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关于男性不育、代谢综合征、肥胖的研究

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这篇综述文章致力于当前对代谢综合征和肥胖男性生殖功能可能产生负面影响的机制的理解。本文介绍了临床研究的结果，证明代谢紊乱的严重程度、交配活动、射精参数、怀孕的可能性以及后代的健康之间存在关系。

关键词：代谢综合征；肥胖；男性不育；男性生殖健康。

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Male infertility, metabolic syndrome and obesity

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The review article is devoted to the current understanding of the mechanisms that can have a negative impact on the reproductive function of men with metabolic syndrome and obesity. The article presents the results of clinical studies proving the existence of a relationship between the severity of metabolic disorders, copulatory activity, ejaculate parameters, the likelihood of pregnancy, as well as the health of the offspring.

Keywords: metabolic syndrome; obesity; male infertility; male reproductive health.

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Мужское бесплодие, метаболический синдром и ожирение

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Обзорная статья посвящена современным представлениям о механизмах, способных оказать негативное влияние на репродуктивную функцию мужчин с метаболическим синдромом и ожирением. Представлены результаты клинических исследований, доказывающих наличие взаимосвязи между выраженностью метаболических нарушений, копулятивной активностью, показателями эякулята, вероятностью наступления беременности, а также здоровьем потомства.

Ключевые слова: метаболический синдром; ожирение; мужское бесплодие; мужское репродуктивное здоровье.

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根据现代观念，约15%的已婚夫妇在不采取避孕措施的情况下，在一年的定期性行为中不能怀孕，被认为是不孕不育，而在大约一半的情况下，由于男性因素而不能怀孕[1]。保护男性生殖健康问题的紧迫性日益增加—从1973年到2011年，在欧洲国家、美国、澳大利亚和新西兰的男性中，射精中的精子数量减少了50-60%[2]。在俄罗斯，在过去的二十年中，患有的男性总数增加了两倍[3]。

专家指出，射精数量指标的下降和无法获得理想怀孕的夫妇数量的增加是在腹部肥胖和其他代谢综合征的总体发病率增加的背景下发生的。代谢综合征—血脂异常、动脉高血压和胰岛素抵抗。在二十一世纪，地球上每四个人中就有一个人是这种综合征的携带者[4,5]。营养过剩、缺乏运动、激素失衡（包括雄激素缺乏）以及遗传易感性被认为是影响男性代谢综合征发展的因素。主要的俄罗斯和外国科学家认为代谢综合征是动脉粥样硬化和2型糖尿病的前兆。科学家们还认为，它的存在是心血管发病率的一个危险因素，并导致所有重要器官的亚临床病变。研究人员找到了代谢综合征对男性生殖健康以及射精的数量和功能特征的负面影响的证据，但作者的结论被证明是矛盾的。目前的工作是专门对它们进行审查。

代谢综合征的组成部分是相互关联和相互依赖的，它们中的每一个都有助于病理代谢和血液动力学过程的进展，这对男性的怀孕能力受孕 负面影响。尽管代谢综合征与不孕之间关系的具体生化机制尚不完全清楚，但有临床证据表明，代谢综合征对参与配子生产的激素水平和代谢的调节具有致病作用[6,7]。已发表的著作证实，反映男性生殖健康的指标依赖于其代谢紊乱的总体情况。F.Lotti等人[8]发现，无论年龄大小，患有代谢综合征的男性中，进行性活动精子和正常精子的比例显著降低，血液中总睾酮水平也显著降低。而在临床表现较明显的代谢综合征患者中，这些参数与正常值的差异更明显。作者证明了代谢综合征的严重程度与前列腺炎症之间存在正相关关系，前列腺炎症是影响射精参数和一般生殖功能的因素之一[9]。这些数据符合代谢综合征病理生理机制的现代概念，其工作伴随着促炎细胞因子的产生[10]。

K.Leisegang等人[11]在病例对照研究中也得到了类似的结果。与健康男性相比，代谢综合征患者血液中游离睾酮水平较低，精子浓度、精子总数、精子活力值较低，而精子DNA碎片程度指标较高。E.Ventimiglia等人证实了研究人员关于性腺功能减退和代谢综合征频繁合并的发现，但是，未能确定原发不育男性中与代谢综合征存在相关的射精参数的差异[12]。K.Ehala-Aleksejev和M.Punab[13]也得出了关于没有这种差异的结论，指出在这个问题上存在相互矛盾的观点，并证明有必要在这一领域进行进一步研究。伴随的阻塞性睡眠呼吸暂停综合征也可促进代谢综合征患者因性腺功能减退而导致的病态精子症的发展，在该综合征中，由于促黄体生成素分泌节律紊乱，进而导致睾酮的产生中断[14]。

众所周知，随着男性代谢综合征成分数量的增加，勃起功能障碍的风险增加，这反过来也降低了受孕的可能性[15]。在包括俄罗斯在内的许多国家进行的大型人群研究已经证实，代谢综合征的组成部分与发生交配障碍的风险之间存在密切关系[16,17]。俄罗斯科学家的研究结果也显示，90%的育龄代谢综合征男性受访者因不同程度的勃起功能障碍和早泄对性生活不满。同时，67.8%代谢综合征患者的精子图与参考值存在偏差[18]。

