•党为人民谋健康的100年•
•专题与讲座•

慢性肾脏病肌肉萎缩机制的研究进展

赵立希[1] 于 艳[1] 马迎春[2]

【摘要】肌肉萎缩是慢性肾脏病(chronic kidney disease,CKD)中后期常见的并发症,主要表现为肌肉质量减轻、肌肉力量降低、肌肉功能减退等。肌肉蛋白降解的增加是肌肉萎缩的主要原因,CKD患者体内有毒代谢产物的累积、血浆pH值的降低等病理状态能够激发肌肉的蛋白质降解途径从而导致肌肉萎缩。本文将从尿毒症毒素、代谢性酸中毒、炎症、激素和肠道菌群5个方面对CKD肌肉萎缩机制的研究进展进行综述。

【关键词】慢性肾脏病;肌肉萎缩;信号通路
中图分类号:R692.5 文献标识码:A doi:10.3969/j.issn.1671-4091.2021.10.002

Advance in mechanism of muscular dystrophy in chronic kidney diseases *ZHAO Li-xi[1], YU Yan[1], MA Ying-chun[2] [1]Institute of Rehabilitation Medicine, China Rehabilitation Science Institute, Beijing Key Laboratory of Neural Injury and Rehabilitation, Center of Neural Injury and Repair, Beijing Institute for Brain Disorders, Beijing 100068, China; [2]Department of Nephrology, Beijing BoAi Hospital, China Rehabilitation Research Center, School of Rehabilitation Medicine, Capital Medical University Beijing 100068, China.*

Corresponding author: YU Yan, Email: yuyancrrc@163.com

【**Abstract**】Muscle atrophy is a common complication in the middle and late stage of chronic kidney disease (CKD), which mainly manifested as decreased muscle mass, decreased muscle strength, and decreased muscle function. The main cause of muscle atrophy is the enhancement of muscle protein degradation. The muscle protein degradation pathway can be stimulated by CKD pathological conditions such as the accumulation of toxic metabolites and the decrease of plasma pH value, then lead to muscle atrophy. This paper reviewed the research progress of muscle atrophy in CKD from the following five aspects: uremia toxin, metabolic acidosis, inflammation, hormones and intestinal flora.

【**Key words**】Chronic kidney diseases; Muscular dystrophy; Signal pathway

慢性肾脏病(chronic kidney diseases,CKD)是指肾脏结构或功能异常超过3个月的疾病,根据肾小球滤过率水平可将其分为5期。其中4～5期患者常并发肌肉萎缩,主要表现为肌肉质量减轻、肌肉力量降低、肌肉功能减退等。

约30%～50%的CKD患者伴有蛋白质分解代谢增加,肌肉蛋白降解的增加是肌肉萎缩的主要原因。CKD肌肉损失是一个复杂的的病理生理过程,本文将对CKD肌肉萎缩的病理机制进行综述。

1 尿毒症毒素

硫酸吲哚酚是一种小分子蛋白质结合型尿毒素,可以在肌肉中沉积,使糖酵解途径和磷酸戊糖途径增强而三羧酸循环途径减弱,导致肌肉线粒体紊乱和ATP减少,引起肌肉萎缩[1]。此外,硫酸吲哚酚还能抑制成肌细胞的增殖和肌管形成能力,诱导氧化应激和炎症因子的分泌,并刺激肌肉生长抑制素(myostatin)和肌萎缩素1(atrogin-1)的表达[2]。硫酸吲哚酚还可通过降低过氧化物酶体增殖物激活受体γ共激活因子1α(peroxisome proliferator-activated receptorγcoactivator-1,PGC-1α)表达、诱导自噬以及降低线粒体膜电位,引起肌肉细胞的线粒体紊乱,从而与肌肉萎缩有关[3]。

基金项目:中央级公益性科研院所基本科研业务费专项资金(2019cz-10)
作者单位:100068 北京,[1]中国康复科学所康复医学所,神经损伤与康复北京市重点实验室,北京脑重大疾病研究院神经损伤与修复研究所
100068 北京,[2]首都医科大学康复医学院,中国康复研究中心北京博爱医院肾内科
通讯作者:于艳 100068 北京,[1]中国康复科学所康复医学所,神经损伤与康复北京市重点实验室,北京脑重大疾病研究院神经损伤与修复研究所 Email:yuyancrrc@163.com

