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COPD与肥胖的相互关系研究进展

王　欣[1]，程恒杰[1]，李风森[1,2*]

[1]新疆医科大学第四临床医学院，新疆　乌鲁木齐
[2]新疆维吾尔自治区中医医院，新疆　乌鲁木齐

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摘　要

慢性阻塞性肺疾病(COPD)是一种严重危害人类健康的常见多发疾病，常与多种疾病合并发生。近年来获越来越多的证据表明慢性阻塞性疾病患者常常合并高脂血症、肥胖等脂质代谢紊乱，虽然肥胖悖论的提出预示了新的诊疗方向，但其机制仍然未知。积极寻找可靠的指标，能早期发现、干预病情，评估疾病严重程度、病情进展，指导临床治疗。

关键词

慢性阻塞性肺疾病，COPD，脂肪，综述

Research Progress on the Relationship between COPD and Obesity

Xin Wang[1], Hengjie Cheng[1], Fengsen Li[1,2*]

[1]The Fourth Clinical College, Xinjiang Medical University, Urumqi Xinjiang
[2]Xinjiang Uygur Autonomous Region Hospital of Traditional Chinese Medicine, Urumqi Xinjiang

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Abstract

Chronic obstructive pulmonary disease (COPD) is a common multiple disease that seriously endangers human health and often occurs in combination with a variety of diseases. In recent years, more and more evidence has shown that patients with chronic obstructive disease are often complicated with lipid metabolism disorders such as hyperlipidemia and obesity. Although the obesity paradox indicates a new direction of diagnosis and treatment, its mechanism is still unknown. Ac-

*通讯作者。

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tively looking for reliable indicators can detect and intervene the disease early, assess the severity and progression of the disease, and guide clinical treatment.

Keywords

Chronic Obstructive Pulmonary Disease, COPD, Fat, Review

1. 引言

慢性阻塞性肺疾病(Chronic Obstructive Pulmonary Disease, COPD)是一种严重危害人类健康的常见多发疾病，是一种以不可逆的进行性气流阻塞、慢性气道炎症和全身效应发病率或合并症为特征的肺功能障碍。肥胖是全球性的问题，男性肥胖率约为 10.8%，女性约为 14.9% [1]，我国肥胖人口总数居世界首位，社会负担持续增加。研究者发现低 BMI 水平可能会加速肺功能的下降，而高 BMI 对 COPD 预后具有明显保护作用[2]，即为肥胖悖论[3]。本综述结合慢阻肺及肥胖的一些相关研究，期望能找到新的防治 COPD 的思路，指导临床早期发现、干预，为治疗提供新的方向。现将 COPD 与肥胖的相互关系研究进展如下展开。

2. 脂肪

肥胖大多是脂肪的异常堆积所致，过量的脂肪会导致体内器官活动空间缩减，特别是胸壁和腹部脂肪，在进行呼吸运动时，使横膈膜维度受限，胸腔的顺应性下降[4]，甚至导致呼吸肌活动能力下降[3] [5]。

人体脂肪组织分布从部位上大致分为内脏脂肪(Visceral Adipose Tissue, VAT)与皮下脂肪(Subcutaneous Adipose Tissue, SAT)，有研究显示人体总脂肪量、腹部脂肪含量均与 FEV、FVC 呈负相关，腰围与 FVC 下降(P = 0.008)和 FEV1/FVC 比值增加(P = 0.031)显著相关[6] [7]；且脂肪面积与 BMI 呈正相关，并随着 BMI 增加，气道壁上沉积的脂肪组织也会随之增加[8]。最近的一项研究指出，腹部肥胖的受试者，肺功能损害的主要决定因素是内脏脂肪的存在[9]，CHOE 等的研究也表明腹部内脏脂肪含量与 FEV1、FVC 的变化呈负相关性(P < 0.05) [3]。肥胖人士脂肪细胞会变大，弹性储存脂质的能力会降低，从而使其他组织中流入过多的脂质。此外，肥胖时脂肪组织血流量减少，影响脂质处理，并进一步导致非脂肪组织中过多的脂肪储存[10]。

随着 COPD 病程的发展，合并症越多，加之患者因气道阻塞的加重，需要更强的呼吸负荷和肺弹性阻力来保护肌肉免受破坏及消耗，而在急性期会产生更多的乳酸及 CO_2，会造成骨骼肌质量减少，活动耐力及运动能力的下降进而导致呼吸困难加重，最终导致内脏脂肪过多积聚，Ogawa [11]等人也报道了以肺气肿为主要表现的 COPD 患者，其 BMI 和皮下脂肪均较低的患者会出现低肌肉指数和内脏脂肪过多的现象；根据一项研究报告说，与从 ECLIPSE 队列中确定的吸烟和不吸烟对照受试者相比，严重气流受限的 COPD 患者胸部的计算机断层扫描图像(平均 FEV1，40.7%预测)增加了内脏脂肪组织和更多的肌肉脂肪积累(通过肌肉组织衰减测量) [12]。

