μ m, 外层脂肪球膜厚度约 90 Å。早在 1967 年, 麻省理工学院的 Dowben 等^[1]用显微镜观察到牛乳中的脂肪球具有微米大小的粒径, 且推测外表面的膜是细胞生物膜衍生物。目前乳脂肪球的形成机理已经较为明

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确^[2],受到泌乳细胞分泌乳汁过程的控制。在泌乳细胞中,甘油三酯小脂滴被来自内质网的单层磷脂膜包裹后不断向细胞顶膜迁移,融合形成微米级别的大脂滴,进而被乳腺细胞顶端的双层磷脂细胞膜包裹分泌至胞外,形成完整的乳脂肪球。

乳脂肪球结构,即中性脂(主要是甘油三酯)构型的核心外包裹乳脂肪球膜^[3]。乳脂肪球膜是具有内侧单层磷脂膜、外侧双层生物膜的三层膜结构^[4]。不同哺乳动物乳的脂肪球粒径分布稍有差异,母乳与牛乳的平均体积粒径较为相近,羊乳有较多的小脂肪球和比母乳更小的平均体积粒径,母乳脂球的粒径范围更大。

2 婴幼儿配方粉中脂肪的存在形式与改进

目前,市售配方奶粉中的脂肪以小脂滴的形式存在,与母乳脂肪球有明显的结构差异。配方奶粉加工过程中会采用高压均质将天然乳脂球打碎以提高稳定性和增加干燥后复溶的溶解性。经高压均质后的配方奶粉脂肪小液滴平均粒径为 $0.2\mu\text{m}$,远小于母乳脂球的 $3\sim 5\mu\text{m}$;且普通配方奶粉(conventional infant milk formula, cIMF)中的脂肪小液滴不具有完整的乳脂肪球膜,油水界面主要是被打碎的脂肪球膜碎片、乳化剂和酪蛋白^[5]。

目前通过改进乳品加工工艺,精准控制,已经可以制备出一种新型配方奶粉,含有 Nuturis 脂球^[6]。Nuturis 脂球具有类似于母乳脂球的 $3\sim 5\mu\text{m}$ 平均粒径和牛乳提取的乳脂肪球膜成分构成的磷脂膜。

3 配方奶粉中脂肪球对婴幼儿健康的临床意义

新型脂肪球配方奶粉(nIMF)对婴幼儿健康的临床意义是多方面的。下面从消化吸收、体格生长与远期肥胖以及对认知的影响三个方面进行阐述。

3.1 乳脂肪球与乳脂消化吸收 消化是婴儿脂质代谢的第一步,消化行为影响后续脂质的吸收利用。婴儿的消化系统尚未发育完全,脂肪消化与成人有显著差异。婴儿胃部脂肪酶活性较高,胃部消化率高达 30%,而成人胃部通常只进行脂肪乳化,几乎不进行脂肪消化^[7-8]。婴儿小肠的酶功能发育不完善,胰脂肪酶的分泌量显著低于成人。

多项研究对比了母乳、nIMF 与 cIMF 在模拟婴儿胃肠道环境下体外消化的行为,结果显示,nIMF 与母乳具有相似的脂肪消化特性,包括消化脂解度和消化乳液形态。首先,母乳脂肪球的胃相脂解度较低^[9-10],而 cIMF 具有更大的比表面积,能够吸附更多的胃脂酶促进脂肪水解^[11]。在肠相消化阶段,

母乳的最终脂解度高,释放了更多中长链饱和脂肪酸^[12-13],nIMF 整体消化脂解曲线趋势与母乳脂球更接近^[14]。其次,nIMF 和母乳在胃中仍能观察到部分完整的磷脂膜^[14-15],而 cIMF 小脂滴能通过蛋白质和两亲性酯类交联形成大的团聚体^[16],胃相消化的不稳定团聚会影响肠相脂肪消化。nIMF 脂质吸收水平也更加接近母乳,肠相中的水解产物被肠上皮细胞吸收后重新合成甘油三酯,nIMF 能够上调脂质转运相关基因和乳糜微粒形成相关基因,增加细胞基底侧甘油三酯的含量^[17]。

