

心肾代谢综合征：从定义到综合管理的新视角

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摘 要

心肾代谢综合征(CKM)是于2023年正式提出的一种全新概念,旨在整合肥胖、糖尿病、慢性肾脏病(CKD)与心血管疾病(CVD)之间复杂的病理生理相互作用。CKM的提出标志着从单病种、分专科的诊疗模式向多系统、跨学科的综合管理模式的转变。本文系统回顾了CKM的定义、分期、全球流行病学特征、诊断方法及管理策略。流行病学数据显示,CKM在全球范围内,尤其是在中老年人群中高度流行,且存在显著的地区、性别和种族差异。诊断方面强调通过临床评估、实验室检查(如尿白蛋白/肌酐比值)和影像学检查进行早期识别。管理策略核心在于综合干预,包括以减重和优化饮食为基础的生活方式干预,以及以肾素-血管紧张素系统抑制剂、钠-葡萄糖协同转运蛋白2抑制剂、胰高血糖素样肽-1受体激动剂和非奈利酮等药物为核心的联合治疗方案。本文旨在为临床医生提供CKM全程管理的系统框架,以降低其疾病负担。

关键词

心肾代谢综合征, 流行病学, 诊断, 综合管理

Cardiovascular-Kidney-Metabolic Syndrome: A New Perspective from Definition to Comprehensive Management

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Abstract

Cardiovascular-kidney-metabolic (CKM) syndrome, a novel concept formally proposed in 2023, aims to integrate the complex pathophysiological interactions among obesity, diabetes, chronic kidney disease (CKD), and cardiovascular disease (CVD). The introduction of CKM signifies a paradigm shift from single-disease, specialty-focused care to a multi-system, interdisciplinary management approach. This review systematically examines the definition, staging system, global epidemiological characteristics, diagnostic methods, and management strategies of CKM. Epidemiological data indicate that CKM is highly prevalent worldwide, particularly among middle-aged and elderly populations, with significant variations across regions, sexes, and ethnicities. Diagnosis emphasizes early identification through clinical assessment, laboratory tests (e.g., urine albumin-to-creatinine ratio), and imaging. The core of management strategies lies in comprehensive intervention, including lifestyle modifications centered on weight loss and dietary optimization, as well as combination pharmacotherapy involving renin-angiotensin system inhibitors, sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and finerenone. This review aims to provide clinicians with a systematic framework for the holistic management of CKM to reduce its disease burden.

Keywords

Cardiovascular-Kidney-Metabolic Syndrome, Epidemiology, Diagnosis, Comprehensive Management

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1. 引言

过去几十年来,肥胖、胰岛素抵抗(Insulin Resistance, IR)、糖尿病(Diabetes Mellitus, DM)、心血管疾病(Cardiovascular Disease, CVD)和慢性肾脏病(Chronic Kidney Disease, CKD)的患病率显著增加,严重危害人类健康,已成为重大公共卫生问题,给社会造成沉重负担。然而,这些疾病长期被孤立地研究和治疗。随着流行病学、机制和临床证据的汇聚,人们认识到代谢、心血管和肾功能障碍之间存在广泛的重叠,而针对多病共存患者的临床诊疗仍缺乏有效的多学科协作。在此背景下,2023年10月,心肾代谢综合征(Cardiovascular-Kidney-Metabolic Syndrome, CKM)这一概念被正式提出[1],标志着诊疗模式从“单病种、分专科”向“多系统、跨学科”的转变。CKM不仅影响患者的生活质量,还增加了心血管系统疾病和肾脏疾病的死亡风险。此外,医护人员普遍工作时间长、压力大,且常存在久坐、缺乏体育锻炼等不

良生活方式，这些因素均与 CVD 风险升高相关[2] [3]。Lin 等人发现，与非医疗工作者相比，医疗工作者的高血压患病率更高，比值比为 1.74 [4]。这要求临床医师需进一步加强 CKM 的早期识别、协调干预，以及生活方式和药物的综合治疗，以预防疾病进展[5] [6]。因此，从预防优先、全生命周期连续性管理的角度出发，对 CKM 进行早期识别、精准分期、系统协作、积极治疗，真正实现以预防为中心的全程管理，对于降低 CKM 的疾病负担、改善患者预后具有重要意义。