3. 化学机制

人体内异常的脂肪沉积亦会产生炎症，包括瘦素、脂联素、肿瘤坏死因子 TNF-α 等，均直接参与机

体炎症反应过程[3] [13] [14]。炎症是慢性阻塞性肺病的重要病理生理特征，与气道结构损伤和气道感染有关。而较低的肺功能会加剧炎症反应[15] [16] [17]。在一项 ECLIPS 研究中，出现持续全身性炎症患者的平均 BMI 为 29.4，而无炎症组为 25.6，C 反应蛋白(C Reactive Protein CRP)是相较于正常体重患者的 3.3 倍[18]，且与腹部脂肪量呈正相关[19]。有研究发现，脂肪还会沉积在呼吸道中，仅限于气道外壁，并且多见于大气道中，脂肪过多沉积在气道壁上，占据了呼吸空间，影响了肺部的空气交换功能[8]。

从功能上大致分为白色脂肪(White Adipose Tissue, WAT)和棕色脂肪(Brown Adipose Tissue, BAT)两种，棕色脂肪组织中有大量线粒体，正是这些线粒体起到了产热的作用，白色脂肪的主要功能是将体内多余的能量以脂肪的形式储存起来，在食物匮乏期间可以被调动，并提供隔热和机械保护[20]。白色脂肪还具有绝热(维持正常体温)、合成瘦素(抑制食欲、促进脂肪燃烧的一种激素)等激素的功能[21]。研究表明，对瘦素缺陷小鼠移植 WAT，能使高血糖水平、体重和生育能力正常化，分泌与保护性代谢和抗炎表型相关的循环因子(如脂联素) [22] [23]。

瘦素是一种主要的促炎症脂肪因子，影响免疫反应，可进一步增加巨噬细胞的吞噬作用，和单核细胞的增殖作用[24]，其水平随肥胖而增加，并与脂肪成正比[25]。在稳定期 COPD [26]患者中，痰中瘦素与其他痰中炎症标志物(如 c 反应蛋白和 TNF-α)呈正相关。此外，COPD 患者支气管黏膜下层瘦素的表达与 CD8 T 淋巴细胞表达(凋亡减少)和疾病严重程度 GOLD 分期呈正相关，与肺活量测定参数[27]呈负相关。

脂联素是一种独特的脂肪因子，在多种器官和细胞中具有抗凋亡、抗炎、抗氧化等多种作用，研究表明脂联素与健康成人肺功能呈正相关[28]。Miller 等报道气道上皮细胞显著表达 APN 和 APNR1 受体，肺上皮细胞上的 APNR1 受体在 APN 刺激后释放 IL-8。稳定期 COPD 患者存在系统性炎症，表现为血清急性期蛋白水平升高，即 c 反应蛋白(CRP)、纤维蛋白原、白细胞介素(IL-6 和 IL-8)和肿瘤坏死因子 α (TNF-α)水平升高，以及循环白细胞数量增加。炎症标志物与 COPD 加重风险增高相关[29]，脂联素也已显示通过气道上皮细胞表达[30]。

Weisberg 等发现肥胖模型动物的脂肪组织普遍存在巨噬细胞浸润现象[31]，脂肪组织堆积产生会产生慢性炎症反应。而慢性阻塞性肺病患者的气道、肺实质、支气管肺泡灌洗液中表现出广泛分布的巨噬细胞[32]。脂质代谢具有调节巨噬细胞功能的关键作用。脂质代谢可以在生理刺激的作用下动态改变，从而促进巨噬细胞的活化，进而调节巨噬细胞的活化。同时，脂质是巨噬细胞的能量来源，也是生物活性脂质和细胞膜成分的前体[33]，而脂肪组织内的巨噬细胞会有助于促进炎性细胞因子产生，还会导致局部炎症反应的增加[12]。所以脂质代谢异常可引起巨噬细胞功能紊乱，降低了慢性阻塞性肺病的患者体内吞噬细菌及损伤气道的修复和重塑功能，加剧慢性阻塞性肺病患者症状。

4. 讨论与展望

肥胖悖论的提出，使人们聚焦于慢阻肺与脂肪间的关系，但其机制尚未明确，目前也尚无相关诊疗方案，在 BMI 等易获得的测量指标的基础上，从多个层面评价或判断 COPD 对人体的影响，同时发现体成分的变化又如何影响着 COPD，进一步明确 COPD 对人体的危害。

参考文献

[1] NCD Risk Factor Collaboration (NCD-RisC) (2017) Worldwide Trends in Blood Pressure from 1975 to 2015: A Pooled Analysis of 1479 Population-Based Measurement Studies with 19.1 Million Participants. *The Lancet*, **389**, 37-55.

