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营养素与静脉血栓栓塞症的关联研究进展

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摘　要

静脉血栓栓塞症(venous thromboembolism, VTE)是临床上的常见并发症，不仅严重威胁患者的生命健康、增加致残和死亡风险，还会带来沉重的医疗经济负担。目前主要依靠抗凝药物预防VTE，但存在出血风险、适用人群有限、患者长期用药依从性差等问题，急需安全有效的非药物防控手段。营养素可以调节人体的凝血－纤溶平衡、炎症反应和血管内皮功能，宏量营养素与微量营养素都会参与VTE的发生发展过程。但目前各类研究对二者和VTE的具体关联、作用机制还没有形成统一结论，研究结果差异较大，也缺乏对这两类营养素与VTE关系的系统整理。本研究系统梳理了宏量、微量营养素和VTE发生发展的关联，分析其调控VTE的核心分子机制，对现有研究的共识与争议进行总结，可为后续构建新的VTE风险评估体系提供参考。

关键词

静脉血栓栓塞症，宏量营养素，微量营养素，血栓预防

Research Progress on the Association between Nutrients and Venous Thromboembolism

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Abstract

Venous thromboembolism (VTE) is a common clinical complication. It not only poses a severe threat

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to patients' life and health and elevates the risk of disability and mortality, but also imposes a substantial medical and economic burden. At present, anticoagulant drugs serve as the primary approach for VTE prevention. However, their application is limited by issues such as bleeding risk, restricted eligible populations, and poor long-term medication adherence in patients, highlighting an urgent demand for safe and effective non-pharmacological prevention and control strategies. Nutrients can modulate the human body's coagulation-fibrinolysis balance, inflammatory response, and vascular endothelial function. Both macronutrients and micronutrients are involved in the initiation and progression of VTE. Nevertheless, current studies have not reached consistent conclusions regarding the specific association and underlying mechanisms between these nutrients and VTE, with highly divergent results. In addition, there remains a lack of systematic collation on the relationship between these two categories of nutrients and VTE. This study systematically reviews the association between macronutrients, micronutrients and the development of VTE, analyzes the core molecular mechanisms by which these nutrients regulate VTE, and summarizes the consensus and controversies in existing research. The results can provide a reference for the subsequent construction of a new VTE risk assessment system.

Keywords

Venous Thromboembolism, Macronutrients, Micronutrients, Thromboprophylaxis

1. 引言

静脉血栓栓塞症(venous thromboembolism, VTE)，是全球高发病率和高死亡率的慢性非传染性疾病之一，包括深静脉血栓形成(deep vein thrombosis, DVT)和肺血栓栓塞症(pulmonary thromboembolism, PTE) [1]，二者为同一病理过程在不同部位的具体表现，其病理生理核心遵循 Virchow 三要素[2]——静脉血流缓慢、血管内皮损伤及血液高凝状态，三者相互作用，共同推动血栓的形成与发展。

VTE 具有显著的公共卫生威胁，全球发病率约为 115~269/10 万人年，且呈逐年上升趋势[3]。在欧洲和美国，VTE 发病率为 1~2 例/1000 人年，新发患者数量庞大[4] [5]。在我国，VTE 的发病情况同样严峻，住院患者的 VTE 新发人数从 2016 年的 53.8 万人(38.17/10 万人)升至 2023 年的 215.6 万人(152.92/10 万人)，增长趋势明显[6]。除高发病率外，VTE 还带来沉重的经济负担。美国 VTE 的医疗成本为 70 至 100 亿美元/年，欧盟为 15 至 33 亿欧元/年[7] [8]。我国近期研究数据显示 VTE 患者围手术期住院费用是未发生 VTE 患者的 2.1~2.4 倍[6]。除此之外，VTE 的复发风险更是不容忽视，首次发作 VTE 且停止抗凝治疗的患者，10 年内复发风险约为 36% [9]。