2. CKM 的定义和分期

CKM 被定义为一种健康紊乱状态，是由肥胖、糖尿病、慢性肾脏病和心血管疾病之间病理生理相互作用导致的全身性疾病。与“代谢综合征[7]、心肾综合征[8]、心血管代谢疾病[9]”等概念不同的是，CKM 明确将肾损伤和心血管疾病纳入一个关系密切的综合征，其基础是共同的病理生理机制和双向相互作用；同时，它也提供了一个分期系统来分层疾病严重程度并指导干预。

CKM 可分为五期：0 期(无心血管肾脏代谢风险因素)、1 期(脂肪组织过剩/失调)、2 期(合并代谢危险因素或 CKD)、3 期(CKM 合并亚临床 CVD)和 4 期(CKM 合并临床 CVD) [1]，具体分期见表 1。通过分期可以发现，代谢功能障碍的出现通常早于心血管和肾脏的损伤，而心血管疾病和肾脏损伤可以相互加速疾病的进展。了解 CKM 的不同分期对于风险评估、早期干预和改善预后至关重要。

Table 1. Staging of CKM and its basis
表 1. CKM 的分期及其依据

分期	依据
0	没有超重/肥胖、CKD 或亚临床/临床 CVD、代谢危险因素(高血压、高三酰甘油血症、代谢综合征、糖尿病)
1	超重/肥胖(BMI ≥ 23 kg/m ²)、腹部肥胖(女性/男性腰围 ≥ 80/90 cm)或脂肪组织功能失调 (空腹血糖 ≥ 100~124 mg/dl 或 HbA1c 在 5.7%~6.4%之间)，无其他代谢危险因素或 CKD 的个体
2	具有代谢危险因素[高三酰甘油血症(≥135 mg/dl)、高血压、代谢综合征、糖尿病]或 CKD 的个体 亚临床粥样硬化性 CVD 或亚临床心力衰竭患者存在功能失调的肥胖、其他代谢危险因素或 CKD 亚临床粥样硬化性 CVD：通过冠状动脉钙化诊断
3	亚临床心力衰竭：通过升高的心脏生物标志物(NT-proBNP ≥ 125 pg/ml，女性/男性高敏肌钙蛋白 T ≥ 14/22 ng/L，女性/男性高敏肌钙蛋白 I ≥ 10/12 ng/L)或超声心动图参数诊断 亚临床 CVD 的风险当量：高风险 CKD 和预测 10 年 CVD 风险高
4	临床 CVD (冠心病、心力衰竭、卒中、外周动脉疾病、心房颤动)，患者存在过度/功能失调肥胖、其他代谢危险因素或 CKD 4a 期：无肾衰竭 4b 期：肾衰竭

注：CKM，心肾代谢综合征；CKD，慢性肾脏病；CVD，心血管疾病；BMI，体质指数；HbA1c，糖化血红蛋白；NT-proBNP，N 末端 B 型利钠肽原。

3. CKM 的流行病学

过去几十年来，由于肥胖、2 型糖尿病、CKD 和 CVD 的发病率不断上升，CKM 综合征在全球范围内高度流行[10]-[12]，并与不良预后密切相关。

关于人群中 CKM 流行病学特征的研究始于北美洲。一项基于 NHANES (2011 年~2020 年) 10,762 名成年人的研究显示，10.6%为 0 期，25.9%为 1 期，49.0%为 2 期，5.4%为 3 期，9.2%为 4 期。其中，45~65 岁年龄段人群的 CKM 分期显著高于 20~44 岁年龄段人群，男性高于女性[12]。研究期间患病率基本保持稳定。无独有偶，另一项针对 NHANES 人群(2011 年~2018 年)的研究报告了几乎相同的分期分布和人口

统计学差异[13]。除 NHANES 以外,来自行为风险因素监测系统的数据表明,CKM 的总体患病率在过去十年中一直在增加,79.5%的成年人患有 CKM 综合征,其中 1 期最常见(41.6%),4 期为 6.7% [14] [15]。