[2] Yang, L., Drake, B.F. and Colditz, G.A. (2016) Obesity and Other Cancers. *Journal of Clinical Oncology*, **34**, 4231-4237. https://doi.org/10.1200/JCO.2016.68.4837

[3] Choe, E.K., Kang, H.Y., Lee, Y., *et al*. (2018) Longitudinal Associations between Abdominal Obesity and Lung Function Using a Linear Mixed Model. *PLOS ONE*, **13**, e0193516.

[4] Elbehairy, A.F., Faisal, A., Mcisaac, H., *et al*. (2021) Mechanisms of Orthopnoea in Patients with Advanced COPD. *European Respiratory Journal*, **57**, Article ID: 2000754. https://doi.org/10.1183/13993003.00754-2020

[5] Donnell, D.E., *et al*. (2013) When Obesity and COPD Collide: Physiological and Clinical Consequences. *Annals of the American Thoracic Society*, **11**, 635-644.

[6] Turi, B.C., Codogno, J.S., Fernandes, R.A., *et al*. (2016) Low Levels of Physical Activity and Metabolic Syndrome: Cross-Sectional Study in the Brazilian Public Health Care System. *Ciência & Saúde Coletiva*, **21**, 1043-1050. https://doi.org/10.1590/1413-81232015214.23042015

[7] Borst, V.D., *et al*. (2016) The Prevalence of Metabolic Syndrome in Chronic Obstructive Pulmonary Disease: A Systematic Review. *COPD*: *Journal of Chronic Obstructive Pulmonary Disease*, **13**, 399-406.

[8] Elliot, J.G., Donovan, G.M., Wang, K.C., *et al*. (2019) Fatty Airways: Implications for Obstructive Disease. *European Respiratory Journal*, **54**, Article ID: 1900857. https://doi.org/10.1183/13993003.00857-2019

[9] Schweitzer, L., Geisler, C., Johannsen, M., *et al*. (2017) Associations between Body Composition, Physical Capabilities and Pulmonary Function in Healthy Older Adults. *European Journal of Clinical Nutrition*, **71**, 389-394.

[10] Goossens, G.H. (2008) The Role of Adipose Tissue Dysfunction in the Pathogenesis of Obesity-Related Insulin Resistance. *Physiology & Behavior*, **94**, 206-218. https://doi.org/10.1016/j.physbeh.2007.10.010

[11] Ogawa, E. (2009) Body Mass Index in Male Patients with COPD: Correlation with Low Attenuation Areas on CT. *Thorax*, **64**, 20-25. https://doi.org/10.1136/thx.2008.097543

[12] Martin, M., Almeras, N., Després, J., *et al*. (2017) Ectopic Fat Accumulation in Patients with COPD: An ECLIPSE Substudy. *International Journal of Chronic Obstructive Pulmonary Disease*, **12**, 451-460. https://doi.org/10.2147/COPD.S124750

[13] Moualla, M., Qualls, C., Arynchyn, A., *et al*. (2017) Rapid Decline in Lung Function Is Temporally Associated with Greater Metabolically Active Adiposity in a Longitudinal Study of Healthy Adults. *Thorax*, **72**, 1113-1120. https://doi.org/10.1136/thoraxjnl-2016-209125

[14] Oliveira, P.D., Wehrmeister, F.C., Horta, B.L., *et al*. (2017) Visceral and Subcutaneous Abdominal Adiposity and Pulmonary Function in 30-Year-Old Adults: A Cross-Sectional Analysis Nested in a Birth Cohort. *BMC Pulmonary Medicine*, **17**, 157. https://doi.org/10.1186/s12890-017-0510-7

[15] Singanayagam, A., Schembri, S. and Chalmers, J.D. (2013) Predictors of Mortality in Hospitalized Adults with Acute Exacerbation of Chronic Obstructive Pulmonary Disease. *Annals of the American Thoracic Society*, **10**, 81-89. https://doi.org/10.1513/AnnalsATS.201208-043OC

[16] Flynn, R., Macdonald, T.M., Chalmers, J.D., *et al*. (2018) The Effect of Changes to GOLD Severity Stage on Long Term Morbidity and Mortality in COPD. *Respiratory Research*, **19**, Article No. 249. https://doi.org/10.1186/s12931-018-0960-3

[17] Soler-Cataluña, J.J., *et al*. (2005) Severe Acute Exacerbations and Mortality in Patients with Chronic Obstructive Pulmonary Disease. *Thorax*, **60**, 925-931.

