# 热量限制防治肾脏纤维化的作用机制

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**摘要：**肾脏纤维化是慢性肾脏病(chronic kidney disease，CKD)进展过程中共同的病理改变，其特征是间质间隙的细胞外基质(extracellular matrix，ECM)过度沉积，这是CKD最突出的标志。既往研究证实，肾纤维化与线粒体、炎症、脂质代谢及自噬有紧密联系。热量限制能通过改善线粒体功能、抑制炎症因子分泌、减少脂质生成、增加脂质分解和增强自噬来减缓肾脏纤维化进程。鉴于肾脏纤维化的潜在患病率和不良预后，目前在临床上对肾脏纤维化的治疗手段相当有限，了解肾脏纤维化的机制和延缓肾脏纤维化的进展具有重要的临床意义。本文就热量限制在肾脏纤维化中的作用原理及研究现状进行综述，以期为临床治疗提供理论指导。

**关键词：**热量限制；肾脏纤维化；线粒体；自噬

# The mechanism of caloric restriction in the prevention and treatment of renal fibrosis

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**Abstract:** Renal fibrosis is a common pathological change in the progression of chronic kidney disease (CKD), which is characterized by excessive deposition of extracellular matrix (ECM) in the interstitial space, which is the most prominent sign of CKD. Previous studies have confirmed that renal fibrosis is closely related to mitochondria, inflammation, lipid metabolism and autophagy. Caloric restriction can slow down the process of renal fibrosis by improving mitochondrial function, inhibiting the secretion of inflammatory factors, reducing lipid production, increasing lipid decomposition and enhancing autophagy. In view of the potential prevalence and poor prognosis of renal fibrosis, the current clinical treatment of renal fibrosis is quite limited, understanding the mechanism of renal fibrosis and delaying the progression of renal fibrosis is of great clinical significance. This work reviewed the principle and research status of caloric restriction in renal fibrosis, in order to provide guidance for clinical treatment.

**Key Words:** calorie restriction; renal fibrosis; mitochondria; autophagy

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慢性肾脏病(chronic kidney disease，CKD)是全球增长最快的导致死亡原因之一，预计到2040年将位于死亡原因的前五位[1]。美国疾控中心预测，47%的30岁以上的人在一生中会患CKD[2]。11%的3期CKD患者最终会发展为终末期肾病(end-stage renal disease，ESRD)，需要透析或肾移植才能存活[3,4]。肾纤维化以细胞外基质(extracellular matrix，ECM)的过度沉积导致组织瘢痕为特征，是CKD-ERSD的共同路径且难以逆转，与患者的长期预后密切相关。目前，肾纤维化的具体分子机制研究虽然在一定程度上得到突破，但在临床上尚无有效药物来防治肾纤维化。肾纤维化的防治给患者、家庭、社会带来沉重的负担。因此，积极寻找减轻肾纤维化或延缓肾纤维化进展的措施具有重要的科学价值和临床意义。

热量限制是在保证机体不发生营养不良的情况下，限制机体摄入的总热量。热量限制能通过调节细胞的代谢适应来调节衰老的内在过程，并降低许多心血管疾病发生的风险，是目前唯一已知的具有减缓衰老潜力的营养干预措施，并且对延缓肾脏纤维化也有一定的积极作用[5]。近年来，学者们围绕热量限制在防治肾脏纤维化中的作用及机制方面进行了深入研究，并取得了许多重要进展。