东亚的 CKM 流行病学数据也较为全面。来自中国的全国性研究显示,CKM 在中老年人群中极为常见,患病率为 83.7%,晚期阶段(3~4 期)患病率为 10.1% [16] [17]。其中,CKM 2 期最为常见,而晚期 CKM 对农村居民、男性和老年人的影响最为突出。在韩国成年人中也观察到了类似的城乡和性别差异,但韩国 CKM 的总体患病率(74.8%)低于中国[11]。

关于欧洲 CKM 患病率的数据较为稀少。一项来自意大利的研究指出,CKM 患病率在 2018 年至 2021 年间有所上升[15]。来自英国生物银行(UK Biobank) 2006 年至 2010 年 40~69 岁成年人的数据显示,CKM 以 2 期为主。仅有 12.7%的成年人没有 CKM 风险因素(即 CKM 0 期),且男性比女性更有可能出现晚期合并症[18]。这些发现与上述的研究结果相似。

不同的种族和族裔使得 CKM 患病率的差异显著。非洲裔人群的高血压相关 CKD 和心力衰竭(Heart Failure, HF)患病率更高,而西班牙裔的肥胖、DM 和 CKD 患病率更高。医疗可及性、营养资源等决定健康的社会因素的差异,进一步加剧了这些不平等[19]-[21]。

在亚洲、欧洲和北美洲的高收入地区之外,CKM 的数据极其有限。但基于人群的流行病学研究表明,即使在肾功能正常的情况下,代谢功能障碍也会显著增加 CKD 和 CVD 的风险,而肾功能的下降会进一步增加心血管风险,这与其它因素无关[22]。因此,需要开展更多研究来全面描述 CKM 相关结局的谱系,包括发病率、残疾和生活质量。此外,目前仍缺乏关于各阶段持续时间、分期上升和下降的发生率及预测因素、以及这些转变的临床后果的数据。填补这些空白对于应对这一疾病至关重要。

4. CKM 的诊断

CKM 的早期识别对于预防其疾病进展至关重要。其多系统的特性要求诊断需采用包括临床评估、实验室检查和影像学检查在内的综合方法[23] [24]。

4.1. 临床评估

内脏脂肪堆积和胰岛素抵抗是 CKM 的基础,因此,评估内脏脂肪和胰岛素抵抗是临床评估中最为关键的第一步。多囊卵巢综合征、代谢相关脂肪性肝病、痛风、妊娠期糖尿病等既往史和 2 型糖尿病家族史也是重要的警示信息。异常的体格检查包括超重、腹型肥胖、黑棘皮病和高血压。此外,详细而全面的病史询问也不可或缺,心血管疾病相关症状(如呼吸困难、胸闷、胸痛和运动耐力下降)和肾脏疾病相关症状(如多尿、夜尿和水肿)也起着重要的提示作用。

4.2. 实验室检查

实验室检查包括空腹血糖、糖化血红蛋白(HbA1c)、肝功能检查、尿酸、血脂和估算肾小球滤过率(eGFR)。若具备条件,还应现场留取尿液样本检测尿白蛋白/肌酐比值(uACR)。尽管 uACR 价格低廉,但在识别和监测疾病发展轨迹方面具有重要作用[25],白蛋白尿是 CKM 的关键生物标志物,不仅能预测肾脏疾病风险,还与 CKM 的不良预后密切相关[26]。

4.3. 影像学检查

影像学检查可对心血管和肾脏进行系统性的结构和功能评估。心血管系统相关的影像学检查,包括超声心动图、心脏磁共振成像(MRI)、颈动脉内膜-中膜厚度和冠状动脉钙化评分等,用于评估左心室壁厚和亚临床动脉粥样硬化程度。肾脏影像学检查,包括超声、CT 和 MRI,用于评估肾脏灌注和纤维化。因此,将实验室检查和影像学检查整合可以有效提升预测 CKM 进展和心血管事件的准确性。