[18] Kiyokawa, H., Hoshino, Y., Sakaguchi, K., *et al*. (2021) Redox Regulation in Aging Lungs and Therapeutic Implications of Antioxidants in COPD. *Antioxidants* (*Basel*), **10**, 1429. https://doi.org/10.3390/antiox10091429

[19] Van Den Borst, B., Gosker, H.R., Wesseling, G., *et al*. (2011) Low-Grade Adipose Tissue Inflammation in Patients with Mild-to-Moderate Chronic Obstructive Pulmonary Disease. *The American Journal of Clinical Nutrition*, **94**, 1504-1512. https://doi.org/10.3945/ajcn.111.023911

[20] Schoettl, T., *et al*. (2018) Heterogeneity of Adipose Tissue in Development and Metabolic Function. *The Journal of Experimental Biology*, **221**, jeb162958. https://doi.org/10.1242/jeb.162958

[21] Buch, A., Carmeli, E., Boker, L.K., *et al*. (2016) Muscle Function and Fat Content in Relation to Sarcopenia, Obesity and Frailty of Old Age—An Overview. *Experimental Gerontology*, **76**, 25-32. https://doi.org/10.1016/j.exger.2016.01.008

[22] Heindel, J.J., Blumberg, B., Cave, M., *et al*. (2016) Metabolism Disrupting Chemicals and Metabolic Disorders. *Reproductive Toxicology*, **68**, 3-33. https://doi.org/10.1016/j.reprotox.2016.10.001

[23] Ali Assad, N. and Sood, A. (2012) Leptin, Adiponectin and Pulmonary Diseases. *Biochimie*, **94**, 2180-2189. https://doi.org/10.1016/j.biochi.2012.03.006

[24] Hornung, F., Rogal, J., Loskill, P., *et al*. (2021) The Inflammatory Profile of Obesity and the Role on Pulmonary Bacterial and Viral Infections. *International Journal of Molecular Sciences*, **22**, 3456. https://doi.org/10.3390/ijms22073456

[25] Creutzberg, E.C., Wouters, E.F., Vanderhoven-Augustin, I.M., *et al*. (2000) Disturbances in Leptin Metabolism Are Related to Energy Imbalance during Acute Exacerbations of Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine*, **162**, 1239-1245. https://doi.org/10.1164/ajrccm.162.4.9912016

[26] Bantulà, M., Roca-Ferrer, J., Arismendi, E., *et al*. (2021) Asthma and Obesity: Two Diseases on the Rise and Bridged by Inflammation. *Journal of Clinical Medicine*, **10**, 169. https://doi.org/10.3390/jcm10020169

[27] Bruno, A., Chanez, P., Chiappara, G., *et al*. (2005) Does Leptin Play a Cytokine-Like Role within the Airways of COPD Patients? *European Respiratory Journal*, **26**, 398-405. https://doi.org/10.1183/09031936.05.00092404

[28] Bianco, A., Mazzarella, G., Turchiarelli, V., *et al*. (2013) Adiponectin: An Attractive Marker for Metabolic Disorders in Chronic Obstructive Pulmonary Disease (COPD). *Nutrients*, **5**, 4115-4125. https://doi.org/10.3390/nu5104115

[29] Dicker, A.J., Huang, J.T.J., Lonergan, M., *et al*. (2021) The Sputum Microbiome, Airway Inflammation, and Mortality in Chronic Obstructive Pulmonary Disease. *Journal of Allergy and Clinical Immunology*, **147**, 158-167. https://doi.org/10.1016/j.jaci.2020.02.040

[30] Miller, M., Cho, J.Y., Pham, A., *et al*. (2009) Adiponectin and Functional Adiponectin Receptor 1 Are Expressed by Airway Epithelial Cells in Chronic Obstructive Pulmonary Disease. *The Journal of Immunology*, **182**, 684-691. https://doi.org/10.4049/jimmunol.182.1.684

[31] Soler-Cataluna, J.J., Martinez-Garcia, M.A., Sanchez, P.R., *et al*. (2006) Severe Acute Exacerbations and Mortality in Patients with Chronic Obstructive Pulmonary Disease: Thorax 2005; 60: 925-31. *Respiratory Medicine*: *COPD Update*, **1**, 104. https://doi.org/10.1016/j.rmedu.2006.01.020

[32] Barnes, P.J. (2016) Inflammatory Mechanisms in Patients with Chronic Obstructive Pulmonary Disease. *Journal of Allergy and Clinical Immunology*, **138**, 16-27. https://doi.org/10.1016/j.jaci.2016.05.011

[33] Yan, J. and Horng, T. (2020) Lipid Metabolism in Regulation of Macrophage Functions. *Trends in Cell Biology*, **30**, 979-989. https://doi.org/10.1016/j.tcb.2020.09.006