Advances in Clinical Medicine 临床医学进展, 2026, 16(2), 2779-2787
Published Online February 2026 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2026.162689

Hans汉斯

瘦素在心血管疾病中作用的研究进展

黄泽雲，武力勇，朱国富*

昆明医科大学第二附属医院心血管内科，云南 昆明

收稿日期：2026年1月12日；录用日期：2026年2月6日；发布日期：2026年2月13日

摘　要

瘦素作为一种多效性脂肪因子，其复杂的心血管调控网络已成为心血管疾病研究的重要靶点。本综述系统阐述了瘦素通过炎症反应、氧化应激、内皮功能障碍、交感神经激活及肾素－血管紧张素－醛固酮系统调控等多重机制，在动脉粥样硬化、高血压、心力衰竭等心血管疾病中的关键作用。

关键词

瘦素，心血管疾病，动脉粥样硬化，高血压，心力衰竭，心房颤动

Research Progress on the Role of Leptin in Cardiovascular Diseases

Zeyun Huang, Liyong Wu, Guofu Zhu*

Department of Cardiology, The Second Affiliated Hospital of Kunming Medical University, Kunming Yunnan

Received: January 12, 2026; accepted: February 6, 2026; published: February 13, 2026

Abstract

Leptin, a pleiotropic adipokine, has emerged as a critical therapeutic target in cardiovascular diseases due to its intricate regulatory network in cardiovascular homeostasis. This review systematically elucidates the pivotal role of leptin in various cardiovascular pathologies, including atherosclerosis, hypertension, heart failure, and atrial fibrillation; mediated through multifaceted mechanisms such as inflammatory cascades, oxidative stress, endothelial dysfunction, sympathetic hyperactivity, and dysregulation of the renin-angiotensin-aldosterone system.

*通讯作者。

文章引用: 黄泽雲, 武力勇, 朱国富. 瘦素在心血管疾病中作用的研究进展[J]. 临床医学进展, 2026, 16(2): 2779-2787. DOI: 10.12677/acm.2026.162689

Keywords

Leptin, Cardiovascular Diseases, Atherosclerosis, Hypertension, Heart Failure, Atrial Fibrillation

1. 引言

心血管疾病是全球范围内发病率和死亡率最高的疾病之一，其病理机制复杂，且与代谢紊乱密切相关。近年来，作为由肥胖基因(obese gene)编码的肽类激素，瘦素(Leptin)因在代谢调节及心血管系统中的多重作用而受到广泛关注。瘦素不仅通过作用于下丘脑调控食欲及交感神经活性，还可直接影响心肌细胞、血管平滑肌细胞和内皮细胞等，从而参与多种心血管疾病的发生与发展过程。本文将围绕近年来瘦素在心血管疾病中的研究进展，重点论述其在相关病理机制中的作用及潜在意义。

2. 概述

瘦素的发现始于 1949 年，当时在杰克逊实验室(Jackson Laboratories)偶然发现了第一种自然发生的隐性单基因突变肥胖小鼠。这些小鼠因其发病早，出现严重肥胖以及明显的糖尿病表型而引人注目，当时相关基因被命名为肥胖基因。1994 年瘦素被发现于肥胖小鼠中[1]。从此我们对瘦素及其功能展开了深入的研究。

2.1. 瘦素结构

瘦素位于 7 号染色体上的瘦素基因，该基因转录为一个由 167 个氨基酸组成的肽，分子量为 16 kD。瘦素基因序列在哺乳动物中高度保守，其属于长链螺旋细胞因子家族[2]，包括白细胞介素(IL-6, IL-11, IL-12)和抑癌素 M [3]。瘦素由四个反向平行的 α 螺旋(A、B、C 和 D)组成，通过两个长交叉连接(AB 和 CD)和一个短环(BC)相连，并以左手扭曲的螺旋束形式排列。这种四螺旋束采用“上–上–下–下”折叠方式，形成由反向平行螺旋对 A/D 与 B/C 构成的双层堆叠结构[4]。

2.2. 瘦素生物学功能

瘦素主要由白色脂肪组织(White Adipose Tissue)分泌，其分泌水平与脂肪组织的量呈正相关[5]。其合成和分泌受多种因素调节，包括胰岛素、类固醇激素、细胞因子、去甲肾上腺素和糖皮质激素等各种激素[6]。瘦素的主要功能是：(1) 调节能量平衡和食欲：其中最著名的是瘦素对弓状核(arcuate nucleus, ARC)的作用。ARC 核在调节食欲和能量稳态方面发挥着重要作用。它含有促进食欲的刺鼠相关蛋白/神经肽 Y (agouti-related peptide/neuropeptide Y, AgRP/NPY)神经元，以及抑制食欲的阿片黑素皮质素原(proopiomelanocortin, POMC)神经元。瘦素作用于 ARC 核，通过刺激 POMC 神经元并抑制 AgRP/NPY 神经元，最终导致食欲下降[7]。(2) 代谢调节：瘦素通过调节胰岛素敏感性，影响血糖水平[8]，通过促进脂肪分解和氧化，减少脂肪合成[9]。(3) 免疫与炎症调节：瘦素是免疫系统的关键调节剂，在先天性和适应性免疫反应中均发挥广泛功能[10]，瘦素已被证明能激活脂肪组织中募集和驻留的免疫细胞(包括巨噬细胞)，诱导产生与炎症过程有关的细胞因子[11]。(4) 内分泌调节：瘦素对下丘脑–垂体–性腺轴的活动有显著影响，可影响睾酮、雌二醇、促卵泡激素的分泌[12]。瘦素通过作用于下丘脑室旁核(PVN)中的促甲状腺激素释