CKM 的早期识别对于及时干预至关重要。高风险人群,如肥胖、糖尿病前期患者,应接受多维度评估。对体格检查体征、实验室检查指标和影像学指标的连续监测,有助于进行生活方式指导和药物治疗方案的动态调整。以调整饮食和体力活动等生活方式为导向的预防措施,能够有效阻止甚至逆转心血管系统和肾脏的早期损伤[27]。

5. CKM 的管理策略

CKM 的疾病特点要求其管理需采用多重路径并重的方法,即需同时针对心血管疾病、肾损伤和代谢功能障碍进行干预。早期干预对于延缓或逆转疾病进展至关重要[28] [29],干预的主要措施包括调整生活方式和药物治疗。

5.1. 生活方式干预

体重管理、饮食均衡和体力活动等一系列健康行为是一级预防和二级预防的关键。不良的生活方式是可改变的风险因素,且能够导致代谢功能障碍进而引发多系统疾病进展,因此改变生活方式是管理 CKM 的基础[29]-[31]。

由于 CKM 由多余的脂肪组织所驱动,因此减重对于延缓 CKM 的进展至关重要;通常减重的目标为 5%,这往往需要在多学科团队的协作下进行[32]。过度加工的食品通常热量高、营养价值低,食用这类食品是肥胖的危险因素之一[33]。澳大利亚的一项横断面研究发现,超加工食品的平均热量摄入可占总热量的 40% [34]。减少超加工食品的摄入可降低由葡萄糖和脂质代谢产物与氨基酸反应形成的晚期糖基化终末产物(AGEs)的产生,进而减轻炎症和氧化应激,从而改善胰岛素抵抗和延缓 eGFR 的下降[35]。地中海饮食、终止高血压膳食疗法(DASH)饮食等强调蔬菜、水果摄入的饮食模式是较为推荐的饮食模式,它们可改善胰岛素抵抗、降低动脉硬化、延缓 eGFR 的下降和减轻白蛋白尿[29]。

规律的体力活动,尤其是有氧运动,可提升心血管功能、改善胰岛素抵抗。而抗阻运动是通过体力活动预防 CKM 的核心[36],可降低内脏脂肪、改善代谢功能。理想情况下的体力活动应每周进行至少 150 分钟的中等强度有氧活动和 2~3 次的抗阻运动。减重手术联合 GLP-1 受体激动剂可显著降低不良心血管事件和肾脏结局的发生率,尤其适用于通过体力活动减重效果不佳的 CKM 患者。减重手术可显著改善胰岛素抵抗和心力衰竭、降低血压和低密度脂蛋白胆固醇;在改善肾脏结局方面更为显著,可延缓 eGFR 下降和推迟透析的启动时机[37] [38]。

因此,在 CKM 早期持续进行体重管理、优化饮食结构和规律地进行体力活动,能够有效降低 BMI 和内脏脂肪,从而降低心血管风险、控制血糖和改善肾脏功能,进而降低不良预后的风险[29]。

5.2. 药物治疗

CKM 的药物治疗既需要针对共同的病理生理机制,同时也需要根据不同患者的器官受累程度制定个体化的治疗方案[23] [39] [40]。

使用血管紧张素转换酶抑制剂(ACEi)或血管紧张素受体阻滞剂(ARB),即肾素-血管紧张素系统抑制(Renin-Angiotensin System Inhibition, RASi),是治疗 CKM 的基石。RASi 可有效降低血压、改善不良心脏重构,并使白蛋白尿减少至少 30% [41] [42]。慢性肾脏病患者无论处于何期,只要患者未出现低血压或高钾血症,即使 eGFR 下降也不应停药[43]。

对于 2 型糖尿病、慢性肾脏病和心力衰竭患者,应考虑应用钠-葡萄糖协同转运蛋白 2 (Sodium-Dependent Glucose Transporters 2, SGLT-2)抑制剂。SGLT2 抑制剂通过渗透性利尿、利钠以及减轻肾脏炎症和肾脏纤维化等多重机制,使患者改善血糖控制、降低心力衰竭住院率和保护肾脏功能,实现多系统获