婴儿粪便能够直接反映肠道对营养物质的吸收和肠道菌群特征。2012—2014 年间,4 个国家的 17 个研究中心纳入 311 例婴儿的多中心、双盲随机对照临床试验表明,nIMF 组喂养的婴儿在出生后 5~12 周龄期间,nIMF 的水样便发生率高于 cIMF ($P<0.001$),并与母乳喂养组的粪便特征更加接近^[18]。Heijning 等^[19]监测了上述 311 例婴儿在基线、13 周和 52 周龄时粪便样本中的平均粪便脂肪含量、磷和钙的含量以及脂肪酸的总和,发现在第 13 周时,nIMF 组大便中的磷、钙含量及脂肪酸总量低于 cIMF 组,与母乳喂养组更为接近。这在一定程度上说明 nIMF 喂养能更好地吸收矿物质与脂质,可能对婴儿的生长发育产生影响。Cianci 等^[20]继续对上述婴儿粪便样品中的微生物群组成进行分析比较,发现一些低丰度菌群在 nIMF/母乳与 cIMF 组间也存在差异,但 nIMF 与母乳之间的差异并不显著。

3.2 乳脂肪球与婴幼儿生长发育 婴儿期是人一生中代谢率最高的时期,大脑快速发育需要大量的能量,从出生到 1 周岁期间的能量需求迅速增加,单位体重能量消耗比成人高出 1 倍。脂肪是母乳和配方奶粉中主要提供能量的成分,也是影响婴儿体脂积累的重要物质。母乳喂养可以预防远期肥胖是不争的事实。与配方奶粉喂养的婴儿相比,母乳喂养的婴儿肥胖发生率更低。此外,在长期母乳喂养的背景下调查肥胖发生率,结果显示较长时间的母乳喂养群体与肥胖发生率呈反比关系^[21]。

Abrahamse-Berkeveld 等^[22]进行的长期临床研究表明,nIMF 支持健康婴儿的充分发育,具有降低远期肥胖潜在风险的作用。跟踪 4 个国家、17 个研究中心 311 例婴儿的多中心、双盲随机对照试验^[18],其中干预分为 nIMF 组($n=115$)、cIMF 组($n=108$)和母乳组($n=88$),收集 1、3、4 和 5 岁儿童的人体数据,评估婴儿成长至学龄期间的体质量指数(body mass index, BMI)及血压的长期变化。结果

表明 nIMF 组婴儿成长过程中的平均 BMI 低于 cIMF 组,1 岁时差异有统计学意义($P=0.001$),其均值与母乳喂养组相近($P>0.05$);cIMF 组婴儿 1~5 岁期间的平均 BMI 显著高于母乳喂养组($P<0.05$);5 岁时,nIMF 组婴儿的平均舒张压和动脉血压显著低于 cIMF 组($P=0.01$)。早期接受 nIMF 喂养的婴儿在成长过程中 BMI 的发展轨迹与母乳喂养婴儿更为接近,并且在进入学龄期时表现出较低的血压水平。

2011—2023 年间,众多研究团队通过动物实验研究 nIMF 的作用效果,包括使用 nIMF 和两种 cIMF(含有或不含乳脂肪球膜成分)配方奶粉对幼年小鼠进行早期喂养干预,随后进行西方饮食(含 10%~20% 脂肪)或高脂饮食(含 45% 脂肪)挑战,探究乳脂肪球对小鼠身体组成和脂质代谢的影响。Oosting 等^[23]发现在西方饮食喂养 84 天后,与 cIMF 组相比,nIMF 组小鼠的脂肪量降低了 28%,其空腹血浆中瘦素、抵抗素、血糖和血脂指标也显著降低。Teller 等^[24]发现 nIMF 使大鼠瘦素和胰岛素样生长因子 1 的基因表达水平显著降低,有益于胎儿时期生长受限大鼠的长期内脏脂肪积累和代谢健康。此外,与喂养含有或不含乳脂肪球膜成分的 cIMF 两组对照组相比,仅早期喂养 nIMF 可降低腹部白色脂肪,这一结果支持了喂食 nIMF 的小鼠体内脂肪质量减少的现象^[25]。

