中国科学: 生命科学 2024 年 第 54 卷 第 1 期: 103 ~ 115
SCIENTIA SINICA Vitae lifecn.scichina.com
《中国科学》杂志社 SCIENCE CHINA PRESS

评 述 生殖健康专辑

高能量饮食及肥胖影响男性生育力的研究进展

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收稿日期: 2023-07-12; 接受日期: 2023-08-29; 网络版发表日期: 2024-01-12

国家自然科学基金(批准号: 82171589, 82203709)资助

摘要 饮食对人体正常生理活动有重要影响. 高能量饮食和肥胖对男性生殖健康的潜在有害影响一直备受关注. 多项研究表明, 高能量饮食和肥胖通过直接或/和间接的途径影响男性生殖轴、精液质量、肠道菌群和睾丸微环境等, 在男性不育的发生中发挥重要的作用. 父系肥胖不仅影响自身健康, 也可通过精子的表观遗传调控作用对子代造成影响. 同时, 改善饮食结构和采取适当的减重措施可以在一定程度上逆转高能量饮食和肥胖对男性生育力造成不利影响. 本文旨在综述目前关于高能量饮食和肥胖与男性生育力之间的研究进展, 探讨其导致男性不育的内在机制, 探寻其潜在的干预措施, 以提高男性生殖健康的水平, 具有重要的临床价值.

关键词 高能量饮食, 肥胖, 男性不育

近年来, 精液质量和男性生殖潜力的持续下降一直备受关注. 精液质量的显著下降对男性生育能力带来了负面影响, 并可能是导致男性生育能力整体下降的原因[1]. 值得注意的是, 从1973年到2011年, 西方国家男性的精子质量已经下降了50%以上, 目前还没有有效的措施来缓解这一趋势[2,3]. 精子质量的迅速下降并非主要由遗传因素引起, 越来越多的研究表明生活环境在其中扮演核心角色[4,5], 包括环境毒素、热量、压力[6,7]、吸烟[8]、饮酒[9]以及饮食结构的变化. 随着食品制造业的快速发展, 人类的生活方式和饮食模式不断发生改变, 尤其是高脂饮食(high fat diet, HFD)已变得相当普遍[10,11]. 饮食对正常生理产生重大影响, 高热量饮食和久坐不动的生活方式又有利于肥胖的发展[12]. 肥胖是多种因素(如代谢、遗传、环境、营养和社会心理因素)之间复杂相互作用的结果. 肥胖的判断依据是身体质量指数(body mass index, BMI). 根据美国国立卫生研究院的数据, BMI在25~29.9 kg/m^{2}之间的个体被归类为"超重", 而BMI大于或等于30 kg/m^{2}的个体被归类为"肥胖", 重度肥胖则定义为BMI >40 kg/m^2. 然而, 身体脂肪的分布, 尤其是在腹部中央区域, 也被用来诊断一个人是否肥胖[13]. 目前, 腰围被认为是一个更准确的肥胖指标.

当前, 肥胖已成为一个令人震惊的全球大流行问题, 是重要的公共卫生挑战. 根据世界卫生组织(World

引用格式: 李校敏, 陈志聪, 安庚. 高能量饮食及肥胖影响男性生育力的研究进展. 中国科学: 生命科学, 2024, 54: 103–115
Xiaomin L, Zhicong C, Geng A. Research progress on the association of high-energy diet and obesity with male infertility (in Chinese). Sci Sin Vitae, 2024, 54: 103–115, doi: 10.1360/SSV-2023-0147

Health Organization, WHO)的数据, 自1975年以来, 全球肥胖人口几乎增加了三倍. 到2016年, 约有19亿成年人超重, 约有6.5亿成年人患有肥胖, 其中男性占比39%, 女性占比40%[14]. 与体重过低相比, 肥胖与死亡风险更高. 然而, 这些数字可能在不久的将来还会增加. 随着全球肥胖问题的不断增加, 男性性功能和生殖能力下降成为生殖健康领域重点关注的问题[15,16]. 关于高能量饮食和肥胖引起男性不育相关机制的研究也在不断进展. 通过结合多组学、单细胞组学和基因敲除模型等前沿技术, 从多个角度筛选和验证高能量饮食和肥胖对不育的作用靶点, 为挽救生精功能和干预生殖损伤提供了一系列策略.