然而，VTE 的预防并不充分。全球约 54.4% VTE 高风险患者接受了充分的血栓预防[10]，我国整体 VTE 预防率仅为 40.2% [6]，显著低于全球水平。当前预防 VTE 的药物主要包括低分子肝素、新型口服抗凝剂等，虽然能降低血栓风险，但存在明确局限性。一方面，抗凝治疗伴随出血风险，有可能发生颅内出血、消化道大出血等严重出血事件；另一方面，抗凝治疗周期长，部分患者存在耐受不佳或依从性差的问题[11]。为提高 VTE 预防率，需进一步探索更加安全可及的预防方案。

营养素作为心血管疾病、糖尿病等慢性病的重要影响因素[12]，其对 Virchow 三要素的潜在调控作用已得到初步证实[13]-[15]。早在十多年前已有研究聚焦于营养素与 VTE 的关系[16]，一项纳入约 13 万人的前瞻性研究[17]发现，西方饮食模式(高碳水、高脂肪、高蛋白)与男性 VTE 风险升高有关(RR = 1.43, 95%

CI: 1.16~1.78)，而维生素 B6、维生素 E 及膳食纤维摄入与 VTE 风险呈负相关。然而，当前研究多关注某一类营养素与 VTE 的关系，且部分结论存在争议，缺乏系统的整合，难以形成明确的临床指导依据。

本综述覆盖两类核心营养素：一是宏量营养素，包括蛋白质、脂质、碳水化合物；二是微量营养素，涵盖铁、锌等微量元素，以及维生素 D、维生素 B 等各类维生素。旨在梳理、整合相关研究，明确各类营养素与 VTE 之间的关系，为 VTE 的多维度防治提供参考。

2. 宏量营养素与 VTE 的关系

宏量营养素是人体能量供应和组织构成的基础，包括脂质、蛋白质、碳水化合物三大类，其通过调节凝血功能、保护血管内皮、改善血流动力学等对 VTE 的发生发展产生重要影响。

2.1. 脂质

脂质是一类不溶于水的有机化合物，是人体必需的宏量营养素之一，也是构成细胞结构、提供能量、调节生理功能的核心物质，主要包含甘油三酯(triglycerides, TG)、磷脂及以胆固醇为核心的固醇类三大类。其体内代谢与转运状态可通过相关指标进行评估。血脂水平直接反映血液中脂质的实际含量，脂蛋白(脂质 + 载脂蛋白)作为脂质转运载体，其水平可间接反映机体脂质的转运代谢状态。不同的血脂和脂蛋白会对凝血功能、血流状态及血管内皮产生不同的效应，暗示脂质与 VTE 的发生发展密切相关[18] [19]。

三种经典血脂包括 TG、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)及高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)，上述血脂以及载脂蛋白 A (apolipoprotein A, ApoA)与 VTE 之间的关系尚存在争议。既往研究表明，LDL-C 水平升高仅与男性 VTE 风险升高相关[20]，TG 升高与绝经后妇女 VTE 风险增加相关，而 HDL-C 水平升高与 VTE 风险降低相关[21]。并且肝脏 TG 含量可增强凝血因子Ⅸ活性，从而增加肥胖患者 VTE 风险[18]。然而一项病例对照研究显示，血清胆固醇(total cholesterol, TC)、HDL-C、LDL-C 和 ApoA 水平在肺栓塞患者中均降低[22]。Jones 等在颈动脉血栓形成和肺栓塞小鼠模型中也发现，外源性人 ApoA-I 可抑制花生四烯酸和胶原蛋白介导的血小板聚集，降低 P-选择素表面表达和蛋白激酶 B 激活，导致血栓强度降低从而减少动脉和静脉血栓形成[23]。为验证脂质与静脉血栓形成的因果关联，Lin 等利用双向孟德尔随机化(MR)分析三种经典脂质(TG、LDL-C、HDL-C)与该病的关联，未发现明确因果关系[24]。与之结果相似的是，除了经典三种脂质外，ApoA1 和 ApoB 与 DVT 之间也没有明确的因果关联[25]。