放激素(TRH)神经元来维持甲状腺轴，从而调节甲状腺激素[13]。生长激素可对血清瘦素产生直接的影响[14]。(5) 心血管系统的调节：瘦素可促进炎症因子的释放，诱导心肌细胞的肥大，促进血栓的形成，引起内皮细胞紊乱，产生氧化应激反应等。这些作用机制直接对心血管系统疾病产生影响。近年来瘦素对高血压、动脉粥样硬化、心力衰竭、心房颤动的研究一直是研究的重点。

3. 瘦素与动脉粥样硬化

动脉粥样硬化被定义为大、中动脉的低度慢性炎症。其病变的产生依赖于多个过程，例如内皮细胞的功能障碍，血管平滑肌细胞的迁移及增殖，细胞外基质蛋白的过量产生以及血管壁内皮下层巨噬细胞(泡沫细胞)内脂质的积聚。这些过程加速了动脉血管的硬化，从而增加了心肌梗死的风险[15]，而瘦素参与了其发病过程。

3.1. 瘦素与内皮细胞

动脉粥样硬化的发生始于血管对内皮损伤的初始反应。内皮功能障碍是动脉粥样硬化的早期标志[16]。在高血糖、肥胖、高血脂等危险因素的刺激下，内皮细胞屏障会受损，导致其表面黏附分子(如 VCAM-1、ICAM-1)表达上调。这一变化促使循环中的单核细胞黏附于受损内皮，并迁移至血管内皮下基质的内膜层。同时，内皮细胞结构和功能的改变(如紧密连接破坏)增加了血管通透性，使循环中的脂蛋白颗粒(如 LDL、VLDL)更容易进入血管壁。在内膜层，LDL 被氧化修饰而形成致动脉粥样硬化脂质，而浸润的单核细胞则分化为巨噬细胞。

高瘦素血症会导致内皮功能障碍[17]。瘦素可促进炎症因子例如 C 反应蛋白(CRP)、肿瘤坏死因子-α (TNF-α)的释放[18]。瘦素浓度升高会促使细胞间粘附分子-1(ICAM-1)及血管细胞粘附分子-1 (VCAM-1)的表达[19]，这些分子会与瘦素受体相互作用，进而激活炎症反应的分子机制。这些分子机制也会损伤平滑肌细胞的功能，最终导致内皮依赖性血管扩张受损，从而引发动脉粥样硬化。在肥胖大鼠中，瘦素已被证实会使动脉内皮细胞依赖性血管舒张被阻断。Jamroz-Wisniewska [20]等人认为，在高瘦素血症肥胖大鼠模型中会存在一氧化氮(NO)生成不足的情况，但内皮源性超极化因子(EDHF)的代偿性上调可在一定程度上弥补这一缺陷，而该上调过程部分依赖于硫化氢(H_2S)的介导作用。Sebastian [21]认为，瘦素也可上调神经元型一氧化氮合酶(nNOS)表达，从而触发对 NO 缺少的补偿机制，以维持内皮依赖性舒张。这种对内皮细胞舒张作用的特异性反应，可能与瘦素抵抗有关。瘦素抵抗可能是与 caveolin-1 蛋白的表达增加以及 caveolin-1 依赖的瘦素反馈机制有关[22]。

瘦素可能通过增加活性氧(ROS)的生成来触发氧化应激，ROS 是被认为是内皮功能障碍的主要原因[23]。高瘦素水平可诱导 ROS 的形成，主要是由于烟酰胺腺嘌呤二核苷酸磷酸(NADPH)氧化酶的活化所导致[24]。ROS 的增加会阻碍内皮的舒张功能，从而引发内皮功能障碍及动脉粥样硬化。

瘦素对内皮细胞短时间的作用可能通过增加 NO 的生成，对心血管系统产生有益作用。而长时间的作用内皮细胞会导致 NO 减少，超氧化物($O2^-$)和过氧亚硝酸盐($ONOO^-$)生成增加，最终导致内皮损伤，增加患动脉粥样硬化的风险[25]。

3.2. 瘦素与平滑肌细胞

平滑肌细胞的迁移和增殖是发生动脉粥样硬化的关键。瘦素能通过增强基质金属蛋白酶-9 (MMP-9)表达来增加平滑肌细胞迁移[26]，也可促进细胞周期 G1 期-S 期的转变来刺激平滑肌细胞的增殖，这一过程通过 ERK1/2 和 NF-κB 通路发挥作用[27]。瘦素可调节肌动蛋白的表达来影响细胞的迁移和增殖[15]。瘦素不仅可直接促进动脉粥样硬化斑块的不稳定性，还在易损斑块的平滑肌细胞(SMCs)中表现出显著增