1 高能量饮食及肥胖影响男性生育力的人群研究

每天摄入食物是人类获取营养最有效和最常见的方式之一. 高能量饮食是指摄入大量能量的饮食模式, 通常富含高脂肪、高糖分和高盐分的食物. 热能摄入与消耗的失衡, 造成脂肪在体内的过度蓄积, 引起肥胖. 高能量饮食和肥胖对男性生殖健康的负面影响已在大量临床调查中得到认可[17~19]. 根据美国国家环境健康科学研究所的一项研究, 身体质量指数增加的男性比正常体重的男性更容易不育[20]. 精子质量, 包括精子浓度、数量和活力, 与BMI的增加呈负相关[21]. 不同人群的研究数据一致表明, BMI与生育能力呈反比关系[22~25]. 尽管有大量有力的证据表明过多的体脂对精子形成不利, 但并非所有研究都得出相同的结论[26~30], 比如肥胖男性的精子浓度降低, 但精子活力和形态似乎没有受到影响[31]. 虽然目前的数据高度矛盾, 在多数研究中发现在接受辅助生殖技术(assisted reproductive technology, ART)的夫妇中, 男性肥胖与受孕时间延长、妊娠率降低和妊娠丢失率增加有关[32]. 肥胖不仅与糖尿病、心血管疾病、癌症和全因死亡的风险增加有关. Fanelli等人[33]发现, 大多数慢性疾病患者具有特定的饮食特征, 包括过多的饱和脂肪摄入、总碳水化合物和纤维摄入不足、糖摄入过多. HFD与人类健康呈负相关, 包括体重增加、脂肪积累、肠道微生物群失调、胰岛素抵抗、氧化应激、认知障碍等问题[34,35].

1.1 高能量饮食及肥胖影响男性生殖轴

下丘脑-垂体-性腺轴(hypothalamic-pituitary-gonadal axis, HPG)是调节生精过程的重要机制, 涉及下丘脑、垂体和睾丸之间的相互作用. 下丘脑的特殊神经元通过脉冲方式释放促性腺激素释放激素(gonadotropin-releasing hormone, GnRH), 进入垂体-门静脉循环. GnRH到达垂体前叶促性腺激素细胞, 刺激促黄体生成素(luteinizing hormone, LH)和促卵泡生成素(follicle stimulating hormone, FSH)的释放, 从而实现大脑和睾丸之间的功能联系[36]. 任何影响下丘脑GnRH分泌或垂体FSH和LH分泌的紊乱都会对精子发生产生负面影响, 从而影响生育能力[37].

研究发现, 肥胖男性与非肥胖男性相比, 在HPG轴的激素水平上存在异常. 肥胖男性的总睾酮水平降低, 性激素结合球蛋白(sex hormone binding globulin, SHBG)水平降低[38~40]. 男性BMI的增加与血浆SHBG浓度的降低有关, 从而导致睾酮水平降低, 伴随雌激素浓度升高[41~44]. 而青春期男性的睾丸发育及成年后男性睾丸次级精母细胞的减数分裂及精子细胞的成熟都必须依赖于睾酮, 且睾丸内高水平的睾酮是维持血睾屏障(blood-testis barrier, BTB)与支持细胞以及支持细胞与生殖细胞之间连接所必须的. 此外, 肥胖男性的LH和FSH水平通常较低, 这些异常激素水平可能是肥胖对生育能力产生负面影响的重要原因之一.

部分研究揭示了高能量饮食和肥胖对HPG轴的影响机制. 正常情况下, 睾丸内高水平的睾酮维持着睾丸的血睾屏障、维护睾丸细胞之间的特定细胞连接, 并促进支持细胞和生殖细胞之间的细胞黏附[45]. 高水平的睾酮为适宜的生殖细胞发育提供了必要的生态环境. FSH在睾丸中也起着关键的调节作用, 涉及精子细胞的分裂、成熟、以及支持细胞的调节和营养供应等方面. 而高能量饮食和肥胖常伴有白色脂肪组织(white adipose tissue, WAT) 的过度积累. 白色脂肪组织会引起脂肪相关激素和因子的过度活跃, 包括芳香化酶[46]. 芳香化酶在雌激素生物合成中起关键作用, 导致睾酮过度转化为雌激素[47]. 这种过度的雌激素产生会抑制下丘脑和垂体的促性腺激素分泌, 减少GnRH-LH/FSH脉冲的频率, 从而影响睾酮的产生[48,49]. 过量脂肪细胞导致胰岛素抵抗增加, 进而抑制下丘脑-垂体水平的促