不同的脂质在静脉血栓形成中可能存在相反的作用[26]。一项双样本 MR 研究探讨了不同脂质与静脉血栓栓塞之间的关联。结果发现，中等低密度脂蛋白(intermediate-density lipoprotein, IDL)对静脉血栓形成具有保护作用，较高的脂肪酸(fatty acids, FA)不饱和度会增加 DVT 和 PTE 风险。而不同亚型的磷脂酰胆碱(phosphatidylcholine, PC)对静脉血栓形成风险的影响存在明显异质性：部分亚型(如 PC 酰基烷基 C40：4)与 VTE 风险呈负相关，而另一些 PC 亚型与 PTE 呈正相关[26]。并且一些氧化脂质代谢产物的上调也可能是 PE 的重要致病因素[22]。此外，一些 FA 和 FA 代谢物与静脉血栓之间也存在密切相关[27] [28] [29]。既往研究发现在长期棕榈油饲养的小鼠中观察到 ADP 诱导的血小板聚集和静脉血栓重量增加，导致血栓风险升高[30]。一项前瞻性研究发现血清 n-3 多不饱和脂肪酸(n-3 polyunsaturated fatty acids, n-3 PUFA)浓度与 VTE 风险呈负相关，富含 n-3 PUFA 的饮食可以预防 VTE 发生[31]。另一项随机对照临床试验表明术后 30 天内每日口服 1000 毫克 n-3 PUFA 可降低术后 PTE 和有症状的 DVT 风险，且不会增加出血风险[27]。在老年 VTE 患者中，n-3 PUFA 水平越高，VTE 复发风险或总死亡率越低[32]。亚油酸氧化产物十八碳二烯二羧酸是 PC 和 DVT 风险因果关联的潜在介导因素[29]。L-棕榈酰肉碱(L-palmitoylcarnitine, L-PC) (一种 FA 代谢产物)可通过增强纤溶酶和组织型纤溶酶原激活剂(tPA)的活性发挥抗血栓作用[28]。

综上，不同脂质对 VTE 的影响不同，并且在 DVT 及 PTE 之间的作用存在差异。TG、LDL-C、HDL-C、ApoA1 与静脉血栓形成之间的关系存在争议。IDL 对静脉血栓形成具有保护作用，较高的 FA 不饱和度会增加 VTE 风险。而 n-3 PUFA 可预防静脉血栓的形成和复发。一些脂肪酸代谢物(如十八碳二烯二羧酸和 L-PC)可能具有降低 VTE 风险的作用。

2.2. 蛋白质

众所周知，蛋白质对人类生命活动起着至关重要的作用，几乎参与所有生物过程(如催化反应、物质运输、基因调控等)。膳食蛋白质是血浆蛋白合成的最主要氨基酸来源，其摄入水平、质量与类型，直接决定血浆蛋白的表达水平与功能状态[33]。其中，部分血浆蛋白在静脉血栓形成中发挥重要调控作用[34]。

纤维蛋白原、凝血因子 VIII 和 IX 可促进凝血级联反应，增加血栓风险[35] [36]。而抗凝血酶、蛋白 C 和蛋白 S 等则通过抑制凝血酶活性或灭活因子 Va、VIIIa 发挥抗凝功能[37] [38]。蛋白 C 或蛋白 S 的缺乏可能是反复 DVT 以及血栓形成后综合征的独立危险因素[39] [40]。另外，炎症相关蛋白如 C 反应蛋白和血清淀粉样蛋白 A 也可通过激活内皮细胞和血小板间接促进血栓形成[41]-[43]。蛋白质作为氨基酸的重要来源，其摄入水平可调控肝脏 Apo 的合成，进而影响血浆脂蛋白的组装与脂质转运。某些 Apo 除参与脂质代谢外，还具有调节凝血和纤溶的双重作用[44] [45]。白蛋白是人体最主要的血浆蛋白，在静脉血栓形成中也起着重要调节作用[46] [47]。一项双向 MR 研究发现白蛋白水平降低与 VTE 风险增高有关[47]。白蛋白可通过保护和恢复血管内皮细胞的糖萼来降低血管通透性，以减少血小板粘附[46]。这种内皮保护机制可能与防止血栓形成有关。并且白蛋白还可抑制细胞因子产生，发挥抗炎作用，从而降低血栓风险[48] [49]。目前仅有少数研究直接探讨蛋白质摄入与 VTE 的因果关联。Saran 等利用结肠癌-VTE 小鼠模型发现高色氨酸饮食会增加癌症相关 VTE 的风险[50]，然而另一项动物实验发现乳清蛋白浓缩物具有时间和剂量依赖性抗血栓作用[51]。