同型半胱氨酸在健康人体中含量很低，随着血同型半胱氨酸水平的增高，肌肉力量随之降低[4]。高同型半胱氨酸可以通过活化内质网应激反应，降低腓肠肌和股四头肌的重量[5]。高同型半胱氨酸还可能通过氧化应激和p38丝裂原活化蛋白激酶(p38 mitogen-activated proteinkinase,p38MAPK)信号通路，导致肌肉卫星细胞增殖能力下降[6]。

2 代谢性酸中毒

CKD患者不可避免会出现代谢性酸中毒现象。代谢性酸中毒同时还会加重CKD患者的肾脏和其他系统的损伤，加速肌肉退化。慢性酸中毒会增加血尿素氮水平和糖皮质激素水平，并增强肌肉蛋白质的降解能力。糖皮质激素能诱导MuRF1、atrogin-1中SCF复合物的肌肉泛素连接酶(muscle ubiquitin ligase of the SCF complex in atrophy-1,MUSA1)高表达，以及增强Notch信号通路，与肌肉萎缩有关[7]。在酸性环境下，L6-G8C5肌肉细胞的L-谷氨酸转运体(SNAT2)活性受到抑制，导致总蛋白水解的增加[8]。通过口服高剂量碳酸氢盐补充剂提高血碳酸氢根离子水平，CKD3～4期患者生物电阻抗检测的肌肉质量与低剂量组比有所提高[9]。

3 炎症

CKD患者常常呈现慢性炎症状态，Romanova Y等检测出CKD患者血清中白细胞介素-6(interleukin-6，IL-6)、肿瘤坏死因子-α(tumor necrosis factor-α，TNF-α)等25种细胞因子和趋化因子，以及大部分补体因子显著增高[10]。在CKD患者的骨骼肌中Toll样受体4(Toll-like receptor4,TLR4)和TNF-α表达上升，用尿毒症患者血清处理后C2C12骨骼肌细胞同样出现TLR4和TNF-α表达的上升[11]。

IL-6和TNF-α均可增强信号传导与转录激活因子3(signal transducer and activator of transcription 3,STAT3)的磷酸化水平。磷酸化的STAT3不仅可以通过激活半胱氨酸天冬氨酸蛋白酶3(caspase3)、myostatin以及泛素-蛋白酶途径介导肌肉蛋白质的流失，还可以与核因子κB(nuclear factor kappa-B,NF-κB)结合上调诱导型一氧化氮合酶(inducible nitric oxide synthase,iNOS)的表达从而引起肌肉萎缩[12]。而TLR4的上调可以激活p38 MAPK-C/EBPβ信号途径，从而参与泛素-蛋白酶体途径和自噬途径的蛋白质降解[11]。

4 激素

CKD患者血浆血管紧张素Ⅱ(angiotensinⅡ，AngⅡ)水平显著高于正常对照。AngⅡ水平的增高，将会激活PKD1/HDAC5/TFEB/MuRF1途径，引起肌肉萎缩。AngⅡ还可通过TNF-α活化胆固醇-25-羟化酶，引发泛素-蛋白酶体降解途径，从而引发肌肉萎缩[13]。另外，PPAR-γ/MtD/NLRP3 炎症小体轴也参与AngⅡ诱导的肌肉萎缩[14]。

肾脏的损伤还会导致下丘脑-垂体-性腺内分泌功能紊乱。在临床研究中发现睾酮水平的降低与CKD男性患者肌肉力量的降低以及肌肉萎缩有关[15]。睾酮对肌肉的影响表现在能够增加肌肉纤维横截面积和肌肉卫星细胞的数量[16]，以及抑制氧化应激导致的骨骼肌细胞凋亡等[17]。

在CKD患者中还存在生长激素半衰期增长，分泌不足的现象。给予CKD患者生长激素治疗可以减轻蛋白质营养不良的症状和炎症反应，同时提高胰岛素样生长因子(insulin-like growth factor，IGF-1)的表达[18]。生长激素与生长激素受体结合后，可以调节IGF-1的表达，在5/6肾切除大鼠中可以通过调节IGF-1/PI3K/Akt信号通路来缓解肌肉萎缩[19]。临床研究表明，在老年人中，低IGF-1水平与低握力、低身体活动能力相关[20]。