性腺激素分泌，降低睾丸中睾酮的产生[50]. 另一方面，肥胖也导致瘦素抵抗. 瘦素是一种由脂肪细胞产生的激素，对HPG轴的调节起重要作用. 瘦素抵抗会降低GnRH、LH和FSH的释放，进一步减少睾酮的产生[44]. 肥胖还可激活下丘脑-垂体-肾上腺轴(hypothalamic-pituitary-adrenal axis, HPA), 导致雌激素水平升高[51], 过多的脂肪组织会增加循环雌激素的水平，并引发慢性炎症状态，同时还会增加对瘦素和胰岛素的抵抗. 这些因素共同降低了Kisspeptin的分泌水平，从而减少了GnRH、LH和FSH的释放，进一步影响睾丸激素的产生[50]. 因此, 高能量饮食和肥胖引起会HPG轴失衡, 从而导致男性睾酮和FSH水平降低，这可能是精子生成受损的原因之一，进而造成精子数量减少和生育能力下降[52,53].

1.2　高能量饮食及肥胖影响男性精液质量

男性生育能力通常通过标准精子参数来评估，如精子浓度、活力和形态等[54,55]. 据报道，高脂饮食与精子浓度降低、活力减退以及畸形精子发生率增加相关, 可能导致男性不育[56,57]. 临床前动物研究提示, 高饱和脂肪饮食与精子浓度呈负相关，这种关系可能与摄入量相关[58]. 此外, 多个研究表明, 肥胖与男性生育能力低下和精子质量下降有关[59~63]. 在男性肥胖中, 阴囊区的高脂肪含量导致阴囊温度的升高，进而引起睾丸温度升高[64,65]. 精子发生的过程对温度非常敏感, 最佳温度在34~35℃之间[66]. 睾丸温度升高与精子活力显著降低、精子DNA损伤增加和氧化应激水平增加有关[67~69]. 阴囊脂肪组织过多可通过增加睾丸温度或影响睾丸内信号影响精子发生[70]. 研究显示手术切除阴囊脂肪可改善精子参数[71].

2　高能量饮食及肥胖影响男性生育力的机制研究

高能量饮食及肥胖与男性生殖功能受损之间的联系是多因素的，它通过多种途径直接或间接地影响精子质量，包括炎症介质和活性氧(reactive oxygen species, ROS)水平升高、肠道菌群紊乱、睾丸微环境破坏及重塑精子DNA和改变表观遗传等，这些机制累积起来会对精子发生产生实质性的有害影响(图1).

2.1　氧化应激及炎症自噬

活性氧介导的精子损伤是导致男性不育的主要因素之一[72]. 氧化应激表示ROS产生与抗氧化能力之间的不平衡[73]，且精子氧化应激水平与男性BMI呈明显正相关[74,75]. 肥胖会增加精子的氧化应激和DNA受损, 进而降低受精能力[75,76]. 在生理浓度下, 活性氧作为信号分子介导精子功能的多个方面，包括获能、顶体反应、膜流动性、卵母细胞融合和受精能力[77]，然而, 过量的ROS会氧化生殖细胞中的脂质、蛋白质和DNA, 导致生育能力下降甚至不育[78,79]. ROS可通过诱导DNA链断裂、碱基错配和突变引起精子DNA损伤[80,81]. 精子细胞核中DNA的完整性是精液质量的一个重要决定因素，对受精率、胚胎质量、妊娠率和流产率也至关重要. 多项研究表明肥胖和精子DNA完整性之间存在显著的负相关关系[82~85]. DNA碎片指数(DNA fragmentation index, DFI)代表精液样本中核DNA中单链或双链断裂精子的百分比，其正常值为3%~5%，当DFI上升到25%~30%时，将增加不孕症的风险[86]. 另一方面，精子的活力和随后的受精在很大程度上取决于精子的线粒体功能. 线粒体膜电位(mitochondrial membrane potential, MMP)由质子泵(复合物Ⅰ, Ⅲ和Ⅳ)在氧化磷酸化过程中产生[87]. MMP的大小是精子活力的指标，与男性生育能力密切相关[88]. 研究表明，ROS的产生会导致精子线粒体内膜损伤, 直接损害mtDNA的合成并破坏MMP. 而功能失调的线粒体会产生更多的ROS, 形成恶性循环[89]. HFD小鼠和超重/肥胖患者的精子MMP明显低于正常对照组[90], 这种下降伴随着线粒体结构的损害，从而降低ATP的可用性和精子中的线粒体呼吸效率.

