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生酮飲食、酮體代謝與心血管風險：從脂質中心論到心臟代謝重編程的新典範

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Abstract

The ketogenic diet (KD) has emerged as a widely adopted metabolic intervention for weight loss, glycemic control, and management of metabolic syndrome. In clinical practice, KD is frequently associated with improvements in insulin resistance, triglyceride levels, and body weight. However, a subset of individuals develops marked elevations in low-density lipoprotein cholesterol (LDL-C), sometimes exceeding traditional high-risk thresholds, raising concerns regarding its potential impact on atherosclerotic cardiovascular disease (ASCVD).

This paradox has led to renewed interest in the heterogeneity of lipid responses to carbohydrate restriction. Notably, the lean mass hyper-responder (LMHR) phenotype—characterized by elevated LDL-C, high high-density lipoprotein cholesterol (HDL-C), and low triglycerides—illustrates that KD does not uniformly induce hypercholesterolemia. These observations challenge the conventional lipid-centric model and suggest that metabolic context, genetic predisposition, and dietary composition play critical roles in modulating cardiovascular risk. Importantly, animal-based fats are not equivalent to saturated fatty acids, and saturated fat intake alone does not necessarily translate directly into atherosclerotic disease.

In parallel, emerging evidence highlights the role of ketone metabolism in cardiac energetics. In heart failure with reduced ejection fraction (HFrEF), the failing myocardium demonstrates increased reliance on ketone bodies as an efficient energy substrate. Clinical studies have shown that β-hydroxybutyrate infusion can improve cardiac output and myocardial perfusion. Furthermore, the benefits of sodium-glucose cotransporter-2 inhibitors (SGLT2i) may be partially mediated through enhanced ketone availability and utilization.

Recent updates in U.S. dietary policy have also acknowledged the limitations of long-standing low-fat, high-carbohydrate recommendations, which have not effectively curbed the rising prevalence of metabolic syndrome. Collectively, these findings suggest that the relationship between KD and cardiovascular risk extends beyond LDL-C alone and reflects a complex interplay between lipid metabolism, energy metabolism, and individual variability. A precision medicine approach is therefore essential for individualized risk assessment and clinical decision-making.

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過去數十年，心血管疾病的預防策略幾乎建立在單一核心假設之上：低密度脂蛋白膽固醇 (LDL-C) 是動脈粥狀硬化的主要驅動因子[1-3]。因此，「降低 LDL-C」被視為最關鍵的治療目標。然而近年來，隨著生酮飲食 (ketogenic diet, KD) 在臨床與社會中的快速普及，一種難以忽視的現象逐漸浮現——在部分患者中，LDL-C 顯著上升的同時，體重、血糖、三酸甘油酯與胰島素阻抗卻同步改善[4]。這種「風險指標與代謝健康脫鉤」的現象，正在挑戰傳統以脂質為中心的風險模型。

在進一步討論之前，需先釐清幾個常見的過度簡化。首先，**生酮飲食並不等同於高膽固醇血症**。臨床觀察顯示，只有一部分族群會出現顯著 LDL-C 上升，其中最具代表性者為「瘦體超高反應者」(lean mass hyper-responder, LMHR)[5]。此類個體通常具備 LDL-C 升高、HDL-C 偏高與三酸甘油酯極低的脂質三聯徵，且多為體型瘦、運動量高且代謝健康者[5]。因此，**LDL-C 反應具有高度個體差異，而非飲食的必然結果**。

其次，在營養學層面，臨床上亦常見過度簡化的脂肪觀念。**動物性脂肪並不等同於飽和脂肪酸，而飽和脂肪酸亦不應被視為心血管阻塞的直接因果因素**。現有研究顯示，不同脂肪酸種類、食物來源及整體飲食結構，均會影響其對心血管風險的實際作用[6,7]。這意味著單一營養素導向的風險判斷，可能忽略更重要的代謝背景。

從公共衛生角度來看，這一轉變亦逐漸反映於政策層面。長期以來，低脂、高碳水飲食被視為預防心血管疾病的主要策略。另一方面，**近期美國飲食建議已逐漸正視：過去過度強調低脂飲食，未能有效改善整體健康，反而與肥胖與代謝症候群的增加並行** (Dietary Guidelines Advisory Committee. 2025; https://www.dietaryguidelines.gov/; https://realfood.gov/)。這一歷史經驗顯示，單一營養素比例並不足以解釋複雜的人體代謝反應。

在機轉層面，LMHR 現象常以「脂質能量模型」解釋，即在碳水攝取極低的狀態下，人體需透過脂蛋白輸送脂質以滿足能量需求，導致 LDL-C 與 HDL-C 同步上升[8]。然而，關鍵問題仍在於：這種代謝適應是否等同於動脈粥狀硬化風險？

目前影像研究提供了部分但尚未定論的答案。部分冠狀動脈電腦斷層血管攝影 (CCTA) 研究顯示，在代謝健康的生酮飲食者中，即使 LDL-C 顯著升高，短期內並未觀察到斑塊負荷顯著增加[9]。然而，動脈粥狀硬化為長期累積過程，現有證據仍不足以排除長期風險。相對而言，大型族群研究則顯示低碳高脂飲食可能與 LDL-C 上升及心血管事件風險增加相關[10]，且個體差異可能與遺傳背景密切相關[11]。

值得注意的是，若僅以膽固醇解釋生酮飲食的影響，可能忽略更關鍵的心臟代謝變化。近年研究顯示，心衰竭，特別是射出分率降低型心衰竭 (HFrEF)，其心肌能量代謝會發生重編程，包括脂肪酸氧化下降與粒線體功能受損[12]。在此背景下，酮體（如 β-羥基丁酸）被證實可作為高效率的替代能量來源[12,13]。臨床研究亦顯示，短期酮體輸注可改善心輸出量與心肌灌流[13]。

此外，鈉 - 葡萄糖共同轉運蛋白 2 抑制劑 (SGLT2 inhibitors) 在心衰竭治療中的顯著成效，亦可能部分透過促進輕度酮症而達成[14]。該類藥物可增加酮體生成並提升心肌利用能力，進而改善心肌能量效率[15]。這一觀點顯示，酮體不僅是飲食產物，更可能是心臟能量代謝中的關鍵調節因子。

因此，生酮飲食所引發的臨床現象，或許不應被簡化為「LDL-C 升高是否危險」的單一問題，而應被視為一個更大的轉變：**從脂質中心論走向心臟代謝醫學 (metabolic cardiology)**。

在臨床實務上，這意味著需要更精準的風險評估方式。對於採行生酮飲食且 LDL-C 顯著升高的患者，應進行整體評估，包括家族史、代謝狀態與必要時的冠狀動脈影像檢查[16]。若

已存在動脈斑塊或 LDL-C 持續高度升高，仍應依循現行證據考慮降脂治療。然而，對於代謝健康且無斑塊證據的個體，則可能需要不同於傳統的風險判讀方式。

總結而言，生酮飲食並非傳統脂質理論的例外，而是揭示其邊界的現象。它提醒我們，動脈粥狀硬化風險不僅來自脂蛋白濃度，更來自整體代謝環境[17]。在精準醫療時代，臨床問題的核心或許不再是「LDL-C 是否升高」，而是：在特定代謝背景下，LDL-C 代表的是風險，還是適應。

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