## 1 热量限制与线粒体

线粒体是与能量产生、活性氧产生和细胞凋亡及钙稳态密切相关的细胞器[6]。在各种真核生物中，线粒体动力蛋白1(dynamin-related protein 1，Drp1)和线粒体分裂蛋白1(mitochondrial fission protein 1， FIS1)是参与线粒体分裂的主要蛋白质[7]。当机体受损时，FIS1与Drp1相互作用，使线粒体分裂、活性氧产生增加、氧化应激增强以及线粒体膜电势下降[8]。细胞内约90%的活性氧由损伤的线粒体产生，增加的活性氧也可以进一步诱导线粒体分裂[9]。生理情况下，活性氧作为一种重要的信号分子调节细胞稳态、分裂、分化等生理活动；过量则会使脂质、蛋白质和DNA等生物分子氧化诱导纤维化。同时，活性氧能刺激多种促纤维化生长因子如转化生长因子-β1(transforming growth factor-β1，TGF-β1)、血管内皮生长因子(vascular endothelial growth factor，VEGF)和结缔组织生长因子(connective tissue growth factor，CTGF)的表达，诱导细胞外基质蛋白的沉积，导致肾功能损伤，引起肾纤维化[10,11]。当摄入热量过量时，氧化磷酸化和抗氧化防御反应被下调，线粒体电子传递链功能障碍，诱使线粒体DNA发生突变，导致细胞不同程度的程序性死亡。然而热量限制干预能通过改善电子传递链功能、降低活性氧产生、诱导氧化磷酸化和抗氧化防御反应来减少线粒体损伤[12]。由此可见，线粒体损伤引起的活性氧增加是肾纤维化进展的一个重要环节，改善线粒体功能和增加线粒体再生是减轻和延缓肾纤维化进展的有效干预措施。线粒体活性、生物发生、周转和动力学与细胞中的主要代谢传感器，如哺乳动物雷帕霉素靶蛋白(mammalian target of rapamyein，mTOR)、AMP激活蛋白激酶(AMP activates protein kinase，AMPK)和去乙酰化酶有关[13]。Dugan等[14]发现，在几种糖尿病肾病小鼠模型中，AMPK的激活显著减少了肾小球TGF-β1、纤连蛋白和胶原蛋白的沉积。此外，有研究已经证实，mTOR在高脂糖尿病模型中被激活，抑制mTOR能减缓糖尿病肾纤维化的进展[15]。解耦联蛋白(uncoupling proteins，UCPs)是线粒体阴离子载体蛋白家族成员，与线粒体膜上阴离子的转运有关。在能量较低时，AMPK和去乙酰化酶被激活[16]。激活的AMPK增强线粒体UCP2的表达，UCP2通过解偶联线粒体来降低线粒体活性氧的产生。据报道，激活的AMPK可以通过诱导内源性的抗氧化剂硫氧还蛋白抑制活性氧[17,18]。AMPK作为mTOR的拮抗因子，当AMPK被热量限制激活时mTOR触发的信号通路被AMPK抑制[16]。Sirtuins是一种烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide，NAD)依赖性组蛋白，被认为是抗衰老分子，热量限制能诱导其表达[19]。同时有研究发现，热量限制诱导激活SIRT1/AMPK调节网络进而激活核因子E2相关因子，通过增加抗氧化酶(如超氧化物歧化酶2、过氧化氢酶、谷胱甘肽过氧化物酶和过氧化物还原蛋白)的表达来增强对氧化应激的抵抗，降低活性氧生产酶(如可诱导一氧化氮合酶)的表达，并增加线粒体生物发生[20]。叉头盒O转录因子(forkhead box O transcription factor，

