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代谢失衡：从分子机制到多系统疾病干预的研究新范式

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摘要：代谢失衡作为现代医学的核心议题，通过干扰物质与能量代谢稳态，驱动多系统疾病发生。本文系统整合最新研究，揭示代谢失衡通过胰岛素抵抗、炎症级联、氧化应激等通路，与脑梗死、慢性肾脏病、糖尿病等疾病形成双向调控网络。当前研究聚焦于分子机制解析与个体化干预策略开发，但个体异质性、菌群-代谢互作等领域仍需突破。本综述旨在构建“代谢失衡-疾病发生-精准管理”的完整认知框架，为临床转化提供理论基础。

关键词：代谢失衡；　多系统疾病；　病理机制；　精准干预

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Metabolic Imbalance：A New Research Paradigm from Molecular Mechanisms to Multi-System Disease Intervention

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Abstract　Metabolic imbalance，as a core issue of modern medicine，drives the occurrence of multi-system diseases by disrupting the homeostasis of material and energy metabolism. This article systematically integrates the latest research，revealing that metabolic imbalance forms a bidirectional regulatory network with diseases such as cerebral infarction，chronic kidney disease，and diabetes through pathways like insulin resistance，inflammatory cascades，and oxidative stress. Current research focuses on the analysis of molecular mechanisms and the development of individualized intervention strategies，but breakthroughs are still needed in areas such as individual heterogeneity and the interaction between microbiota and metabolism. This review aims to construct a comprehensive cognitive framework of “metabolic imbalance-disease occurrence-precise management”，providing a theoretical basis for clinical translation.

Keywords　metabolic imbalance；　multi-system diseases；　pathological mechanism；　precision intervention

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代谢失衡是指机体内物质和能量在代谢过程中，其产生、转化及利用等环节出现异常现象，导致代谢产物堆积或缺乏，从而影响机体的正常生理功能。近年来，随着全球代谢性疾病患病率的持续攀升，代谢失衡与器官功能损伤的交互作用已成为医学研究的焦点。目前，研究人员已发现许多与代谢失衡相关的基因、蛋白质和代谢产物，并且正在探索这些基因、蛋白质和代谢产物之间的相互作用和调控机制。代谢失衡不仅是心血管疾病、慢性肾脏病(chronic kidney disease，CKD)等慢病的病理基础，其与器官损伤的双向调控更形成了“代谢-疾病”恶性循环。代谢失衡与多种疾病的发生发展密切相关，如脑梗死、高血压、CKD、糖尿病、肥胖和高血脂等，见图 1。因此，深入研究代谢失衡的机制和影响，对预防和治疗这些疾病具有重要意义。本综述将从代谢失衡的共性机制出发，系统阐述其与多系统疾病的临床关联，并展望精准干预策略前景。

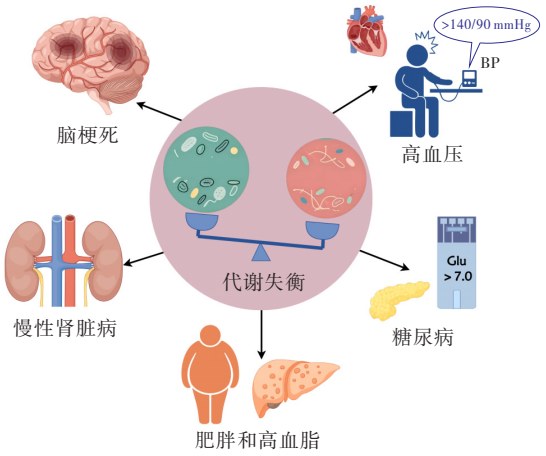

图 1　代谢失衡相关疾病

1　代谢失衡的共性病理机制

1.1　胰岛素抵抗与能量代谢紊乱

胰岛素抵抗以靶器官对胰岛素敏感性下降为特征，致使葡萄糖摄取障碍，进而诱发高胰岛素血症[1]。分子机制显示，胰岛素受体底物的磷酸化异常可阻断磷脂酰肌醇-3 激酶-蛋白激酶 B 信号通路，导致葡萄糖转运蛋白转位障碍[2]。这种代谢紊乱不仅局限于糖代谢，还通过激活激素敏感脂酶，促进脂肪细胞释放游离脂肪酸，进而诱发肝脏极低密度脂蛋白胆固醇合成增加，最终导致高脂血症的发生[3]。临床数据显示，胰岛素抵抗使脑梗死发病风险增加 1.92 倍[4]，并与高血压形成“代谢-血压”调控失衡[5]。