5 肠道菌群

通过研究CKD患者肠道菌群的改变，发现肠道菌群在不同病程的CKD患者中也有不同，如霍尔德曼氏菌属、巨单胞菌属、普雷沃菌属主要在健康人中检出，Dielma属主要在非透析患者中检出，韦格斯卡多维亚菌属主要在透析患者中检出[21]。CKD患者中肠道菌群的变化，还与炎症有一定的相关性，如霍尔德曼氏菌属与IL-6正相关[22]。而且许多尿毒素的产生也与肠道菌群有关[23]。目前，研究发现肠道菌群也与肌肉萎缩有关，其机制涉及myostatin/activin、IGF1/PI3K/AKT/mTOR、NF-κB和FOXO信号通路[24]。Lahiri S等研究表明，无肠道菌群的小鼠骨骼肌明显萎缩，并伴随IGF-1表达的下降[25]。

6 小结

近年来，CKD在我国的患病率呈上升趋势，CKD病理状态能够激发肌肉的蛋白质降解途径从而导致肌肉萎缩，包括患者体内尿毒素的聚集、血浆pH值的降低、炎症的激发、激素水平的改变以及肠道菌群的变化等。低频电刺激[26]、运动[27]等干预手段可以通过调控炎症因子、激素等因素从而起到改善肌肉萎缩的作用。对CKD肌肉萎缩机制的深入研究将有利于提高CKD患者的生活质量和对治疗的耐受性，降低死亡风险。

作者贡献：赵立希：查阅文献、撰写论文；于艳：查阅文献、指导论文撰写及投稿；马迎春：指导论文

撰写及投稿。

利益冲突声明：本文作者无相关利益冲突。

参 考 文 献

[1] Sato E, Mori T, Mishima E, et al. Metabolic alterations by indoxyl sulfate in skeletal muscle induce uremic sarcopenia in chronic kidney disease[J]. Sci Rep, 2016, 6:36618.

[2] Enoki Y, Watanabe H, Arake R, et al. Indoxyl sulfate potentiates skeletal muscle atrophy by inducing the oxidative stress-mediated expression of myostatin and atrogin-1 [J]. Sci Rep, 2016, 6:32084.

[3] Enoki Y, Watanabe H, Arake R, et al. Potential therapeutic interventions for chronic kidney disease-associated sarcopenia via indoxyl sulfate-induced mitochondrial dysfunction [J]. J Cachexia Sarcopenia Muscle, 2017, 8(5): 735-747.

[4] Vidoni ML, Pettee Gabriel K, Luo ST, et al. Relationship between homocysteine and muscle strength decline: the baltimore longitudinal study of aging [J]. J Gerontol A Biol Sci Med Sci, 2018, 73(4): 546-551.

[5] Majumder A, Singh M, Behera J, et al. Hydrogen sulfide alleviates hyperhomocysteinemia-mediated skeletal muscle atrophy via mitigation of oxidative and endoplasmic reticulum stress injury[J]. Am J Physiol Cell Physiol, 2018, 315(5): C609-C622.

[6] Veeranki S, Lominadze D, Tyagi SC. Hyperhomocysteinemia inhibits satellite cell regenerative capacity through p38 alpha/beta MAPK signaling [J]. Am J Physiol Heart Circ Physiol, 2015, 309(2): H325-334.

[7] Sato AY, Richardson D, Cregor M, et al. Glucocorticoids induce bone and muscle atrophy by tissue-specific mechanisms upstream of E3 ubiquitin ligases [J]. Endocrinology, 2017, 158(3): 664-677.

[8] Blbas S, Watson E, Butler H, et al. Dexamethasone acutely suppresses the anabolic SNAT2/SLC38A2 amino acid transporter protein in L6-G8C5 rat skeletal muscle cells [J]. FASEB Bioadv, 2021, 3(1): 36-48.

[9] Kittiskulnam P, Srijaruneruang S, Chulakadabba A, et al. Impact of Serum Bicarbonate Levels on Muscle Mass and Kidney Function in Pre-Dialysis Chronic Kidney Disease Patients [J]. Am J Nephrol, 2020, 51(1): 24-34.

[10] Romanova Y, Laikov A, Markelova M, et al. Proteomic analysis of human serum from patients with chronic kidney disease [J]. Biomolecules, 2020, 10(2): 257.