益[44]-[48]。

2型糖尿病可使盐皮质激素受体过度激活,进而通过促进炎症和纤维化而导致肾脏功能的持续下降。盐皮质激素受体拮抗剂(Mineralocorticoid Receptor Antagonists, MRA)通过抗纤维化保护心血管系统和肾脏[49][50]。因此,非奈利酮尤其适用于出现白蛋白尿的糖尿病患者;此外,研究表明,SGLT2抑制剂和非奈利酮也可同时应用且风险较低[51]。

胰高血糖素样肽-1 (GLP-1)受体激动剂在降低体重、治疗2型糖尿病及诱导糖尿病缓解方面的疗效确切[52]。此外,研究表明,司美格鲁肽在2型糖尿病肾病患者中延缓肾衰竭、降低肾功能下降和心血管死亡风险方面效果明显[53]。越来越多的证据表明, GLP-1受体激动剂通过改善代谢、降低白蛋白尿和抗炎作用,来改善血糖控制、降低心血管风险、保护肾脏,同时实现持续减重[54]-[56]。

对于动脉粥样硬化性心血管疾病(Atherosclerotic Cardiovascular Disease, ASCVD)高风险患者,指南建议立即启动降脂治疗[57]。众多降脂药物中,尤其是他汀类药物,可降低CKD所有分期患者的ASCVD风险。而针对甘油三酯、脂蛋白(a)和前蛋白转化酶枯草溶菌素/kexin 9型(Proprotein Convertase Subtilisin/Kexin Type 9, PCSK9)的药物,可能会对患者带来潜在的心血管获益。

鉴于CKM累及多系统的特点,因此通常需要联合用药以同时调节代谢、降低心血管风险和保护肾脏。通过不同作用机制的药物进行互补,从而能够在血流动力学、炎症、纤维化和代谢失调等关键的病理生理通路上产生相加效应乃至协同效应。从安全性角度来看,联合治疗方案需要注意不同药物类别之间是否存在不良的相互作用。现有证据未提示上述药物类别间存在有临床意义的药效学不良相互作用,这为在经适当筛选的患者中联合用药提供了支持。总体而言,在CKM的治疗中,制定合理、安全的个性化联合治疗方案,对于最大化治疗获益和最小化伤害至关重要。

6. 总结与展望

心肾代谢综合征(CKM)的提出,是对当前全球范围内肥胖、糖尿病、慢性肾脏病与心血管疾病高度共病现状的深刻回应。它突破了传统专科壁垒,为理解和管理这些相互关联的疾病提供了全新的、系统性的框架。本文通过CKM的定义与分期、全球流行病学特征、诊断路径及综合管理策略,强调了从预防优先、全生命周期管理的角度进行早期识别和综合干预的重要性。

尽管取得了显著进展,CKM领域仍面临诸多挑战。首先,全球流行病学数据仍不均衡,尤其缺乏来自低收入和中等收入国家的代表性数据,限制了对该疾病全球负担的准确评估。其次,CKM各分期之间的动态转变规律、驱动因素及其对远期预后的影响,仍需大规模、长周期的队列研究来阐明。第三,当前诊断工具虽然有效,但如何将其整合为简便、高效的社区筛查方案,以实现更广泛的早期识别,是未来的重要方向;此外,循环微RNA、代谢组学和蛋白质组学组合以及特定氧化应激标志物等新兴生物标志物目前仍处于研究阶段,这些标志物有望用于早期检测、精准表型分析、个体化治疗指导及风险分层的进一步完善,从而推动CKM的真正个体化干预。第四,在治疗策略上,虽然多种药物(如SGLT2抑制剂、GLP-1受体激动剂、非奈利酮等)已显示出多系统获益,但最优的联合用药方案、治疗时机及在不同亚群(如不同种族、不同肾功能分期)中的疗效差异,仍需更多头对头研究和真实世界证据来指导。展望未来,CKM的研究与管理将朝着更精准、更整合、更智能的方向发展。持续的研究和协作将继续完善诊断和个性化治疗,从而确保所有受CKM影响的患者都能获得最佳结局。

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