1.2　炎症-氧化应激级联反应

代谢失衡状态下，脂肪组织巨噬细胞浸润可分泌肿瘤坏死因子-α、白细胞介素-6 等炎症因子，通过 c-Jun 氨基末端激酶/IκB 激酶信号通路抑制胰岛素信号传导[6]。同时，线粒体功能异常导致活性氧过度生成，形成氧化应激与胰岛素抵抗的恶性循环。在 CKD 中，氧化应激可通过激活核苷酸结合寡聚化结构域样受体蛋白 3(NOD-like receptor family pyrin domain containing 3，NLRP3)炎症小体，加速肾小管上皮细胞铁死亡[7]，而铁死亡驱动的脂质过氧化又进一步损伤肾小球滤过屏障[8]。这种炎症-氧化应激网络在代谢相关性疾病中呈现高度保守性。

1.3　肠道菌群-代谢轴紊乱

肠道菌群通过调节胆汁酸代谢与短链脂肪酸(short-chain fatty acids，SCFAs)生成参与宿主代谢调控。代谢失衡时，菌群多样性降低(如厚壁菌门/拟杆菌门比值升高)可增强小肠脂质吸收，并通过 SCFAs-游离脂肪酸受体通路促进肝脏糖异生[9]。值得注意的是，CKD 患者肠道菌群失调可通过“肠-肾轴”加剧尿毒症患者毒素蓄积，通过益生菌干预(如双歧杆菌)可降低促炎细胞因子水平改善肾功能[10-11]。这种菌群-代谢互作成为近年研究热点。

2　代谢失衡与多系统疾病的临床关联

2.1　脑梗死与代谢失衡的交互作用

2.1.1　发病机制的代谢基础

脑梗死发生时，局部缺血缺氧可导致神经元线粒体腺苷三磷酸生成减少 40%以上[12]，同时激活钙超载与自由基瀑布效应。代谢失衡通过三重机制加剧脑损伤：①胰岛素抵抗抑制葡萄糖摄取，使缺血半暗带能量供给进一步恶化；②高脂血症通过氧化低密度脂蛋白胆固醇损伤血脑屏障，增加脑水肿风险[13]；③高血压诱导的脑血流动力学异常，可破坏脑血管自动调节功能[14]。临床研究显示[15]，合并代谢综合征的脑梗死患者，90 天神经功能预后不良率较非代谢紊乱者高 2.34 倍。

2.1.2　诊断技术的代谢视角

传统影像学中，MRI 扩散加权成像可早期识别缺血病灶，但正电子发射断层扫描(positron emission tomography，PET)通过 18F-FDG 摄取率能更精准评估脑代谢活性[16]。最新研究表明[17]，PET 检测的脑葡萄糖代谢率与脑梗死体积呈显著负相关($r=-0.72$，$P<0.01$)。新兴分子影像技术(如靶向 α7 烟碱受体的 PET 探针)可实时监测炎症反应强度，为代谢调节治疗提供靶点可视化依据[18]。

2.1.3 代谢调节治疗新策略

除传统溶栓与机械取栓外，代谢干预成为改善预后的新方向。动物实验显示[19]，补充线粒体靶向抗氧化剂可使脑梗死面积减少 38%。临床研究中，利拉鲁肽通过改善胰岛素敏感性，使合并糖尿病的脑梗死患者 90 天脑卒中改良 Rankin 量表评分改善率提高 22%[20]。值得关注的是，调节肠道菌群的合生元疗法可通过降低血清内毒素水平，减轻脑梗死后神经炎症[21]。

2.2 慢性肾脏病与代谢失衡的双向调控

2.2.1 代谢紊乱驱动 CKD 进展的机制

糖尿病作为 CKD 的首要病因，其所致的肾小球高滤过状态可通过“代谢记忆”效应持续损伤肾单位[22]。脂质代谢异常在 CKD 中表现为肾小管脂质沉积，激活蛋白激酶 C 与转化生长因子-β 通路，促进肾纤维化[23]。最新研究发现[24]，铁死亡在 CKD 进展中起关键作用，肾小管上皮细胞内铁超载可通过脂质过氧化导致细胞死亡，而铁螯合剂去铁胺(deferoxamine)可显著延缓 CKD 进展。