[11] Verzola D, Bonanni A, Sofia A, et al. Toll-like receptor 4 signaling mediates inflammation in skeletal muscle of patients with chronic kidney disease [J]. J Cachexia Sarcopenia Muscle, 2017, 8(1): 131-144.

[12] Ma JF, Sanchez BJ, Hall DT, et al. STAT3 promotes IFN-gamma/TNFalpha-induced muscle wasting in an NF-kappaB-dependent and IL-6-independent manner [J]. EMBO Mol Med, 2017, 9(5): 622-637.

[13] Shen C, Zhou J, Wang X, et al. Angiotensin-II-induced muscle wasting is mediated by 25-hydroxycholesterol via GSK3beta signaling pathway[J]. EBioMedicine, 2017, 16:238-250.

[14] Liu Y, Bi X, Zhang Y, et al. Mitochondrial dysfunction/NLRP3 inflammasome axis contributes to angiotensin II-induced skeletal muscle wasting via PPAR-gamma[J]. Lab Invest, 2020, 100(5): 712-726.

[15] Chiang JM, Kaysen GA, Segal M, et al. Low testosterone is associated with frailty, muscle wasting and physical dysfunction among men receiving hemodialysis: a longitudinal analysis[J]. Nephrol Dial Transplant, 2019, 34(5): 802-810.

[16] Dalbo VJ, Roberts MD, Mobley CB, et al. Testosterone and trenbolone enanthate increase mature myostatin protein expression despite increasing skeletal muscle hypertrophy and satellite cell number in rodent muscle [J]. Andrologia, 2017, 49(3):1-11.

[17] Pronsato L, Milanesi L, Vasconsuelo A, et al. Testosterone modulates Fox03a and p53-related genes to protect C2C12 skeletal muscle cells against apoptosis[J]. Steroids, 2017, 124:35-45.

[18] Dai G, Wang D, Dong H. Effects of recombinant human growth hormone on protein malnutrition and IGF-1 and IL-2 gene expression levels in chronic nephrotic syndrome[J]. Exp Ther Med, 2018, 15(5): 4167-4172.

[19] Xia H, Zhang B, Yang D, et al. Yi-Qi-Jian-Pi-Xiao-Yu-Xie-Zhuo formula improves muscle atrophy via modulating the IGF-1/PI3K/Akt signaling pathway in 5/6 nephrectomized rats[J]. Front Pharmacol, 2021, 12: 624303.

[20] van Nieuwpoort IC, Vlot MC, Schaap LA, et al. The relationship between serum IGF-1, handgrip strength, physical performance and falls in elderly men and women [J]. Eur J Endocrinol, 2018, 179(2): 73-84.

[21] Lun H, Yang W, Zhao S, et al. Altered gut microbiota and microbial biomarkers associated with chronic kidney disease[J]. Microbiologyopen, 2019, 8(4): e00678.

[22] Li F, Wang M, Wang J, et al. Alterations to the Gut Microbiota and Their Correlation With Inflammatory Factors in Chronic Kidney Disease[J]. Front Cell Infect Microbiol, 2019, 9:206.

[23] Kikuchi M, Ueno M, Itoh Y, et al. Uremic toxin-producing gut microbiota in rats with chronic kidney disease [J]. Nephron, 2017, 135(1): 51-60.

[24] de Sire R, Rizzatti G, Ingravalle F, et al. Skeletal muscle-gut axis: emerging mechanisms of sarcopenia for intestinal and extra intestinal diseases[J]. Minerva Gastroenterol Dietol, 2018, 64(4): 351-362.

[25] Lahiri S, Kim H, Garcia-Perez I, et al. The gut microbiota influences skeletal muscle mass and function in mice[J]. Sci Transl Med, 2019, 11(502):eaan5662.

[26] Hu L, Klein JD, Hassounah F, et al. Low-frequency electrical stimulation attenuates muscle atrophy in CKD--a potential treatment strategy[J]. J Am Soc Nephrol, 2015, 26(3): 626-635.

[27] Saud A, Luiz RS, Leite APO, et al. Resistance exercise training ameliorates chronic kidney disease outcomes in a 5/6 nephrectomy model[J]. Life Sci, 2021, 275: 119362.

(收稿日期：2021-05-06)

(本文编辑：苏华)