肥胖可以通过诱导炎症发生来降低精子的质量. 肥胖男性的精浆中炎症介质TNF-α和IL-6水平升高, 而血管内皮生长因子(vascular endothelial growth factor, VEGF)水平下降[65]. HFD小鼠模型表明，睾丸中TNF-α，MCP-1和F4/80的mRNA表达水平增加，而GLP-1受体(glucagon like peptide-1 receptor, GLP-1R)激动剂可通过减少促炎细胞因子的表达来改善精子质量[91]. 此外, 白色脂肪细胞产生的炎性细胞因子, 如TNF-α，IL-1和IL-6，可能通过多种机制直接影响精子发生，包括破坏支持细胞间隙连接通讯来改变血睾丸屏障[92]，减少精原细胞分化，抑制减数分裂DNA合成

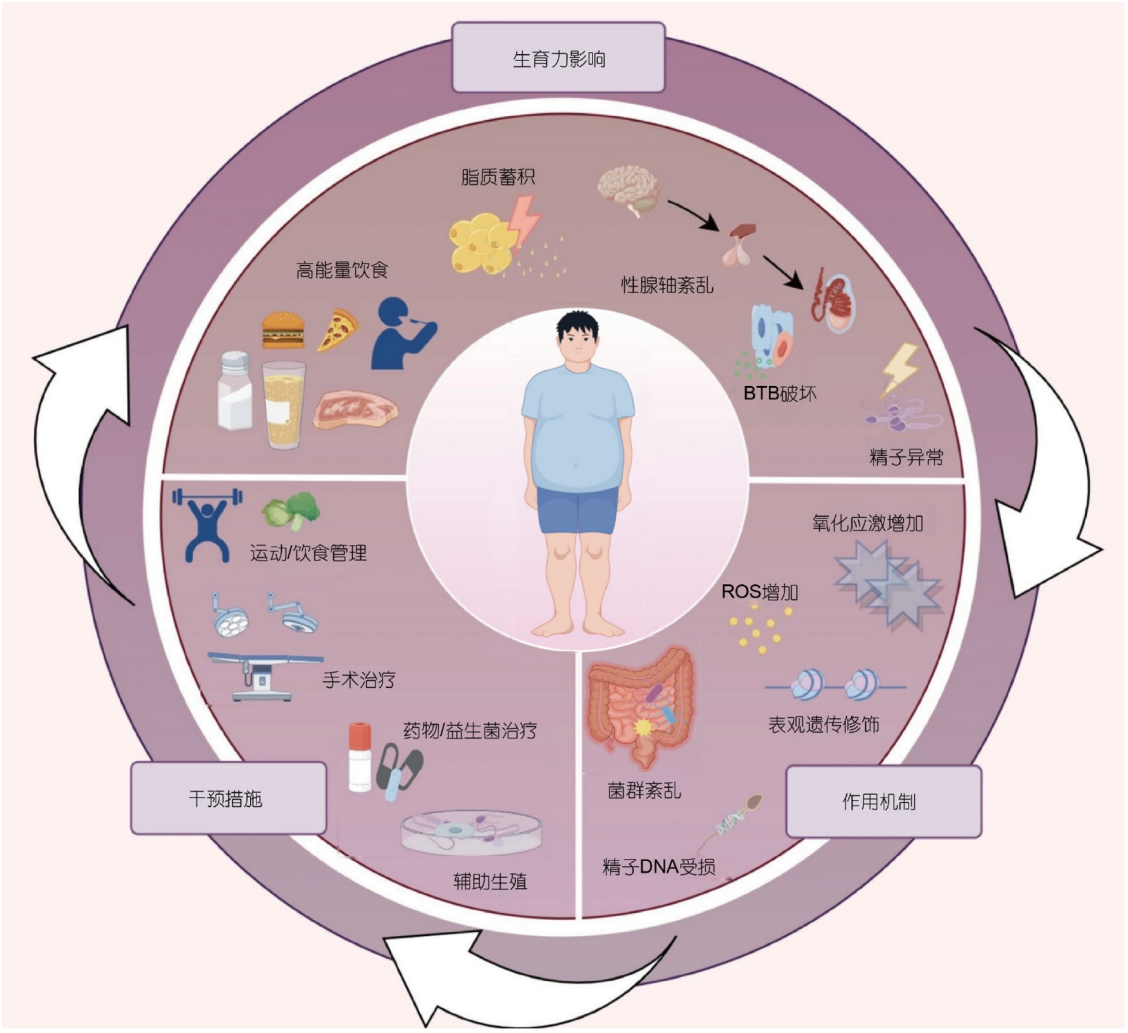

图 1 肥胖对男性不育的影响及其机制
Figure 1 Effects of obesity on male infertility and the underlying mechanisms

和降低精子活力[93].

肥胖还可能通过诱发异常自噬相关的mRNA表达来损害生精功能. 自噬在精子中起着重要作用, 对细胞存活和运动至关重要[94,95]. 正常情况下, 自噬可以裂解受损的细胞器并提供细胞存活所需的生物能量底物. 然而, 过度激活的自噬会引发细胞死亡并降低发育能力[96]. 研究评估肥胖患者精子中自噬相关基因(*AMPKα1*, *Beclin1*, *ULK1*, *BAX*和*BCL2*)mRNA表达的变化, 结果显示*Beclin1*, *ULK1*和*Bcl-2*的mRNA表达显着上调. 