强的局部合成能力[28]。值得注意的是，这些平滑肌细胞分泌的基质金属蛋白酶(MMP)能够特异性降解细胞外基质中的胶原蛋白[29]，这一机制在斑块纤维帽变薄和最终破裂过程中起着至关重要的作用。瘦素还能增加平滑肌细胞培养中促炎细胞因子(如 TNF-α 和 IL-1β)的表达及增加活性氧的形成[15] [30]。瘦素也可促进平滑肌细胞转化为成骨样细胞，并伴随有矿化作用。在小鼠模型中通过 2 个月持续给予瘦素，显著增加了血管的钙化程度及骨桥蛋白、骨钙素等成骨标志物[31]。Zeadin [32]的研究发现，用瘦素处理培养的牛主动脉平滑肌细胞(BASMC)能够剂量依赖性地诱导成骨细胞分化，研究结果提示瘦素在体内可能促进成骨细胞分化和血管钙化的机制。

3.3. 瘦素与巨噬细胞

单核－巨噬细胞在动脉粥样硬化发生发展中扮演着重要角色。单核细胞在趋化因子引导下浸润血管内膜后，会分化为巨噬细胞并大量吞噬氧化型低密度脂蛋白(ox-LDL)，形成泡沫细胞这是动脉粥样硬化的标志性病变。瘦素是单核细胞和巨噬细胞的强效趋化剂，浓度为 1 ng/ml 时即可诱导最大趋化反应[33]。这一机制可能促进单核细胞向血管内膜的迁移，加剧病变。高瘦素水平也会增强人类单核细胞中炎症因子 TNF-α、IL-6 和 IL-1β 的表达[34]。动脉粥样硬化的一个典型特征是巨噬细胞来源的泡沫细胞大量聚集。之前有研究表明，过氧化物酶体增生激活受体 γ (PPAR-γ)在冠状动脉脂质蓄积的巨噬细胞中高表达，同时它还与巨噬细胞分化和炎症反应相关[35]。随后 Cabrero [36]等人就发现，PPARγ 在巨噬细胞和泡沫细胞中的表达下调可能是高瘦素水平与心血管疾病发生发展的重要联系机制之一。这提示瘦素可能通过抑制 PPARγ，加剧脂质蓄积和炎症反应。

4. 瘦素与高血压

4.1. 瘦素通过影响交感神经升高血压

瘦素通过作用于下丘脑，调控交感神经活动从而影响血压的变化[37]。Rahmouni [38]等人将 500 ng 的瘦素注射到下丘脑弓状核中可激活肾脏交感神经并升高动脉压。Samuelsso [39]等发现瘦素可作用在下丘脑黑皮质素系统的信号通路，来影响肾交感神经活动和血压。瘦素也可通过调节延髓腹侧前区(RVLM)来影响血压及肾交感神经活动[40]。RVLM 是交感神经系统的主要调节器，它向交感神经节前神经元发送兴奋性纤维，以调节交感神经对阻力血管和血压的控制。

4.2. 瘦素通过影响 RAAS 系统升高血压

在高脂饮食的大鼠中，瘦素可增强血管紧张素II的升压效应，其机制涉及中枢肾素－血管紧张素系统(RAS)和促炎细胞因子(PICs)的上调[41]。瘦素也可能在一定程度上通过调节醛固酮分泌来介导肥胖对血压的影响[42]。在难治性高血压患者中，瘦素水平较高，其原因与血浆醛固酮和血压水平升高有关[43]。金卫东[44]等人发现，在肥胖高血压患者中，瘦素与肾素、血管紧张素II和醛固酮水平均呈正相关。

4.3. 瘦素通过损伤内皮细胞升高血压

内皮细胞的舒张因子 NO 及内皮细胞收缩因子内皮素(ET-1)的失衡是导致高血压内皮功能障碍的原因之一[45]。Schinzari [46]等，在健康个体中发现，急性瘦素输注会同时提高 ET-1 和 NO 活性，表明二者对血管张力的调控平衡。但在代谢综合征患者中，这种同步调节失衡，而高瘦素状态可能偏向 ET-1 主导的血管收缩效应。Juan [47]等人认为，瘦素可增加与 ET-1 的结合，这个过程且呈时间和剂量依赖性，最终导致高血压的发生。

4.4. 瘦素通过炎症及氧化应激升高血压

在肥胖患者中发现一些炎症因子会增加，同时瘦素处于高表达状态，在这些人群中患高血压的风险更大[48]。Chen [49]认为瘦素与 C-反应蛋白(CPR)存在相关性，人群中 CRP 与肥胖和血浆瘦素水平升高相关。然而在一项针对高血压患者的研究中，并没有发现这种相关性[50]。瘦素可刺激大鼠肾小管上皮细胞(NRK-52E)诱导氧化应激和炎症[51]。瘦素通过对炎症因子及氧化应激损伤血管内皮及产生缩血管效应，引起血压升高。