nIMF 有助于代谢改善和降低体脂积累,可以用健康与疾病发育起源理论(Developmental Origins of Health and Disease,DOHaD)解释。研究揭示,nIMF 可以降低成年期白色脂肪组织中代谢活动的关键调节因子的表达^[26]。nIMF 可以增强小鼠白色脂肪组织中柠檬酸合成酶活性和线粒体 DNA 表达,增加氧化磷酸化途径中线粒体细胞色素 c 氧化酶亚基 I 的蛋白表达,以更好地应对由西方饮食导致的多余脂肪积累^[27]。nIMF 喂养的小鼠肝脏中参与 β -氧化、三羧酸循环的关键蛋白浓度显著提高($P<0.05$)^[28],在长期肥胖因素诱导下,脂质吸收和转运机制的调整可能是降低体脂率和体脂积累的关键因素^[29]。此外,nIMF 还可能通过影响调节小胶质细胞^[30]和特定甘油二酯水平和线粒体功能^[31],从而减低脂肪组织积累和保护西方饮食诱导的胰岛素抵抗和全身性氧化应激。

3.3 乳脂肪球与婴儿认知发育 母乳喂养的婴儿通常比配方奶喂养的婴儿表现出更好的神经认知功能,重要的原因是母乳和婴儿配方奶粉在乳脂成分和乳脂肪球结构上的差异。研究显示,nIMF 具有促

进 ω -3 长链多不饱和脂肪酸吸收的作用,对婴儿认知发育具有积极影响。Schipper 等^[32]跟踪研究了前期招募的 311 例^[18]婴儿生长至学龄期的认知发育情况,发现 nIMF 组在 Flanker 抑制控制和注意力评估测试中表现最好,与母乳组类似。此外,在儿童执行功能任务评估中,nIMF 组得分也高于 cIMF 组($P=0.021$),这可能是由于 nIMF 中的脂类具有特殊的乳脂肪球结构,在生命早期有助于吸收长链多不饱和脂肪酸并改变细胞膜的脂质,从而提高认知发育。

近年来学者们也通过动物实验探究 nIMF 对认知行为的长期影响。早期喂养 nIMF 的小鼠改善了特定认知行为^[33],包括青少年时期的短期记忆任务以及成年时期对新物体的识别能力。这可能因为膳食脂质会影响肠道内饱腹感激素的释放,例如胆囊收缩素释放增加能够促进学习和记忆过程。此外,骨骼发育和稳态可能有助于大脑发育,例如,骨组织根据成骨细胞的成熟度和维生素 K 的可用性分泌骨钙素(包括血清素、多巴胺和去甲肾上腺素),影响认知和行为表型。Heijningen 等^[34]发现 nIMF 有助于小鼠肌肉(瘦体重)增加和骨骼发育,同时能减少焦虑情绪并改善成年后的认知功能。Oosting 等^[35]对比了添加乳脂肪球膜配料的 nIMF 和 cIMF 对早期干预后的成年小鼠记忆力的影响,结果发现 nIMF 组小鼠的记忆力更强,同时肝脏和大脑中积累更多的 ω -3 脂肪酸,与神经发育相关的脑髓鞘相关蛋白也有更高表达($P=0.04$),由于此研究中 nIMF 与 cIMF 均添加了乳脂肪球膜,因而推测这可能与 nIMF 模拟母乳脂球的结构更利于特定脂质的吸收相关。

综上所述,母乳脂肪球的结构是母乳生态系统中的重要部分,其对婴儿生长发育的影响是近年来新的研究热点。临床干预试验表明,含有模拟母乳脂肪球结构的新型配方奶粉具有良好的安全性和耐受性,BMI 发展轨迹更贴近于母乳喂养婴儿,可以降低婴儿远期肥胖风险;在粪便样本中的平均粪便脂肪含量、磷和钙的含量以及脂肪酸的总和优于传统配方奶粉,并可调节婴儿的肠道菌群;通过促进 ω -3 长链多不饱和脂肪酸吸收促进婴儿认知发育。

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