2.2.2 CKD 加剧全身代谢失衡的病理效应

肾功能损伤时，1，25-二羟维生素 D 合成减少可诱发继发性甲状旁腺功能亢进，导致矿物质代谢紊乱[25]。同时，尿毒症患者毒素蓄积可抑制胰岛素受体信号，致使 CKD 患者胰岛素抵抗发生率达 67.5%[26]。血管钙化作为 CKD 的特征性并发症，其发生与钙磷代谢失衡、骨形态发生蛋白信号异常密切相关[27]，而新型磷酸盐结合剂(如司维拉姆)可降低 31%血管钙化风险[28]。

2.2.3 靶向代谢的 CKD 治疗新进展

除传统肾素-血管紧张素系统抑制剂外，新型药物展现出代谢调节优势。可妥度肽(cotadutide)作为胰高血糖素样肽-1(glucagon-like peptide-1，GLP-1)/胰高血糖素受体双重激动剂，可使糖尿病肾病患者尿蛋白排泄率降低 24%[29]。针对铁死亡的干预研究显示[30]，抑制脂酰辅酶 A 合成酶 4 可减少肾小管上皮细胞脂质过氧化，改善肾功能。中医药研究发现[31]，茶多糖可通过调节过氧化物酶体增殖物激活受体 γ 信号，减轻肾小管脂质沉积，为代谢干预提供了新的候选药物。

2.3 肥胖-高血脂与代谢失衡的恶性循环

2.3.1 能量代谢失衡的中枢调控异常

肥胖发生的核心是长期能量摄入超过消耗，其中下丘脑弓状核的神经肽 Y/阿黑皮素原神经元失衡起关键作用。研究显示[32]，肥胖个体的瘦素受体敏感性降低，导致中枢性食欲抑制信号减弱。外周层面，白色脂肪组织过度扩张可引发缺氧微环境，激活缺氧诱导因子-1α 通路，促进血管生成，同时加剧脂肪炎症[33]。值得注意的是，亚洲人群身体质量指数(body mass index，BMI)≥23.0 kg/m^2 时，代谢异常风险显著升高[34]，提示种族差异在代谢失衡中的重要性。

2.3.2 脂质代谢紊乱的多重病理效应

高血脂状态下，低密度脂蛋白胆固醇氧化修饰可损伤血管内皮，而高密度脂蛋白胆固醇抗炎功能缺陷进一步促进动脉粥样硬化[35]。在非酒精性脂肪性肝病中，肝脏脂质过度沉积可诱发内质网应激，通过肌醇需求酶 1α-X-box 结合蛋白 1 通路激活肝星状细胞，导致肝纤维化[36]。最新研究表明[37]，靶向单酰甘油脂肪酶可减少脂肪细胞脂毒性，改善胰岛素敏感性，为脂质代谢调节提供了新靶点。

2.3.3 代谢手术的机制突破与临床应用

对于重度肥胖(BMI≥32.5 kg/m^2)合并代谢紊乱者，代谢手术展现出药物无法比拟的疗效。胃旁路术通过减少胃容积、改变肠道激素分泌(如 GLP-1、酪酪肽增加)，使 83%的 2 型糖尿病患者术后血糖达标[38]。机制研究显示[38]，代谢手术可通过“肠-脑轴”重塑下丘脑代谢调控网络，恢复瘦素敏感性。但需注意，术后维生素 B_{12} 缺乏等并发症发生率约为 15%[39]，提示长期随访的必要性。

2.4 糖尿病与代谢紊乱的交互作用网络

2.4.1 胰岛素抵抗与 β 细胞功能衰竭的协同机制

2 型糖尿病中，骨骼肌、肝脏的胰岛素抵抗与胰腺 β 细胞功能衰竭形成恶性循环。分子层面，慢性高血糖可通过己糖胺通路激活，导致胰岛素原错误折叠，触发 β 细胞内质网应激[40]。脂毒性则通过抑制葡萄糖诱导的胰岛素分泌，进一步损伤 β 细胞功能[41]。值得注意的是，1 型糖尿病虽以胰岛素缺乏为主，但长期血糖波动仍可通过氧化应激诱发外周组织胰岛素抵抗[42]。