5. 瘦素与心力衰竭

Wannathee [52]等人对 4080 名年龄在 60 至 79 岁之间的男性进行了研究，血清瘦素水平与心力衰竭(heart failure)发病风险的关系存在显著差异，对于无冠心病病史者，基线瘦素水平升高可显著增加心衰发生风险，而在已确诊冠心病患者中，瘦素水平与心衰发病率仅表现出有限的关联性。一项荟萃分析也发现心力衰竭患者的瘦素水平显著高于健康个体[53]。研究发现，高瘦素水平已可用于评估心力衰竭的严重程度[54]。大多数学者认为神经内分泌系统的过度激活是心力衰竭发生重塑重构的原因。瘦素可直接引起心肌细胞的肥大[55]。在缺血再灌注的状态下，瘦素会增加心肌细胞纤维化，加重心肌功能障碍[56]。在肥胖患者中，瘦素会抑制心脏的收缩功能，增加对心肌细胞的损伤[57]。研究指出瘦素通过 ET-1 受体和 NADPH 氧化酶途径抑制心肌收缩[58]。

在射血分数保留型心衰(HFpEF)中，瘦素作为核心驱动因素，通过慢性高瘦素血症介导肥胖相关代谢异常，引发全身炎症反应、交感神经过度激活、动脉硬化及心肌重构等病理过程，最终导致特征性的舒张功能障碍。而在射血分数降低型心衰(HFrEF)中，瘦素水平升高则继发于心肌损伤后的神经激素激活和低灌注状态，通过放大炎症与心脏重塑而加重病情[59]。

也有研究发现，瘦素在中枢神经系统对心脏功能具有双向调节作用：在过氧化物酶体增殖物激活受体 β/δ (PPARβ/δ)信号通路正常的情况下，瘦素既能诱导心室萎缩，又能发挥心脏保护效应；而一旦 PPARβ/δ 信号通路受到抑制，瘦素的心脏保护作用即被消除[60]。

6. 瘦素与房颤

Anaszewicz [61]等发现房颤患者的脂肪量更大，血清瘦素水平更高，高瘦素血症略微增加房颤风险。Zhu [62]等发现在新发阵发性房颤患者中，脂联素与瘦素的比值与心脏自主神经功能相关。Li [63]等认为提高脂联素、降低瘦素的治疗策略可能有利于控制房颤。López-Canoa [64]等人发现脂肪酸结合蛋白 4 (FABP4)和瘦素水平与心房颤动(AF)负荷的关系存在显著的性别差异。关于瘦素与心房颤动的病理生理关联机制仍有待更深入的探索。

7. 治疗展望

随着对瘦素作用机制认识的不断深入，针对瘦素信号通路的干预策略逐渐成为心血管疾病潜在的治疗方向。理论上，通过改善瘦素抵抗状态，降低慢性高瘦素血症所介导的炎症反应、交感神经系统过度激活及内皮功能障碍，或可为心血管疾病的防治提供新的思路。然而，目前直接应用瘦素补充治疗在肥胖及心血管疾病中的疗效仍然有限，其主要障碍在于外周及中枢瘦素抵抗的普遍存在。因此，相较于单纯补充瘦素，瘦素增敏剂被认为更具临床转化潜力，其通过改善瘦素受体信号转导、恢复下游通路(如 JAK/STAT、PI3K/Akt)的生物学效应，可能在减轻心血管损伤方面发挥积极作用，但相关研究仍主要停留在基础和动物实验阶段，尚缺乏充分的临床证据支持。一些已广泛应用于代谢性疾病治疗的药物显示出对瘦素水平及其相关病理通路的间接调控作用。例如，钠－葡萄糖协同转运蛋白 2 (SGLT2)抑制剂不仅可

改善糖脂代谢和体重状态，还可降低系统性炎症水平、改善内皮功能并调节交感神经活性，其心血管获益可能部分通过调控瘦素及其相关信号网络实现。类似地，胰高血糖素样肽-1 (GLP-1)受体激动剂通过减重、改善胰岛素抵抗及抑制炎症反应，已被证实可降低血清瘦素水平或改善瘦素/脂联素比值，从而在动脉粥样硬化、高血压及心力衰竭等疾病中发挥心血管保护作用。