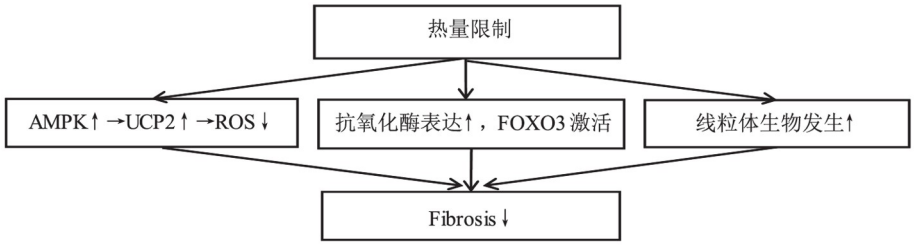


**图1 热量限制与线粒体信号通路**

FOXO)被确定为胰岛素/胰岛素样生长因子1信号通路的下游调节因子，控制许多调节关键生物过程基因的表达，如代谢稳态、氧化还原平衡、应激反应、细胞活力及增殖[21]。FOXO3是FOXO家族成员之一，当AMPK活化时能直接被激活，从而抑制线粒体相关的铁死亡[22]。因此，热量限制能通过AMPK、Sirtuins、mTOR等不同的路径来抑制活性氧的产生、增强肾脏对氧化应激的抵抗，进而改善线粒体功能，延缓肾脏纤维化(图1)。

## 2 热量限制与炎症

炎症是对多种外源性病原体相关分子模式和内源性危险相关分子模式的免疫反应，包括先天性免疫和适应性免疫[23]。中性粒细胞、单核细胞和巨噬细胞在先天性免疫系统抵御外界病原体入侵中发挥了重要作用[24]。这些细胞通过使用模式识别受体，如Toll样受体(Toll-like receptors，TLRs)和核苷酸结合的寡聚结构域样受体(NOD-like receptors，NLRs)来感知识别外源性病原体相关分子模式和内源性危险相关分子模式。炎症小体是一组胞质多聚体蛋白复合物[25]。NLRP3是炎症小体之一，其由三个结构域组成：一个氨基末端的PYRIN结构域、一个包含ATP酶活性的核苷酸结合的NACHT结构域和一个羧基末端的富亮氨酸重复序列结构域[26]。NLRP3激活会促使多蛋白信号传导复合物形成，导致半胱氨酸蛋白酶-1的自身蛋白水解激活，从而引起促炎细胞因子白介素-1β(interleukin-1β，IL-1β)、IL-18的成熟和分泌，及焦亡底物GSDMD(gasdermin D)的裂解，加重炎症损伤[27]。炎症是肾纤维化的一个重要诱因，有研究证实，热量限制期间产生的β-羟基丁酸酯酮代谢物，能通过抑制各种NLRP3相关疾病小鼠模型的半胱天冬酶1(cysteinyl aspartate specific proteinase 1，Caspase-1)的活化、减少单核细胞中NLRP3炎症小体介导的IL-1β和IL-18的产生来发挥抗炎作用[28]。同时，Gong等[29]用*Nlrp3*敲除小鼠和野生型C57BL/6J小鼠建立5/6肾切除术模型，发现野生型小鼠肾脏细胞外基质明显沉积，纤维胶原Ⅰ、Ⅲ的表达与NLRP3的表达成正相关；苏木精-伊红染色结果显示，*Nlrp3*敲除鼠细胞外基质沉积明显减少，表明抑制NLRP3的激活和表达能显著减轻肾间质纤维化。核因子κB(nuclear factor kappa-B，NF-κB)一种转录因子，其介导的信号通路在调节炎症、免疫应答和细胞凋亡中起关键作用。有研究证实，热量限制能通过糖皮质激素来抑制关键的炎症转录调节因子(如激活蛋白-1和NF-κB)发挥抗炎作用[30]。据报道，过量的能量摄入和肥胖会导致全身炎症，而没有营养不良的中度热量限制则具有强大的抗炎作用，热量限制已经成为一种治疗炎症性疾病的新方法[31]。同时，热量限制对潜在慢性炎症的表观遗传重编程可导致免疫代谢适应，提高生活质量，延长寿命，并延迟慢性疾病的发病[32]。由此可见，热量限制能通过抑制炎症因子的分泌来减轻炎症损伤，对延缓肾脏纤维化具有重要意义(图2)。