许多研究人员认为，腹部肥胖在代谢综合征患者代谢紊乱的进展和增加2型糖尿病和心血管疾病的可能性方面起着主导作用。与皮下不同，脂肪组织在肠系膜和大网膜中聚集，神经支配良好，血供丰富，其允许脂质代谢产物直接进入肝脏门静脉，有助于抑制确保碳水化合物代谢的酶的活性，从而导致胰岛素抵抗的发展。此外，内脏脂肪组织合成大量参与调节代谢过程和重要功能的生物活性物质（瘦素、肿瘤坏死因子-α、胰岛素样生长因子、纤溶酶原激活物抑制剂I、血管紧张素原、血管紧张素II、白细胞介素、前列腺素、雌激素、脂联素，抵抗素等），这让我们认为它是一个独立的内分泌器官。在这方面，在肥胖男性中出现了多种扰乱生殖系统正常功能的病理机制，并对精子产生直接影响[19]。

肥胖是代谢综合征的重要组成部分，它通过激活多种病理生理机制对男性生殖功能产生负面影响，近年来许多研究者对此进行了研究。

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肥胖和性腺机能减退

肥胖会导致身体整个内分泌系统的失调。肥胖和男性性腺功能减退之间的关系，由于在脂肪组织中占优势的雌激素合成和瘦素的产生，已经被许多包括人口在内的研究结果所知道和证实[20]。雌激素能抑制下丘脑神经元的活动，抑制垂体分泌促性腺激素释放激素，进而抑制黄体生成素、卵泡刺激素和催乳素的分泌，从而影响睾丸的生发细胞（雄激素的靶器官）。雄激素的产生通常会抑制瘦素的产生，在雄激素缺乏的情况下，瘦素可以抑制精子发生[21]。

对被检查的肥胖患者的观察表明，随后的体重指数下降或增加，分别伴随着体内睾酮饱和的正常化，或雄激素缺乏程度的增加，这反过来，可导致精子发生受损和射精中精子数量减少。BMI增加的男性通常会出现其他内分泌系统紊乱，导致促卵泡激素/黄体生成素比值的变化，抑制素B和球蛋白结合性激素含量的变化，对生精上皮和支持细胞的工作产生负面影响[22]。肥胖时，细胞色素P450系统的活性也发生变化，导致细胞因子的过量产生，特别是肿瘤坏死因子和白细胞介素，导致莱迪希间介细胞的激素产生功能不足[23]。与此同时，男性往往有一个恶性循环：在睾丸激素下降的背景下，内脏脂肪的沉积更大。另一方面，在相反的方向上也可以追踪到类似的模式—在体重减轻的男性中，睾酮水平可以恢复正常，并恢复因雄激素缺乏而失去的功能[24]。

肥胖和2型糖尿病

肥胖是2型糖尿病的主要危险因素之一，因此在同一患者中经常可以诊断出这两种疾病，这就为对男子生殖健康产生不利影响以及使碳水化合物代谢正常化和实现正常体重带来困难创造了额外的先决条件。高血糖可减少促性腺激素的分泌[25]，并导致肝脏中与性类固醇结合的球蛋白的分泌减少，从而降低睾酮的生物利用度[26]。糖尿病患者血糖水平控制不足常伴有进行性活动精子比例下降，并伴有DNA碎片水平升高[27]。

因肥胖引起的身体结构变化而引起的男性生殖功能障碍

据了解，在超重和肥胖的男性中，在性腺机能减退的背景下，由于性欲减弱，以及皮下脂肪组织的过度积累，出现性交困难，导致性交活动减少[28]。一些男性患上了所谓的隐性阴茎综合征，在这种综合征中，尽管勃起时阴茎的大小是正常的，但很大一部分阴茎仍然存在于阴部悬垂的脂肪组织的厚度中，这阻碍了性交[29]。由于对一个人的身体形象的负面感知而产生的心理因素可以显著加重性交障碍[30]。肥胖男性大腿和小腹脂肪组织过多，可使阴囊温度维持在33-35°C以内，导致体温过高，进而损害精子生成[31]。A.Garolla等人[32]对肥胖男性阴囊温度成像的结果尤其证明了这一点。在一些严重肥胖的男性中，可以观察到阴囊脂肪瘤病，其中脂肪组织可导致精索动脉和静脉受压，随后发展为缺血和睾丸功能受损[33]。

肥胖对精子发生和精子功能的影响

在世界许多国家进行的流行病学研究揭示了超重对男性精子数量和生殖功能的负面影响。对丹麦47835对已婚夫妇的调查资料进行分析后发现，体重指数超过30 kg/m^{2}的男性一年内怀孕的概率降低1.53倍，伴肥胖的男性一年内怀孕的概率降低2.75倍[34]。挪威专家在调查26303对夫妇时获得了类似的数据：超重和肥胖男性未能如愿怀孕的风险分别是预期的1.2倍和1.36倍[35]。美国研究人员的计算显示，体重指数超过25 kg/m^{2}的男性，体重指数每增加3 kg/m^2，婚姻不孕的风险就增加1.21倍[36]。在俄罗斯，E.A.Epanchintseva等人[37]写道，在那些申请不孕不育生殖医学中心的人中，超重和肥胖的男性普遍存在。