目前大量学者已对瘦素在心血管疾病中的作用机制开展了深入研究，这些研究成果为阐明疾病发生发展机制及探索治疗新策略奠定了重要理论基础。现有研究已系统揭示了瘦素在多种心血管病变中的调控作用，这些发现不仅深化了我们对心血管疾病的认识，更为基础研究与临床转化应用提供了关键科学依据。需要指出的是，现有研究多基于“高瘦素血症”与疾病表型之间的相关性，而未充分区分瘦素水平升高与瘦素信号有效传导之间的差异。在肥胖及代谢异常状态下，机体普遍存在外周及中枢瘦素抵抗，其特征为瘦素受体敏感性下降及下游信号通路活性受损。在此背景下，高循环瘦素水平并不等同于瘦素生物学效应增强，其对心血管系统的影响可能呈现复杂甚至双向特征。一方面，高瘦素血症可通过非经典或组织特异性通路持续激活炎症反应、氧化应激及交感神经系统；另一方面，经典瘦素信号的缺失可能削弱其代谢调控及心肌保护等生理作用。因此，有必要区分高瘦素血症的病理效应与瘦素信号缺失的生理后果，以更准确理解其在心血管疾病发生发展中的角色。

基金项目

项目名称：昆明医科大学硕士研究生创新基金；项目编号：2025S087。

参考文献

[1] Münzberg, H., Heymsfield, S.B., Berthoud, H. and Morrison, C.D. (2024) History and Future of Leptin: Discovery, Regulation and Signaling. *Metabolism*, **161**, Article ID: 156026. https://doi.org/10.1016/j.metabol.2024.156026

[2] Münzberg, H. and Morrison, C.D. (2015) Structure, Production and Signaling of Leptin. *Metabolism*, **64**, 13-23. https://doi.org/10.1016/j.metabol.2014.09.010

[3] Paz-Filho, G., Mastronardi, C., Wong, M. and Licinio, J. (2012) Leptin Therapy, Insulin Sensitivity, and Glucose Homeostasis. *Indian Journal of Endocrinology and Metabolism*, **16**, S549-S555. https://doi.org/10.4103/2230-8210.105571

[4] Zhang, F., Chen, Y., Heiman, M. and DiMarchi, R. (2005) Leptin: Structure, Function and Biology. In: *Vitamins & Hormones*, Elsevier, 345-372. https://doi.org/10.1016/s0083-6729(05)71012-8

[5] Nakagawa, T. and Hosoi, T. (2023) Recent Progress on Action and Regulation of Anorexigenic Adipokine Leptin. *Frontiers in Endocrinology*, **14**, Article ID: 1172060. https://doi.org/10.3389/fendo.2023.1172060

[6] Lee, M., Wang, Y., Ricci, M.R., Sullivan, S., Russell, C.D. and Fried, S.K. (2007) Acute and Chronic Regulation of Leptin Synthesis, Storage, and Secretion by Insulin and Dexamethasone in Human Adipose Tissue. *American Journal of Physiology-Endocrinology and Metabolism*, **292**, E858-E864. https://doi.org/10.1152/ajpendo.00439.2006

[7] Qi, Y., Lee, N.J., Ip, C.K., Enriquez, R., Tasan, R., Zhang, L., *et al*. (2023) AGRP-Negative Arcuate NPY Neurons Drive Feeding under Positive Energy Balance via Altering Leptin Responsiveness in POMC Neurons. *Cell Metabolism*, **35**, 979-995.e7. https://doi.org/10.1016/j.cmet.2023.04.020

[8] Casado, M.E., Collado-Pérez, R., Frago, L.M. and Barrios, V. (2023) Recent Advances in the Knowledge of the Mechanisms of Leptin Physiology and Actions in Neurological and Metabolic Pathologies. *International Journal of Molecular Sciences*, **24**, Article No. 1422. https://doi.org/10.3390/ijms24021422

[9] Shimabukuro, M. (2017) Leptin Resistance and Lipolysis of White Adipose Tissue: An Implication to Ectopic Fat Disposition and Its Consequences. *Journal of Atherosclerosis and Thrombosis*, **24**, 1088-1089. https://doi.org/10.5551/jat.ed083

[10] Kiernan, K. and MacIver, N.J. (2021) The Role of the Adipokine Leptin in Immune Cell Function in Health and Disease. *Frontiers in Immunology*, **11**, Article ID: 622468. https://doi.org/10.3389/fimmu.2020.622468

[11] Monteiro, L., Pereira, J.A.d.S., Palhinha, L. and Moraes-Vieira, P.M.M. (2019) Leptin in the Regulation of the Immunometabolism of Adipose Tissue-Macrophages. *Journal of Leukocyte Biology*, **106**, 703-716. https://doi.org/10.1002/jlb.mr1218-478r

[12] Al-Hussaniy, H.A., Alburghaif, A.H. and Naji, M.A. (2021) Leptin Hormone and Its Effectiveness in Reproduction,

Metabolism, Immunity, Diabetes, Hopes and Ambitions. *Journal of Medicine and Life*, **14**, 600-605. https://doi.org/10.25122/jml-2021-0153

[13] Flier, J.S., Harris, M. and Hollenberg, A.N. (2000) Leptin, Nutrition, and the Thyroid: The Why, the Wherefore, and the Wiring. *Journal of Clinical Investigation*, **105**, 859-861. https://doi.org/10.1172/jci9725

[14] Elimam, A., Norgren, S. and Marcus, C. (2001) Effects of Growth Hormone Treatment on the Leptin System and Body Composition in Obese Prepubertal Boys. *Acta Paediatrica*, **90**, 520-525. https://doi.org/10.1080/080352501750197656