总体而言，蛋白质在静脉血栓形成中发挥着重要调节作用。除了特定的抗凝蛋白的缺乏或异常会增加血栓风险外，体内某些 Apo 以及白蛋白水平的降低也会使静脉血栓形成风险升高，这提示我们平衡营养需求或许可以预防静脉血栓形成。并且在临床中，可通过监测一些易获取的生化指标(如 Apo、白蛋白)评估血栓风险，进行相应干预以达到预防 VTE 的目的。

2.3. 碳水化合物

碳水化合物是人体最主要的能量来源，可维持人体的基础代谢、神经传导等生命活动，其代谢还会直接影响机体血糖稳态。研究表明，血糖升高或许在 VTE 的发生中起到推动作用[52]。

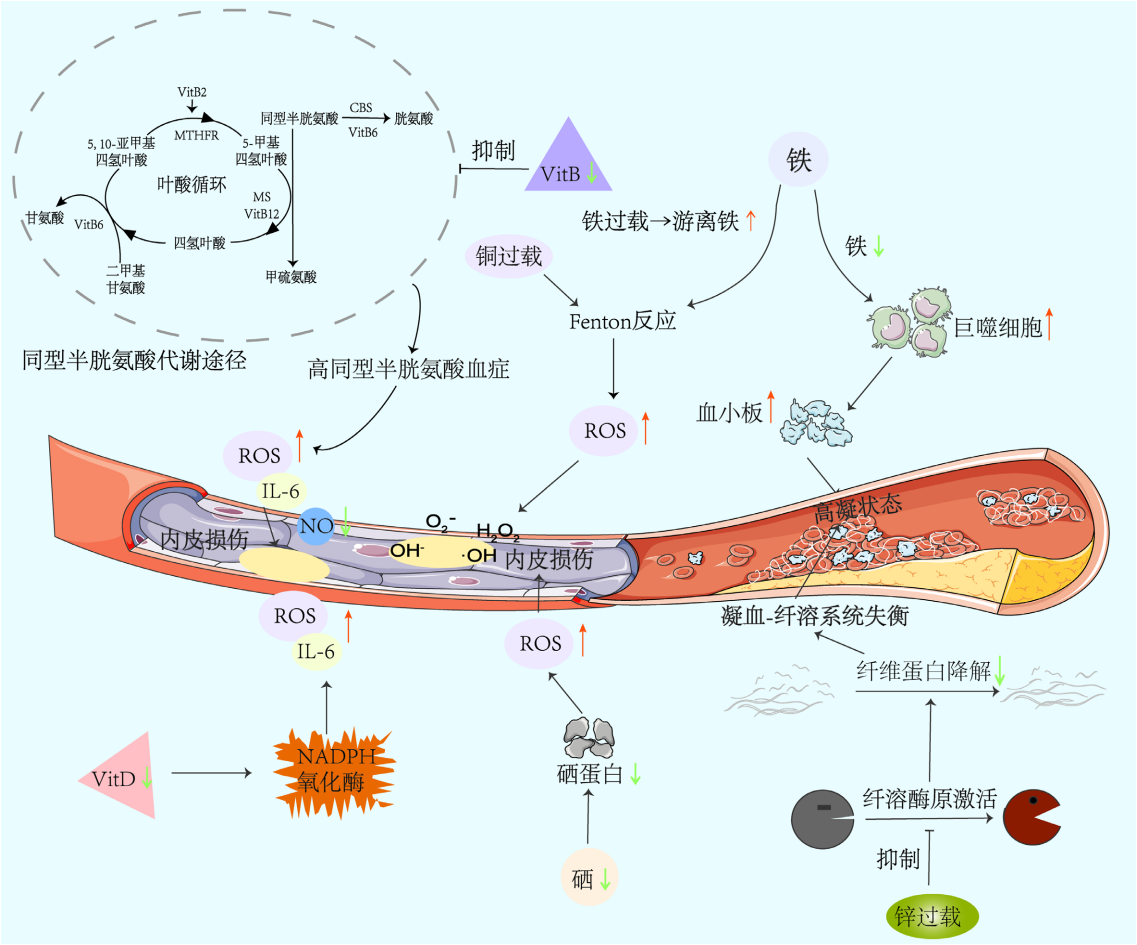
高糖饮食可通过诱发胰岛素抵抗与持续性高血糖，上调促凝介质的水平，从而导致血液高凝状态[53]。同时，过量糖分摄入会诱导氧化应激，产生大量活性氧(reactive oxygen species, ROS)从而损伤血管内皮完整性，为血栓形成创造前提条件[54]。高浓度血浆同型半胱氨酸(homocysteine, Hcy)可损伤血管内皮、导致抗凝系统功能障碍，进而诱发血栓形成[55]。Zhang 等发现 Hcy 浓度与各类添加果糖的饮料及食品摄入量呈正相关[56]，提示高果糖饮食可能通过升高 Hcy 水平间接促进血栓形成。此外，一项双样本 MR 发现偏好含糖咖啡和高糖芝士蛋糕可能会增加肺栓塞的风险[57]，侧面验证高糖饮食也许是 VTE 的危险因素。