研究肥胖对精子形成影响的作者得出的结论是矛盾的，这可能部分是因为实验室数据主要来自于那些因不孕而寻求医疗帮助的男性。T.K.Jensen等人[38]发现，与BMI在20-25 kg/m^{2}范围内的男性相比，超重男性的精子浓度和精子总数分别减少了21和24%。这项研究的作者，基于对1558名男

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性精子图谱的研究，也注意到身体质量指数对进行性活动和正常精子的数量没有影响[38]。同时，M.I.Eisenberg等人[39]无法证实身体质量指数、腰围与除射精量以外的精子造影参数之间的关系。2010年发表的5项研究的荟萃分析也没有证实这种关系[40]。这些发现随后被N.Sermondade等人[41]纳入了另一项分析，在该研究中，一项针对13077名男性的调查结果的31份出版物的研究揭示了身体质量指数与检测少精子症和无精子症风险之间的j型关系。对于超重、1级和2级肥胖的男性，该风险分别为1.11、1.28和2.04。J.Campbell等人[42]在分析31项研究中对115158对使用辅助生殖技术治疗不孕症的已婚夫妇进行了最全面的研究。结果表明，男性的肥胖显著降低了使用辅助生殖技术方案后生育孩子的可能性（OR=0.65，95% CI 0.44–0.97），在10%的情况下，妻子的怀孕率下降。

这些发现让研究人员开始研究精子细胞的功能特征，以及辅助生殖技术项目的实验室结果，这些结果让他们发现了一些之前未知的模式。因此，研究发现，在体外受精协议中，当使用超重男性的精子时，卵子受精的频率高于男性。男性BMI不超过25 kg/m^2，而在实验室条件下，BMI对胚胎发育指标以及生化和临床妊娠的发生均无显著影响。与此同时，当肥胖男性使用单纯子卵胞浆显微注射时，生孩子的几率显著降低[43]。这也是由V.Moragianni等人[44]撰写的，他们分析了4609例患者使用辅助生殖技术治疗的结果。体重指数在30–34.9、35–39.9和40 kg/m^{2}及以上的男性生育孩子的优势比持续下降，分别从0.63（0.47–0.85）降至0.39（0.25–0.61）和0.32（0.16–0.64）[44]。

肥胖男性使用辅助生殖技术失败的原因之一可能是胚胎发育的终止。这与精子DNA过度断裂有关，但目前还没有足够的数据来证实这一假设。在14项荟萃分析中，只有3项研究的作者能够证明，身体质量指数高于30 kg/m^{2}的男性精子DNA碎片水平更高[45]。

肥胖导致的精子功能受损也可能是氧化应激的结果：在30–80%的不育男性中，射精中活性氧的含量增加，可导致男性配子的膜[46]和DNA分子损伤[47,48]。R.V.Rozhivanov和D.G.Kurbatov还写道，患有青春期后消化道内脏肥胖的年轻男性射精时抗氧化活性下降[49]。尽管事实并非总是能够将精液中活性氧水平的增加与妊娠频率进行临床比较[50]，有证据表明，使用抗氧化剂后[51]，辅助生殖技术成功的可能性增加，包括超重男性的参与。肥胖患者血液中胆固醇含量高还会在精子颈部沉积，导致精子形状改变、活动能力下降和与卵子相互作用的能力丧失[52]。

肥胖的表观遗传效应

近年来，对家庭、双胞胎和寄养儿童在多种族人群中的研究提供了体重指数遗传的证据[53]。在大多数情况下，专家面对的是它的变异性，它与已确认的单核苷酸多态性无关，而是由于基因与环境相互作用引起的个体变异性，即所谓的表观遗传因素。有几种表观遗传机制提供了多种基因表达谱在同一生物体的细胞；特别是包括DNA甲基化[54]，这种甲基化在精子中观察到，并取决于代谢紊乱的程度[55]。研究表明，参与甲基化反应的精子DNA片段提供了精子发生、受精和随后的胚胎发育[56,57]；也有证据表明，肥胖对代谢、后代发病率和死亡率的表观遗传影响，伴随代谢紊乱的疾病[58–60]。

结论

因此，目前有充分的证据表明，代谢综合症和肥胖对男性生育能力产生负面影响，其表现形式为射精参数紊乱、受孕几率降低，并导致后代代谢紊乱和疾病发展。提供这种影响的许多致病机制已经被很好地理解了，就其他一些方面而言，还需要进一步的研究，但很明显，这一领域的知识可以帮助不同专业的从业者提高计划怀孕的已婚夫妇的医疗保健质量，以及在未来的父母中进行适当的解释工作。

附加信息

利益冲突作者声明，没有明显的和潜在的利益冲突相关的发表这篇文章。

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