[15] Hariri, M.A., Jaffa, M.A., Saoud, R., Zhao, J., Zhu, R., Jaffa, A.A., *et al*. (2020) Vascular Cells Proteome Associated with Bradykinin and Leptin Inflammation and Oxidative Stress Signals. *Antioxidants*, **9**, Article No. 1251. https://doi.org/10.3390/antiox9121251

[16] Mudau, M., Genis, A., Lochner, A. and Strijdom, H. (2012) Endothelial Dysfunction: The Early Predictor of Atherosclerosis. *Cardiovascular Journal of Africa*, **23**, 222-231. https://doi.org/10.5830/cvja-2011-068

[17] Kwaifa, I.K., Bahari, H., Yong, Y.K. and Noor, S.M. (2020) Endothelial Dysfunction in Obesity-Induced Inflammation: Molecular Mechanisms and Clinical Implications. *Biomolecules*, **10**, Article No. 291. https://doi.org/10.3390/biom10020291

[18] Singh, P., Hoffmann, M., Wolk, R., Shamsuzzaman, A.S.M. and Somers, V.K. (2007) Leptin Induces C-Reactive Protein Expression in Vascular Endothelial Cells. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **27**, e302-e307. https://doi.org/10.1161/atvbaha.107.148353

[19] Manuel-Apolinar, L., López-Romero, R., Zarate, A., *et al*. (2013) Leptin Mediated ObRb Receptor Increases Expression of Adhesion Intercellular Molecules and Cyclooxygenase 2 on Murine Aorta Tissue Inducing Endothelial Dysfunction. *International Journal of Clinical and Experimental Medicine*, **6**, 192-196.

[20] Jamroz-Wiśniewska, A., Gertler, A., Solomon, G., Wood, M.E., Whiteman, M. and Bełtowski, J. (2014) Leptin-Induced Endothelium-Dependent Vasorelaxation of Peripheral Arteries in Lean and Obese Rats: Role of Nitric Oxide and Hydrogen Sulfide. *PLOS ONE*, **9**, e86744. https://doi.org/10.1371/journal.pone.0086744

[21] Benkhoff, S., Loot, A.E., Pierson, I., Sturza, A., Kohlstedt, K., Fleming, I., *et al*. (2012) Leptin Potentiates Endothelium-Dependent Relaxation by Inducing Endothelial Expression of Neuronal NO Synthase. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **32**, 1605-1612. https://doi.org/10.1161/atvbaha.112.251140

[22] Singh, P., Peterson, T.E., Sert-Kuniyoshi, F.H., Jensen, M.D. and Somers, V.K. (2011) Leptin Upregulates Caveolin-1 Expression: Implications for Development of Atherosclerosis. *Atherosclerosis*, **217**, 499-502. https://doi.org/10.1016/j.atherosclerosis.2010.10.012

[23] Teixeira, T.M., da Costa, D.C., Resende, A.C., Soulage, C.O., Bezerra, F.F. and Daleprane, J.B. (2017) Activation of Nrf2-Antioxidant Signaling by 1,25-Dihydroxycholecalciferol Prevents Leptin-Induced Oxidative Stress and Inflammation in Human Endothelial Cells. *The Journal of Nutrition*, **147**, 506-513. https://doi.org/10.3945/jn.116.239475

[24] Morawietz, H. and Bornstein, S.R. (2006) Leptin, Endothelin, NADPH Oxidase, and Heart Failure. *Hypertension*, **47**, e20. https://doi.org/10.1161/01.hyp.0000218452.18010.fb

[25] Korda, M., Kubant, R., Patton, S. and Malinski, T. (2008) Leptin-Induced Endothelial Dysfunction in Obesity. *American Journal of Physiology-Heart and Circulatory Physiology*, **295**, H1514-H1521. https://doi.org/10.1152/ajpheart.00479.2008

[26] Tsai, Y.C., Leu, S.Y., Peng, Y.J., *et al*. (2016) Genistein Suppresses Leptin-Induced Proliferation and Migration of Vascular Smooth Muscle Cells and Neointima Formation. *Journal of Cellular and Molecular Medicine*, **21**, 422-431. https://doi.org/10.1111/jcmm.12986

[27] Huang, F., Xiong, X., Wang, H., You, S. and Zeng, H. (2010) Leptin-Induced Vascular Smooth Muscle Cell Proliferation via Regulating Cell Cycle, Activating ERK1/2 and NF-*κ*B. *Acta Biochimica et Biophysica Sinica*, **42**, 325-331. https://doi.org/10.1093/abbs/gmq025

[28] Schneiderman, J., Schaefer, K., Kolodgie, F.D., Savion, N., Kotev-Emeth, S., Dardik, R., *et al*. (2012) Leptin Locally Synthesized in Carotid Atherosclerotic Plaques Could Be Associated with Lesion Instability and Cerebral Emboli. *Journal of the American Heart Association*, **1**, e001727. https://doi.org/10.1161/jaha.112.001727