在HFD小鼠模型中发现, 在肥胖的情况下自噬被过度激活, 细胞被剥夺了能量底物, 从而触发AMP激活的蛋白激酶(AMP-activated protein kinase, AMPK)信号通路应对营养应激或其他形式的应激. 研究表明, 增加AMPK活性可以导致精子质膜脂质紊乱的增加, 从而影响位于精子鞭毛轴突或其他相关结构中的下游蛋白质底物的磷酸化, 从而降低精子活力[97].

2.2 肠道菌群及睾丸局部微环境

哺乳动物肠道微生物对多种生理功能起到调节作用, 包括能量获取[98]、肠道完整性的维持[99]、免疫调节[100,101]和病原体防御[102,103]等. 肠道微生物群的组成很大程度上受饮食的影响, 并且可以因饮食调整而发生显着变化. 不恰当的饮食习惯, 例如高脂肪和高糖摄入, 会导致肠道微生物群的数量和种类紊乱, 从而

引发菌群失衡. 高脂饮食可能通过改变肠道菌群的组成影响精液质量[104]. 此外, 高脂饮食还可增加肠道屏障的通透性, 并诱发体内慢性炎症的发生[105]. 肠道菌群与外周免疫系统之间的失衡会影响睾丸免疫豁免特性和固有免疫稳态[106]. 微生物相关分子模式(microbial-associated molecular patterns, MAMPs), 如脂多糖(lipopolysaccharide, LPS)、肽聚糖和脂蛋白, 经过肝门静脉或淋巴系统进入血液循环, 再经睾丸动脉到达睾丸, 从而引起损伤[107]. 睾丸作为生殖系统中重要器官, 由生精小管和间质组成, 生精小管包含生精细胞和支持细胞(sertoli cells, SCs), 它们通过交换营养物质和代谢废物来促进生殖细胞的分化和成熟[108], 血液-睾丸屏障由靠近生精小管基底层的SCs形成, 维持着一个独特的微环境[109,110], 让减数分裂后的细胞免受毒性伤害, 并与免疫系统隔离开来[111]. BTB的完整性破坏可能导致生殖功能障碍[112,113].