2.4.2 代谢紊乱介导的糖尿病并发症机制

糖尿病微血管并发症(如视网膜病变、肾病)的发生与多元醇通路激活、晚期糖基化终末产物形成密切相关[43]。大血管并发症中，代谢失衡通过促进泡沫细胞形成与血管平滑肌细胞增殖，加速动脉粥样硬化[44]。最新研究揭示[45]，糖尿病患者的肠道菌群失调可通过“肠-胰轴”加重胰岛素抵抗，菌群代谢产物丙酸可抑制 G 蛋白偶联受体 43 信号，减少 GLP-1 分泌，形成代谢-菌群交互恶化。

2.4.3 基于代谢路径的糖尿病治疗革新

除二甲双胍等传统药物外，钠-葡萄糖协同转运蛋白 2(sodium-glucose cotransporter 2，SGLT2)抑

制剂通过促进尿糖排泄，不仅降低血糖，还可通过减轻肾小球高滤过延缓肾病进展[46]。GLP-1 受体激动剂利拉鲁肽在降糖的同时，可使心血管事件风险降低 13%[47]，其机制涉及改善内皮功能与抑制动脉粥样硬化炎症[48]。值得关注的是，表观遗传干预（如 DNA 甲基转移酶抑制剂）可通过恢复 β 细胞基因表达谱，延缓糖尿病进展[49]，展现出代谢调节的新维度。

2.5　高血压与代谢失衡的调控网络

2.5.1　代谢-血压交互作用的中枢与外周机制

代谢相关性高血压的核心是交感神经系统与肾素-血管紧张素-醛固酮系统的过度激活。胰岛素抵抗通过下丘脑室旁核神经元敏化，使交感神经放电频率增加 25%[50]。外周层面，肥胖诱导的机械压力与脂肪因子（如瘦素）可抑制血管内皮一氧化氮合成，导致血管舒张功能障碍[51]。最新研究发现[52]，肠道菌群代谢产物三甲胺 N-oxide 可通过激活 NLRP3 炎症小体，促进高血压发生。

2.5.2　代谢性高血压的临床特征与诊断革新

与原发性高血压相比，代谢性高血压表现出三大特征：① 血压昼夜节律异常（夜间血压下降率 < 10%）；②合并中心性肥胖（腰围男性≥90 cm，女性≥85 cm）；③糖脂代谢紊乱（空腹血糖≥6.1 mmol/L，甘油三酯≥1.7 mmol/L）[53]。诊断上，除传统血压测量外，24 h 动态血压监测与胰岛素钳夹技术可更精准评估血压-代谢关联。美国心脏协会 2017 年将高血压诊断标准下调为≥130/80 mmHg[54]，旨在更早识别代谢性心血管事件风险。

2.5.3　代谢综合管理的血压干预策略

生活方式干预中，终止高血压饮食可使收缩压降低 7～12 mmHg[55]，而我国特色的辣膳食（含辣椒素）通过激活瞬时受体电位香草酸亚型 1 受体，可改善血管内皮功能[56]。药物选择上，血管紧张素转换酶抑制剂/血管紧张素Ⅱ受体拮抗剂类不仅可以降低血压，还可改善胰岛素抵抗[57]，而 SGLT2 抑制剂达格列净可额外降低收缩压 4～6 mmHg[58]。对于难治性代谢性高血压，代谢手术（如袖状胃切除术）可使 62%的患者术后停用降压药物[59]，但其长期心血管获益仍需更大样本验证。

3　代谢失衡的精准管理策略

3.1　基于风险分层的三级预防体系

代谢失衡的防控需构建分层管理体系。基于风险分层，从健康人群的代谢评估与生活方式干预，到高危人群的药物早期阻断，再到患病人群的多靶点联合治疗，形成全周期精准管理链，实现代谢疾病的三级预防。根据不同的代谢及病理生理状态将人群划分为三类：①健康人群：采用“代谢年龄”评估模型（整合 BMI、腰围、空腹血糖、血脂等指标），对代谢年龄超过实际年龄 5 岁者启动生活方式干预。中国人群研究显示[60]，“5＋2”轻断食模式（每周 5 天控制热量，2 天轻断食）可使代谢综合征发生率降低 34%。②高危人群：对糖尿病前期（空腹血糖受损或糖耐量异常）患者，二甲双胍联合阿卡波糖可使 2 型糖尿病转化率降低 42%[61]。针对腹型肥胖（腰围≥90 cm），利拉鲁肽（3.0 mg/d）可使体重下降 5.08 kg/年，同时改善血脂谱[62]。③患病人群：CKD 合并代谢紊乱者，采用“代谢-肾脏”联合管理，如 GLP-1 受体激动剂联合 SGLT2 抑制剂，可使心血管事件风险降低 28%[63-64]。对于终末期肾病，高通量透析可更好地清除中分子代谢毒素，改善胰岛素敏感性[65]。