[29] Olejarz, W., Łacheta, D. and Kubiak-Tomaszewska, G. (2020) Matrix Metalloproteinases as Biomarkers of Atherosclerotic Plaque Instability. *International Journal of Molecular Sciences*, **21**, Article No. 3946. https://doi.org/10.3390/ijms21113946

[30] Schroeter, M.R., Leifheit-Nestler, M., Hubert, A., Schumann, B., Glückermann, R., Eschholz, N., *et al*. (2013) Leptin Promotes Neointima Formation and Smooth Muscle Cell Proliferation via NADPH Oxidase Activation and Signalling in Caveolin-Rich Microdomains. *Cardiovascular Research*, **99**, 555-565. https://doi.org/10.1093/cvr/cvt126

[31] Zeadin, M., Butcher, M., Werstuck, G., Khan, M., Yee, C.K. and Shaughnessy, S.G. (2009) Effect of Leptin on Vascular Calcification in Apolipoprotein E-Deficient Mice. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **29**, 2069-2075. https://doi.org/10.1161/atvbaha.109.195255

[32] Zeadin, M.G., Butcher, M.K., Shaughnessy, S.G. and Werstuck, G.H. (2012) Leptin Promotes Osteoblast Differentiation and Mineralization of Primary Cultures of Vascular Smooth Muscle Cells by Inhibiting Glycogen Synthase Kinase (GSK)-3*β*. *Biochemical and Biophysical Research Communications*, **425**, 924-930. https://doi.org/10.1016/j.bbrc.2012.08.011

[33] Gruen, M.L., Hao, M., Piston, D.W. and Hasty, A.H. (2007) Leptin Requires Canonical Migratory Signaling Pathways for Induction of Monocyte and Macrophage Chemotaxis. *American Journal of Physiology-Cell Physiology*, **293**, C1481-C1488. https://doi.org/10.1152/ajpcell.00062.2007

[34] Tsiotra, P.C., Boutati, E., Dimitriadis, G. and Raptis, S.A. (2013) High Insulin and Leptin Increase Resistin and Inflammatory Cytokine Production from Human Mononuclear Cells. *BioMed Research International*, **2013**, Article ID: 487081. https://doi.org/10.1155/2013/487081

[35] Chawla, A., Barak, Y., Nagy, L., Liao, D., Tontonoz, P. and Evans, R.M. (2001) PPAR-*γ* Dependent and Independent Effects on Macrophage-Gene Expression in Lipid Metabolism and Inflammation. *Nature Medicine*, **7**, 48-52. https://doi.org/10.1038/83336

[36] Cabrero, À., Cubero, M., Llaverías, G., Alegret, M., Sánchez, R., Laguna, J.C., *et al*. (2005) Leptin Down-Regulates Peroxisome Proliferator-Activated Receptor gamma (PPAR-*γ*) mRNA Levels in Primary Human Monocyte-Derived Macrophages. *Molecular and Cellular Biochemistry*, **275**, 173-179. https://doi.org/10.1007/s11010-005-1353-8

[37] Rahmouni, K. (2010) Leptin-Induced Sympathetic Nerve Activation: Signaling Mechanisms and Cardiovascular Consequences in Obesity. *Current Hypertension Reviews*, **6**, 104-109. https://doi.org/10.2174/157340210791170994

[38] Rahmouni, K. and Morgan, D.A. (2007) Hypothalamic Arcuate Nucleus Mediates the Sympathetic and Arterial Pressure Responses to Leptin. *Hypertension*, **49**, 647-652. https://doi.org/10.1161/01.hyp.0000254827.59792.b2

[39] Samuelsson, A. (2014) New Perspectives on the Origin of Hypertension: The Role of the Hypothalamic Melanocortin System. *Experimental Physiology*, **99**, 1110-1115. https://doi.org/10.1113/expphysiol.2014.080374

[40] Barnes, M.J. and McDougal, D.H. (2014) Leptin into the Rostral Ventral Lateral Medulla (RVLM) Augments Renal Sympathetic Nerve Activity and Blood Pressure. *Frontiers in Neuroscience*, **8**, Article No. 232. https://doi.org/10.3389/fnins.2014.00232

[41] Xue, B., Yu, Y., Zhang, Z., Guo, F., Beltz, T.G., Thunhorst, R.L., *et al*. (2016) Leptin Mediates High-Fat Diet Sensitization of Angiotensin II-Elicited Hypertension by Upregulating the Brain Renin-angiotensin System and Inflammation. *Hypertension*, **67**, 970-976. https://doi.org/10.1161/hypertensionaha.115.06736

[42] Xie, D. and Bollag, W.B. (2016) Obesity, Hypertension and Aldosterone: Is Leptin the Link? *Journal of Endocrinology*, **230**, F7-F11. https://doi.org/10.1530/joe-16-0160

[43] de Haro Moraes, C., Figueiredo, V.N., de Faria, A.P.C., Barbaro, N.R., Sabbatini, A.R., Quinaglia, T., *et al*. (2012) High-circulating Leptin Levels Are Associated with Increased Blood Pressure in Uncontrolled Resistant Hypertension. *Journal of Human Hypertension*, **27**, 225-230. https://doi.org/10.1038/jhh.2012.29

[44] 金卫东, 李艳茹, 陈娟. 肥胖高血压患者血清瘦素与肾素-血管紧张素-醛固酮系统的相关性研究[J]. 中国心血管杂志, 2017, 22(2): 98-102.