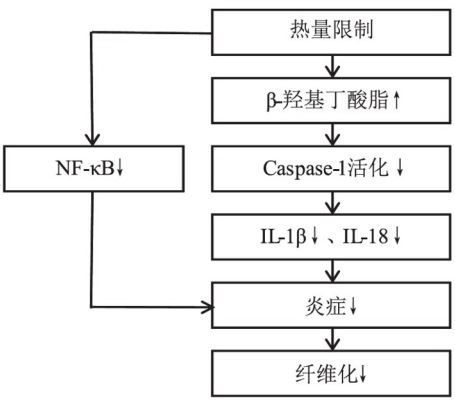


**图2 热量限制与炎症信号通路**

## 3 热量限制与脂质代谢

脂质具有生理活性和多种功能，不仅能作为能量供应的营养成分，而且在维持细胞稳态、膜组织、信号转导、蛋白质功能等生化反应中发挥着重要作用[33]。近年来有学者发现，脂质代谢异常与肾小管间质纤维化有明确相关性，与健康人和正常小鼠相比，在有肾纤维化的人体和小鼠模型中发现脂肪酸的分解代谢速率下降，肾小管细胞内沉积的脂质增多[34]。有研究证据表明，肾细胞中的脂质代谢异常也是引起急性肾损伤向慢性肾脏病转化的明确病因[35]。核受体超家族成员中由配体激活的核转录因子过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptors，PPARs)，包括过氧化物酶体增殖物激活受体α(PPAR-α)、PPAR-β/δ和PPAR-γ 3种亚型，目前已知这类受体与脂质代谢有紧密联系[36]。Chung等[37]研究年龄相关性肾纤维化与脂质代谢关系时发现，24个月大的老龄鼠与6个月、12个月、18个月大的老龄鼠相比，脂质积聚明显增加、间质纤维化明显加重；与此同时，还证实了在24月龄的衰老小鼠中，PPARα及其靶蛋白肉碱棕榈酰转移酶1α(carnitine palmi-toyltransferase 1α， CPT1α)和酰基辅酶A氧化酶1(acyl-coenzyme A oxidase 1，ACOX1)的表达水平显著降低、miR-21的表达显著增强，miR-21通过抑制肾小管上皮细胞中PPARα的翻译和脂肪酸氧化(fatty acid oxidation，FAO)来加重肾纤维化。然而，长期热量限制能通过降低miR-21的表达来减轻肾脏老化和与衰老相关的肾纤维化[38]。同时有研究发现，热量限制延缓了哺乳动物(包括灵长类动物)与年龄相关的DNA甲基化，影响脂质代谢相关基因，最终导致更多的脂质分解为脂肪酸链，从而减少脂质的积累[39,40]。肾小管上皮细胞主要使用脂肪酸作为原料，脂肪酸的线粒体β-氧化反应是ATP生成的主要能量来源[41]。TGF-β1是TGF-β超家族的成员之一，可诱导以FAO下调和脂质积累为特征的代谢重编程，从而引起肾纤维化[42]。另有研究发现，热量限制能降低TGF-β1改善氧化状态，增强肾小管细胞对损伤的抵抗，延缓肾纤维化的进展[43]。当摄入过量热量时，未使用的脂肪酸主要以甘油三酯的形式储存。随着甘油三酯含量的增加，细胞内会形成过多的脂滴，导致细胞脂质毒性，诱导肾纤维化的发展[44]。32周高脂饮食的大鼠肾脏以慢性炎症、高活性氧活性氧水平和肾小球纤维化为特征，表明脂质过载是影响肾纤维化的重要因素[45]。在脂质代谢方面，有研究发现，热量限制能增强AMPK的活性，抑制新生脂肪酸合成，刺激β氧化，降低脂毒性[46]。因此，热量限制能通过降低miR-21的表达、减少脂质的生成、增强脂质的分解代谢来减缓肾纤维化(图3)。