菌群参与精子生成, 并影响精子质量和活力[114]. 高脂饮食小鼠模型可导致肠道菌群失衡, 进而触发宿主免疫反应, 包括一系列慢性炎症[100,115]. 高脂饮食引起的游离脂肪酸直接影响肠道免疫系统, 增加促炎因子如TNF-α, IL-1β, IL-6和IFN-γ的产生, 同时降低抗炎因子如IL-10, IL-17, IL-22的相关表达[116]. 此外, 高脂饮食介导的氧化应激还可进一步导致肠道上皮细胞通透性增加, 促使LPS在体内扩散[117,118]. 这些病理变化包括低度炎症、抗菌肽表达减少、黏液分泌减少和紧密连接蛋白表达减少等, 对多种系统功能产生影响, 从而导致肥胖及其代谢并发症(如胰岛素抵抗、高血糖、全身炎症和血脂异常). 进而导致睾丸免疫微环境受损, 引发睾丸激素紊乱, 从而损害男性生殖能力[119~121]. Alfano等人[122]报告存在着睾丸微生物群, 放线菌属(*Actinomycetes*)、厚壁菌门(Firmicutes)和拟杆菌(*Bacteroides*)在正常睾丸组织中占主导地位, 而生殖细胞发育不良患者睾丸微生物群的多样性和丰富度降低. 此外, 另一项综合了小鼠粪菌移植研究揭示了高脂饮食对男性生殖的肠道菌群机制的损伤. 高脂饮食可引起正常小鼠肠道内菌群紊乱, 其中与之相关的菌属为拟杆菌(*Bacteroides*)和普雷沃菌(*Prevotella*), 同时正常小鼠生精小管中精母细胞和精子数量减少; 这些变化与精子质量和数量的下降有关, 这一发现也在临床样本中得到证实. 此外, 接受高脂饮食小鼠的菌群移植后, 受体小鼠的肠道通透性增加, 睾丸中的炎症因子增加, 提示高脂饮食通过改变肠道菌群而诱发潜在的睾丸炎症, 进而导致精子异常[56].

睾丸微环境具有特定的代谢特点, 其中脂质对精子发生起着关键作用. 脂质是SCs的能量来源, 并在发育过程中参与生殖细胞的膜重塑[44,123]. 生精细胞含有高水平的多不饱和脂肪酸(polyunsaturated fatty acids, PUFA), 维持细胞膜的流动性, 有助于受精过程的进行. 然而, 生精细胞无法合成PUFAs, 而是依赖于SCs的摄取. 持续的高脂饮食可抑制WT-1蛋白表达, 导致生殖功能障碍. WT-1是一种与精子发生相关的蛋白, 也是SCs的特异性标记物[124], 它在性腺发育和性别分化中发挥重要作用. HFD诱导的肥胖小鼠模型中, 脂质在睾丸间质中大量积聚, 进一步破坏了BTB的完整性[125]. 睾丸微环境中脂质积累, 能量过载引起线粒体应激, 破坏了睾丸中电子传递链(electron transfer chain, ETC)的正常功能[126]. 在应激条件下, 睾丸微环境中的线粒体容易引发氧化损伤. 由于精子细胞富含PUFAs, 但抗氧化酶相对缺乏, 膜中的PUFAs成为ROS的直接靶标, 引发脂质过氧化级联反应, 导致细胞膜流动性下降和通透性增加. 同时, 膜功能密切相关的离子泵的功能受到影响, 导致ATP的产生下降, 从而减弱或丧失精子运动能力. 此外, 脂质过氧化产物如丙二醛(malondialdehyde, MDA)还可以进一步抑制男性生育能力[73].

2.3　表观遗传修饰

表观遗传修饰是指在DNA序列不变的情况下, 其生物表型或基因表达发生了稳定的可遗传变化, 即亲代细胞在有丝分裂时, 有能力把自身一整套基因表达程序传递给子代细胞. 表观遗传修饰改变包括DNA甲基化修饰(DNA methylation)、组蛋白共价修饰(covalent histone modification)、染色质重塑(chromatin remodeling)和非编码RNA(noncoding RNA)调节等. 单链非编码RNA分为许多亚群, 如微小RNAs(MicroRNA, miRNA)、小分子RNA(PIWI-interacting RNA, piRNA)、长链非编码RNAs(long non-coding RNA, lncRNA). 过度肥胖对睾丸组织的DNA完整性和表观遗传调控产生负面影响[127]. 这包括DNA甲基化和组蛋白乙酰化的改变, 对后代的发育产生影响[128~130]. 组蛋白的修饰在生殖细胞发育过程中起着重要作用, 包括同源染色体的重组和配对. 在精子形成过程中, 精蛋