目前碳水化合物的摄入与 VTE 关系尚不明确，高糖饮食可能是 VTE 发生发展的可调控危险因素，或许可以通过限制添加糖摄入、减少高糖饮食、优化碳水化合物摄入结构等来降低 VTE 风险。

3. 微量营养素与 VTE 的关系

微量营养素包括微量元素和维生素，尽管机体每日需求量较低，但其在维持机体正常生理功能、保

障生长发育方面均具有至关重要的作用[58] [59]。该类营养素除参与机体基础代谢外，还可通过调节血管功能、参与氧化应激及炎症反应等多种途径，直接或间接对血管壁的结构与稳定性产生影响[60]，其作用机制复杂多样，图 1 仅展示了主要机制[55] [61]-[67]。其中，锌过载能够抑制纤溶酶原激活，延缓纤维蛋白降解，在分子层面具备促血栓形成的潜力，但现有研究未发现血清锌水平与 VTE 风险存在明确关联，这一矛盾现象可能是因为目前对锌调控 VTE 的深层机制探索尚不彻底，且相关研究偏少、部分研究存在设计偏倚或样本量不足等局限；血清铜以及其他微量元素水平与 VTE 风险的关联同样缺乏一致证据，整体提示微量元素与 VTE 的关联存在显著的复杂性以及不确定性。



注：VitB6，维生素 B6；VitB2，维生素 B2；MTHFR，5,10-methylenetetrahydrofolate reductase，5,10-亚甲基四氢叶酸还原酶；MS，methionine Synthase，甲硫氨酸合酶；VitB12，维生素 B12；ROS，reactive oxygen species，活性氧，包括·OH、H_2O_2 等；IL-6，白细胞介素 6；NO，一氧化氮；Fenton 反应，Fe^{2+}催化 H_2O_2 生成羟自由基·OH，放大氧化应激，Cu^{2+}也可参与该反应。

Figure 1. Mechanism of VTE regulation by micronutrients
图 1. 微量营养素调控 VTE 机制

现有研究发现，血清铁水平升高或许会增加 VTE 风险，而缺铁则可能导致 VTE 复发；血清铜、锌水平与 VTE 风险无明显关联，关于微量元素与 VTE 风险的相关研究总结于表 1。

维生素 B、C、D、E 与 VTE 风险的关联尚存争议，有研究显示二者无相关性，亦有研究证实补充上述维生素可降低 VTE 风险，现有多项基于人群大型研究的结果存在矛盾，相关研究汇总于表 2。

Table 1. Studies on the relationship between trace elements and VTE risk
表 1. 微量元素与 VTE 风险的相关研究