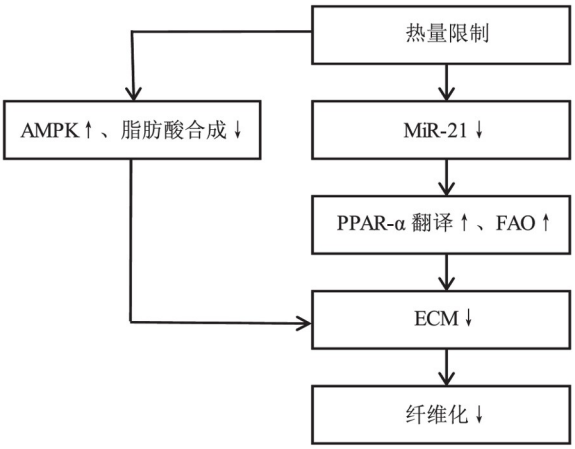


**图3 热量限制与脂质代谢信号通路**

## 4 热量限制与自噬

自噬是各种细胞在应激条件下诱导的高度保守的分解代谢过程，适度的自噬可防止细胞损伤并在能量或营养缺乏的情况下促进细胞存活，并对各种细胞毒性损伤产生抵抗[47]。在临床研究中，自噬激活和抑制与急性肾损伤、CKD、糖尿病肾病和多囊肾病有关，自噬功能异常可诱发足细胞丢失、近端肾小管细胞损伤和肾小球硬化，急性肾损伤后，适度的自噬被激活可保护肾小管细胞免于凋亡并促进细胞再生[48]。AMPK作为细胞能量传感器，在调节自噬过程中起重要作用，Unc-51样自噬激活激酶1(Unc-51-like autophagy activating kinase 1，ULK1)复合物是一种丝氨酸/苏氨酸激酶蛋白质，营养和能量应激是自噬过程中较强的调节因子，当热量限制激活AMPK时，AMPK通过激活ULK1特异性Ser555残基诱导自噬[16,49-51]。自噬抑制剂使肾小管上皮细胞对TGF-β诱导的$G_1$细胞周期