白取代组蛋白可以引起精子DNA进一步浓缩，而组蛋白乙酰化对染色体结构改变和DNA单链或双链断裂的修复具有重要意义. 过早高乙酰化的组蛋白H4可能引发组蛋白-精蛋白交换的提前发生，导致圆形精子成熟停滞，从而导致不育[131]. Barbagallo等人[132]研究发现，高脂饮食小鼠的精子组蛋白乙酰化与精子DNA损伤呈正相关. 饮食诱导的肥胖父代小鼠与正常体重的父代小鼠相比，其精子和子代胎盘中营养物质代谢相关基因*Peg3*，*Peg9*，*Peg10*和营养转运蛋白基因*Slc38a2*等中DNA甲基化异常致使基因表达失调的现象. 在高脂饮食诱导肥胖的雄性小鼠中SIRT6蛋白表达显著降低，从而导致精子中H3K9乙酰化量和DNA的损伤增加[133]. 表观遗传修饰是调控基因表达甲基化标记的重置过程，在胚胎发育过程中建立父系特异性的甲基化. 肥胖男性精子piRNA的表达水平发生改变[134]，在精原细胞减数分裂Ⅰ期piRNA含量丰富，而在精子成熟的前期出现一定程度的消失. *piRNA*基因突变会引起反转录转座子的过度表达,导致生殖细胞DNA损伤[135,136]. 肥胖男性精子DNA中的表观遗传修饰会增加后代患肥胖和代谢紊乱、神经系统障碍(包括注意力缺陷障碍)和各种癌症的风险[128]. 父亲肥胖所引发的修饰基因包括*MEG3*，*NDN*和*SNRPN*以及调节胎儿发育和肿瘤生长的*SGCE*/*PEG10*. 然而，部分临床证据表明，肥胖相关的表观遗传修饰是可逆的，通过减少肥胖可以挽救相关修饰的改变[137].

3 高能量饮食及肥胖相关男性生育力损伤的干预

随着越来越多的研究揭示肥胖对男性生育潜能的多种机制诱发，饮食和肥胖干预策略变得越来越重要. 虽然肥胖对男性生育能力、精子功能和后代健康存在长期负面影响，但通过简单的干预措施，如改变饮食和/或运动锻炼，可以改善这种状态并改善后代的结果. 通过对肥胖或高脂饮食诱导小鼠模型进行饮食和运动干预，相关异常代谢可得到改善，如葡萄糖、胰岛素和胆固醇浓度可恢复到正常水平，同时精子活力和形态也有所改善，包括氧化应激和DNA损伤下降[138,139]. 高脂饮食，尤其是饱和脂肪和反式脂肪的饮食，与肥胖、代谢综合征和胃肠道疾病密切相关. 研究表明，摄入富含有多不饱和脂肪(如Ω-3，Ω-6和Ω-9)的饮食可能是一个替代选择. 增加Ω-3脂肪酸的摄入，无论是作为补充剂还是从食物，似乎对精子形成有积极的影响. 研究发现，精子中Ω-6/Ω-3不饱和脂肪酸的比例与精液质量相关[140]. 此外，补充抗氧化剂和单碳代谢途径相关的营养素(如叶酸、维生素B12和锌)似乎也有益，但仍需要进一步了解饮食模式如何影响精液参数和男性生育能力，以进一步改善肥胖男性的代谢健康和生育能力[141~143]. 到目前为止，有关肥胖男性饮食和运动干预对精液参数影响的临床研究较少. 其中规模最大的一项临床研究针对43名肥胖男性进行为期14周的住院减肥计划. 结果显示，体重减轻最多的男性中，精子总数和精子形态都得到了显著改善[142]. 在一项随机、对照、双盲研究，对肥胖男性进行了为期8周低热量饮食管理，结果显示男性平均体重减轻了16.5 kg(95%CI: 15.2~17.8)，精子浓度增加了1.49倍(95%CI: 1.18~18.88，P<0.01)，精子数量增加了1.41倍. 虽然多数人精液量没有变化，但男性少精症的百分比从17%下降到13%，这表明与肥胖相关的少精症可以通过减肥来减少[144]. 然而，另一个临床病例报告显示，接受减肥手术以实现大幅减肥的三名肥胖患者在手术后出现精子质量下降，尽管具体原因未完全阐明，但可能与术后潜在的营养失衡有关[145].