代谢失衡在健康人群中，可能表现为高盐、高油、吸烟、酗酒等不良生活习惯，导致超重和精神压力；在高危人群中，可能引发高血压、高血脂、高血糖等高危现象；在患病人群中，则可能发展为脑卒中、糖尿病等疾病。针对不同人群，需采取三种管理手段：健康人群开展健康教育、体检和干预；高危人群进行早期诊断、个体化指导和药物治疗；患病人群则需进行临床治疗、规范化管理和康复[66-68]。这种分层管理策略有助于预防和控制代谢失衡相关疾病，见图 2。

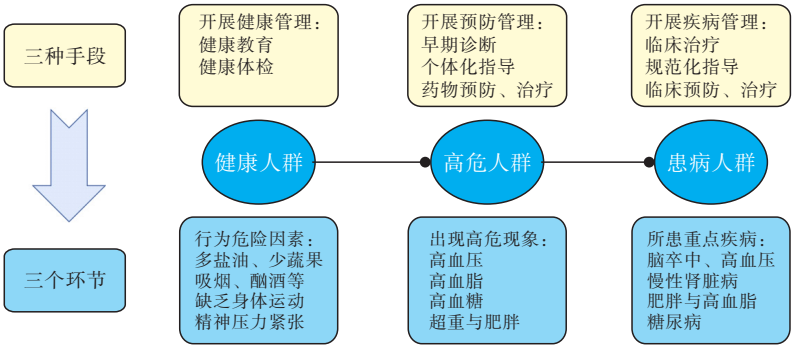

图 2　代谢失衡对不同人群的影响及相应的管理手段

上述分层策略以“评估-干预-治疗”为逻辑主线，通过健康人群风险筛查、高危人群药物介入及患病人群综合管理，构建代谢失衡全链条防控体系，为降低代谢性疾病负荷提供了科学路径。

3.2　靶向代谢通路的新型干预技术

代谢失衡的干预正迈向多技术协同时代。肠道菌群调节通过重塑微生态恢复代谢信号，为代谢-器官交互干预提供生物靶点[69]；代谢手术借助机器人与内镜技术实现微创化升级，提升减重与代谢改善效率[70]；穿戴设备则通过实时监测构建代谢波动预警体系[71]。三者从生物调节、结构干预到动态监测形成闭环，推动精准代谢管理落地。①肠道菌群调节：粪菌移植(fecal microbiota transplantation, FMT)在肥胖小鼠模型中可使体重降低 15%，其机制与恢复 SCFAs 生成相关[72]。临床研究显示[73]，益生菌可使肝硬化患者的内毒素血症改善率达 47%，为代谢-肝脏交互干预提供借鉴。②代谢手术优化：机器人辅助胃旁路术较传统术式术后并发症发生率降低 37%[74]。最新发展的“代谢内镜”技术(如内镜下袖状胃成形术)具有微创优势，6 个月内可使 BMI≥30 kg/m^2 的患者体重下降 12.3%[75]。③穿戴设备监测：连续葡萄糖监测(continuous glucose monitoring, CGM)可实时反馈代谢波动，使 1 型糖尿病患者糖化血红蛋白(glycated hemoglobin, HbA1c)达标率提高 21%[76]。新型汗液传感器通过检测乳酸、酮体水平，可预警代谢失衡风险，其临床有效性仍在验证中[77]。上述干预手段以“生物-结构-监测”为逻辑轴，FMT 通过菌群-代谢轴改善能量稳态，机器人辅助手术与代谢内镜实现干预微创化，CGM 等设备则强化代谢异常预警[78]。这些技术突破既基于机制研究进展，又通过临床数据(如体重下降 12.3%、HbA1c 达标率提升 21%)验证效能，为代谢疾病个体化治疗提供多元路径[79]。