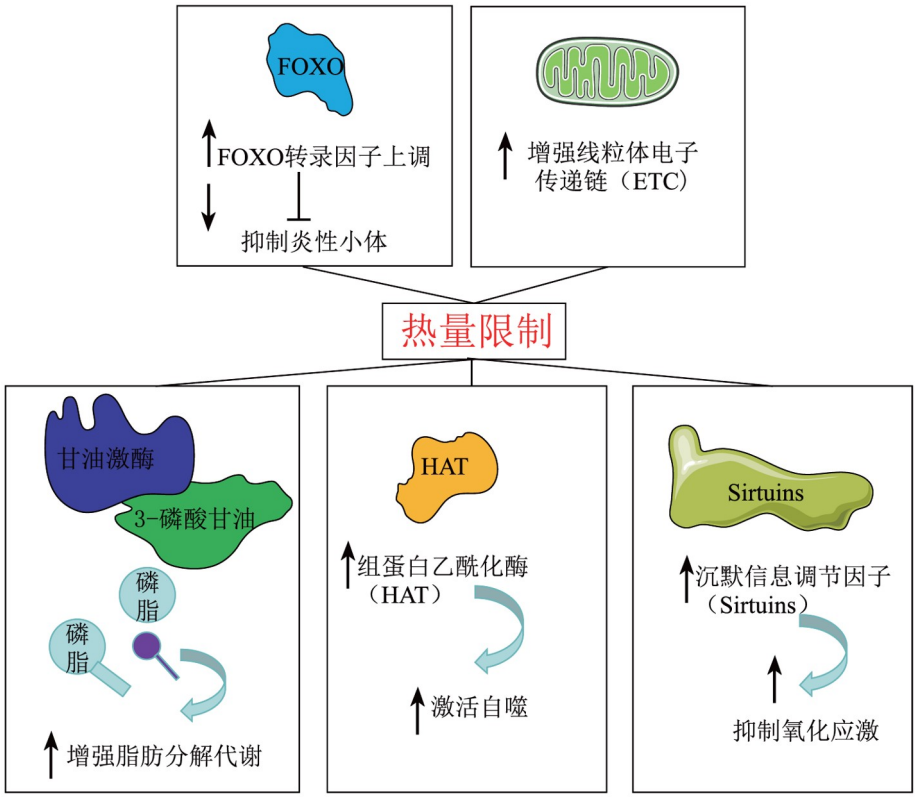


**图4 热量限制的信号通路总结**

停滞进而减少细胞增殖，有助于诱导肾小管间质纤维化[52]。ATG5、LC3是与自噬相关的关键基因，当近端肾小管上皮细胞特异性缺失*Atg5*时，LC3-Ⅱ蛋白水平降低、SQSTM1/p62降解；与野生型小鼠相比，近端肾小管上皮细胞*Atg5*敲除小鼠的细胞周期$G_2$/M期出现明显停滞，单侧输尿管梗阻模型中Ⅰ型胶原蛋白(type Ⅰ collagen，Col1)明显沉积，表明自噬缺陷加重了肾间质纤维化[53]。由此可见，适度的激活自噬能减缓肾纤维化。热量限制也被认为是改善健康、减缓衰老和延长寿命的最佳干预措施，而且没有与之替代干预相关的不良反应[54]。热量限制能减缓衰老、延长寿命，机制之一是适度的增强自噬活性[55]。热量限制能通过ATP-柠檬酸裂解酶(ATP citrate lyase，ACLY)降低葡萄糖来源的代谢通量，以降低细胞质乙酰辅酶A水平，从而降低p300组蛋白乙酰转移酶(histone acetyltransferase，HAT)的活性，激活自噬[56]。在糖尿病肾病小鼠模型中，适度的自噬能抑制肾小管上皮细胞向间充质细胞转化、减少氧化型谷胱甘肽(oxidized glutathione，GSSG)的积累、减少肾间质巨噬细胞浸润，从而延缓肾纤维化的进展[57,58]。因此，鉴于糖尿病肾病的高发病率，热量限制激活自噬可能成为延缓糖尿病肾病纤维化的一种新型干预措施，具有现实意义。也有学者证实，热量限制激活自噬可以去除NLRP3炎症小体激活物，如细胞内损伤相关的分子模式、NLRP3炎症小体成分和细胞因子，减少炎症小体激活和抑制炎症反应。同时，炎症小体信号通路也可以调节自噬过程，以平衡宿主所需的防御炎症反应、防止过度和有害的炎症反应，这对于减缓肾纤维化具有重要意义[59]。除此之外，当热量限制激活自噬时，自噬还能通过清除体内受损的线粒体和其他细胞器，减少活性氧的产生来延缓肾纤维化[60]。由此可见，热量限制激活自噬对延缓肾纤维化的进展具有重要意义(图4)。

## 5 临床应用价值与前景展望

大量证据表明，热量限制可以预防许多与年龄有关的疾病。保持适量的饮食可以帮助维持身体的健康状态，包括控制体重、预防慢性疾病和提

高整体健康水平。适量饮食还有助于将血糖水平和胆固醇水平维持在健康范围内，并有助于提高消化系统功能。过度饮食或不合理饮食可能会导致肥胖、糖尿病、心血管疾病等健康问题。此外，热量限制改善健康与药物改善健康相比，不会产生药物干预带来的不良反应，同时也能减轻病人的部分经济负担，这对于一些病情特殊的患者来说具有独特的优势。目前，热量限制对人体的保护作用已被公认，然而，热量限制也存在一定的局限性，通常是由于热量限制的遵从性个体差异大引起，因为热量限制执行起来较为困难，尤其是当热量限制时间较长时。随着对热量限制与疾病关系的研究深入，相信在未来热量限制有益健康的更多的机制会被发现。同时也应该鼓励研究能够作为热量限制模拟物的功能性食品或药物，以促进健康长寿、减轻肾纤维化，鼓励部分患者摄入能够维持正常代谢所需要的热量，使热量限制能更好地应用于临床，给患者带来新的福音。

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