干预肥胖人群中的非手术策略通常包括调节饮食结构和进行长期规律运动锻炼. 此外，肠道微生物的稳定和关键的时间累积性作用也被认为是干预肥胖的新策略. 虽然肠道微生物群的调节不能替代适当的饮食和锻炼，但其安全性相对较高[146]. 一项研究提出，在使用肠道菌群调节性膳食制剂(如益生元/益生菌/合生制剂)后，成年受试者的BMI、体重和脂肪量均显著下降，这强调了调节肠道菌群的膳食制剂作为干预肥胖的重要工具. 该研究也指出需要进一步确定制剂的理想剂量、补充时长和效果的持久性[147]. 在HFD诱导的小鼠模型中，鼠李糖乳杆菌PL60通过产生共轭亚油酸产生抗肥胖作用[148]. 另外，摄入富含硒的益生菌可以改善肥胖小鼠模型的代谢状态和精液质量[149]. 对于由肠道菌群失调引起的精液质量和生育力下降，肠道菌群移植被认为是一种潜在有效的治疗方法[121,150]. 益生元制剂是一种不可消化的低聚糖，作为结肠微生物群的“肥料”，促进有益的共生生物(如双歧杆菌和乳杆菌)的生长. 另一项研究评估了植物乳杆菌TW1-1在邻苯二甲酸二(2-乙基己)酯(phthalic acid

di-n-hexyl ester, DEHP)诱导的成年雄性小鼠睾丸损伤模型中的作用[151]. 口服TW1-1可以显著提高DEHP小鼠的血清睾酮浓度, 改善精液质量, 并减轻性腺的损伤. 因此, 通过补充适当的益生菌株和高活性的益生菌, 促进肠道上皮细胞生长和肠道黏膜的健康状态, 有助于提高机体免疫功能, 稳定精液质量和男性生育能力.

4　结论与展望

随着高能量饮食的普遍化和肥胖人口的增加, 对男性生育能力的负面影响已成为全球共同关注的问题. 高能量饮食和肥胖通过影响男性生殖轴、精液质量、肠道菌群和睾丸微环境等因素导致男性生殖障碍, 其中的作用机制和转化治疗策略也陆续提出. 除了常规基于运动和饮食的肥胖干预手段, 新兴的肠道菌群治疗策略备受关注. 然而, 人体肠道微生物群调节的交互机制非常复杂, 特别是考虑到饮食对慢性疾病的影响. 因此, 我们需进一步了解微生物群、代谢物和男性生殖之间的作用机制, 以更好地理解肠道微生物群对男性不育的影响. 尽管已知高能量饮食和肥胖对男性不育密切相关, 但目前还没有为备孕中的男性提供明确的饮食指导. 因此, 进一步明确能量饮食和肥胖与男性生殖系统之间病理生理学作用机制, 对于制定个性化的代谢干预措施以治疗男性肥胖相关的生殖功能障碍具有重要的价值.

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Research progress on the association of high-energy diet and obesity with male infertility

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The implications of high-energy diet and obesity on male infertility have garnered significant attention. Numerous studies have emphasized the pivotal roles of high-energy diet and obesity in male infertility, impacting the male reproductive axis, semen quality, gut microbiota, and testicular microenvironment. Paternal obesity affects the health of the offspring through epigenetic modifications in sperm. Nonetheless, improving dietary structure and implementing appropriate weight loss measures can partially alleviate the adverse effects of high-energy diet and obesity on male infertility. This review aims to summarize the current research progress on the relationship between high-energy diet, obesity, and male infertility; investigate the underlying mechanisms leading to male infertility, and explore potential intervention strategies to enhance male reproductive health.

high-fat diet, obesity, male infertility

doi: 10.1360/SSV-2023-0147