4　未来研究方向与挑战

代谢失衡研究正从机制解析向临床转化深度推进。单细胞代谢组学与类器官模型助力揭示细胞异质性及器官交互机制[80-81]，表观遗传调控研究则为逆转代谢记忆提供新路径[82]。然而，临床转化面临遗传异质性整合、菌群-代谢匹配机制不明及新型药物长期安全性待验证的三重挑战，亟需多学科协同突破。

4.1　机制研究的前沿领域

代谢失衡机制研究正朝精细化发展。单细胞代谢组学解析细胞代谢异质性、类器官模型模拟器官间信号串扰及表观遗传调控探索代谢记忆机制，三者从不同层面深化对代谢失衡的理解，为精准干预奠定基础。单细胞代谢组学：解析代谢失衡时不同细胞类型的代谢异质性，如脂肪组织中 M1/M2 型巨噬细胞的脂质代谢差异[83-84]，有望发现新治疗靶点。类器官模型：构建代谢-器官交互类器官(如肝-胰-脂肪共培养模型)，可动态模拟代谢失衡时器官间的信号串扰[85-86]，弥补动物模型的种属差异局限。表观遗传调控：探索代谢记忆的表观遗传机制，如糖尿病中 β 细胞的 DNA 甲基化谱改变[87]，为逆转代谢紊乱提供表观干预靶点。上述研究通过单细胞代谢组学、类器官模型和表观遗传调控，分别从细胞异质性、器官交互和代谢记忆层面揭示代谢失衡机制，为发现新治疗靶点和干预策略提供理论支撑。

4.2　临床转化的关键挑战

代谢失衡临床转化面临多重挑战。遗传层面需整合全基因组关联研究(genome-wide association study, GWAS)识别的代谢位点至决策模型，菌群-代谢互作待明确菌株与宿主基因型匹配机制，新型药物长期安全性需真实世界数据支撑，三者制约精准干预落地。个体异质性解析：GWAS 已识别 100 多个代谢相关位点(如 FTO、MC4R)，但如何将遗传信息整合到临床决策模型仍需突破[88]。菌群-代谢互作：尽管益生菌显示出代谢调节潜力，但菌株特异性(如双歧杆菌 BB-12 vs 乳酸杆菌 GG)与宿主基因型的匹配机制尚未明晰[89]。长期安全性评估：新型代谢药物(如 GLP-1 受体激动剂)的长期使用可能增加甲状腺髓样癌风险[90]，需建立真实世界证据监测网络。机制研究通过单细胞组学、类器官模型及表观遗传分析，为代谢失衡干预提供精准靶点；临床转化则受制于个体遗传差异、菌群-宿主互作复杂性及药物安全隐患[91-92]。未来需构建“机制-遗传-菌群”多维度研究体系，以加速机制发现向个体化代谢管理的临床转化。临床转化需突破遗传信息整合、菌群-宿主匹配及药物安全监测三大瓶颈，通过构建多维度研究体系，推动代谢失衡从机制发现向个体化临床应用跨越。

5　小结

代谢失衡作为现代医学的核心挑战，已被证实通过胰岛素抵抗、炎症级联等多重机制，与糖尿病、心血管疾病、CKD 等形成双向致病网络。当前研究已从单一器官损伤机制，深入到“代谢-器官轴”的系统调控解析，例如肠道菌群与肝脏代谢的交互作用、下丘脑对能量稳态的中枢调控等。临床干预方面，从生活

方式调整到靶向药物研发(如 GLP-1 受体激动剂)、代谢手术优化,已形成分层管理策略。然而,个体遗传异质性、菌群-代谢匹配机制等未解难题,仍制约精准医学落地,亟需多维度证据整合。

未来代谢失衡研究需推动三大转变:①从机制解析向"预测-干预"转化医学跨越,借助多组学(基因组、代谢组、微生物组)构建风险预警模型;②从单靶点治疗向代谢网络调控升级,例如通过表观遗传干预逆转"代谢记忆";③从单一学科研究向跨领域协作发展,整合临床医学、分子生物学、数据科学等,建立代谢性疾病的全周期管理体系。特别值得关注的是,穿戴设备实时监测与 AI 算法的结合,有望实现代谢异常的早期预警,为全球代谢性疾病的防控提供创新范式。

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