作者	发表年份	研究类型	观察指标	结论
Potaczek 等[68]	2016	前瞻性队列研究	血清铁蛋白	缺铁可能是无诱因性 VTE 复发的危险因素
Gill 等[69]	2019	孟德尔随机化研究	血清铁、铁蛋白、转铁蛋白饱和度	血清铁水平升高会增加 VTE 风险
Signorelli 等[70]	2024	病例对照研究	血浆铁	铁过载可能是 VTE 的危险因素
Kunutsor 等[71]	2022	前瞻性队列研究	血清锌	在中老年芬兰男性中，血清锌水平与 VTE 风险无关
Kunutsor 等[72]	2021	前瞻性队列研究	血清铜	在中年男性人群中，血清铜水平与 VTE 风险无关
Ferrante 等[73]	2017	病例对照研究	头发中铜、锌	DVT 患者头发中必需金属铜、锌的浓度低于对照组，微量元素缺乏或许参与 DVT 发病过程

Table 2. Relevant studies on the association between vitamins and VTE risk
表 2. 维生素与 VTE 风险的相关研究

作者	发表年份	研究类型	观察指标	结论
Xiang 等[74]	2025	前瞻性队列研究	血清 25-羟基维生素 D	血清 25-羟基维生素 D 水平与 VTE 风险呈负相关，尤其是在糖尿病患者中
Blondon 等[75]	2015	随机对照试验	是否补充维生素 D + 钙	联合补充维生素 D + 钙未降低绝经后女性总体 VTE 风险，但降低了特发性 VTE 风险
Andro 等[76]	2016	病例对照研究	血清 25-羟基维生素 D	维生素 D 水平与老年人群 VTE 风险无关
Cattaneo 等[77]	2001	病例对照研究	血浆维生素 B6	低血浆维生素 B6 水平与 DVT 风险升高独立相关
Hron 等[78]	2007	前瞻性队列研究	血浆维生素 B6	血浆维生素 B6 偏低是 VTE 复发的危险因素
Shu 等[79]	2017	随机对照试验	是否补充叶酸和维生素 B12	补充叶酸和维生素 B12 可以降低高同型半胱氨酸血症患者的 DVT 复发率
Heijer 等[80]	2007	随机对照试验	是否补充维生素 B	通过补充 B 族维生素降低同型半胱氨酸并不能预防复发性 VTE
Glynn 等[81]	2007	随机对照试验	是否补充维生素 E	补充维生素 E 可能会降低女性的 VTE 风险
Sulaiman 等[82]	2021	回顾性队列研究	是否补充维生素 C	在 COVID-19 重症患者中使用低剂量维生素 C 与较低的 VTE 发生率有关
Vučković 等[83]	2015	病例对照研究	是否补充维生素	补充维生素 B、C、D、E 与降低 VTE 风险无关

目前关于微量营养素与 VTE 关系的研究多为观察性研究，二者之间的因果关系尚未明确；部分研究存在样本量偏小、研究对象局限于特定人群(如男性、欧洲人群)等问题，结果普适性较差。此外，微量营养素的摄入水平受遗传、药物、饮食模式等多种因素的影响[84] [85]，不同地区人群的研究结果存在差异，且其体外检测值不一定反映体内真实水平，二者之间的关系有待进一步验证。

4. 结论

本综述系统梳理了宏量营养素、微量营养素与 VTE 风险的相关研究，在临床层面，均衡饮食(如高蛋白、低脂、低糖饮食)可能会是安全可及的 VTE 预防策略。结合本文结果，临床可将血清铁、铁蛋白、维

生素 D、维生素 B6 等核心营养指标，与外科 Caprini 评分、内科 Padua 评分等现有 VTE 风险评估工具相结合，构建基础血栓风险分层联合营养状态分层的双维度评估体系。对 VTE 高风险且合并维生素 D 缺乏、B 族维生素偏低的人群，可考虑开展营养干预；中低风险人群则保持均衡饮食。老年、肥胖、术后及肿瘤等高危人群，需结合上述营养指标制定个性化干预方案。当前缺乏高质量的随机对照研究来进一步验证营养素与 VTE 之间的因果关系，未来应开展大样本临床研究完善营养风险评估体系，推动营养干预纳入 VTE 标准化预防流程，为 VTE 多维度防治提供更全面的证据支持。

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