[45] Tang, E.H.C. and Vanhoutte, P.M. (2010) Endothelial Dysfunction: A Strategic Target in the Treatment of Hypertension? *Pflügers Archiv-European Journal of Physiology*, **459**, 995-1004. https://doi.org/10.1007/s00424-010-0786-4

[46] Schinzari, F., Tesauro, M., Rovella, V., Di Daniele, N., Mores, N., Veneziani, A., *et al*. (2013) Leptin Stimulates both Endothelin-1 and Nitric Oxide Activity in Lean Subjects but Not in Patients with Obesity-Related Metabolic Syndrome. *The Journal of Clinical Endocrinology & Metabolism*, **98**, 1235-1241. https://doi.org/10.1210/jc.2012-3424

[47] Juan, C.C., Chuang, T.Y., Lien, C., Lin, Y., Huang, S., Kwok, C.F., *et al*. (2008) Leptin Increases Endothelin Type a Receptor Levels in Vascular Smooth Muscle Cells. *American Journal of Physiology-Endocrinology and Metabolism*, **294**, E481-E487. https://doi.org/10.1152/ajpendo.00103.2007

[48] van Niekerk, E., Botha-Le Roux, S., Mels, C.M.C., Swanepoel, M., Delles, C., Welsh, P., *et al*. (2023) Twenty-Four-Hour Ambulatory, but Not Clinic Blood Pressure Associates with Leptin in Young Adults with Overweight or Obesity: The African-Predict Study. *Hypertension Research*, **47**, 478-486. https://doi.org/10.1038/s41440-023-01477-7

[49] Chen, K., Li, F., Li, J., Cai, H., Strom, S., Bisello, A., *et al*. (2006) Induction of Leptin Resistance through Direct Interaction of C-Reactive Protein with Leptin. *Nature Medicine*, **12**, 425-432. https://doi.org/10.1038/nm1372

[50] Koh, K.K., Quon, M.J., Lee, Y., Han, S.H., Ahn, J.Y., Chung, W., *et al*. (2006) Additive Beneficial Cardiovascular and Metabolic Effects of Combination Therapy with Ramipril and Candesartan in Hypertensive Patients. *European Heart Journal*, **28**, 1440-1447. https://doi.org/10.1093/eurheartj/ehm101

[51] Blanca, A.J., Ruiz-Armenta, M.V., Zambrano, S., Salsoso, R., Miguel-Carrasco, J.L., Fortuño, A., *et al*. (2016) Leptin Induces Oxidative Stress through Activation of NADPH Oxidase in Renal Tubular Cells: Antioxidant Effect of L-Carnitine. *Journal of Cellular Biochemistry*, **117**, 2281-2288. https://doi.org/10.1002/jcb.25526

[52] Deswal, A. (2011) Obesity, Leptin, and Incident Heart Failure. *Journal of the American College of Cardiology*, **58**, 1878-

1880. https://doi.org/10.1016/j.jacc.2011.07.030

[53] Sun, X., Xin, C., Yao, J. and Wang, H. (2025) Relationship between Leptin and Heart Failure: A Meta-Analysis. *Global Heart*, **20**, 44. https://doi.org/10.5334/gh.1434

[54] Wannamethee, S.G., Shaper, A.G., Whincup, P.H., Lennon, L. and Sattar, N. (2011) Obesity and Risk of Incident Heart Failure in Older Men with and without Pre-Existing Coronary Heart Disease: Does Leptin Have a Role. *Journal of the American College of Cardiology*, **58**, 1870-1877. https://doi.org/10.1016/j.jacc.2011.06.057

[55] Rajapurohitam, V., Gan, X.T., Kirshenbaum, L.A. and Karmazyn, M. (2003) The Obesity-Associated Peptide Leptin Induces Hypertrophy in Neonatal Rat Ventricular Myocytes. *Circulation Research*, **93**, 277-279. https://doi.org/10.1161/01.res.0000089255.37804.72

[56] Kain, D., Simon, A.J., Greenberg, A., Ben Zvi, D., Gilburd, B. and Schneiderman, J. (2018) Cardiac Leptin Overexpression in the Context of Acute MI and Reperfusion Potentiates Myocardial Remodeling and Left Ventricular Dysfunction. *PLOS ONE*, **13**, e0203902. https://doi.org/10.1371/journal.pone.0203902

[57] Nickola, M.W., Wold, L.E., Colligan, P.B., Wang, G., Samson, W.K. and Ren, J. (2000) Leptin Attenuates Cardiac Contraction in Rat Ventricular Myocytes. Role of NO. *Hypertension*, **36**, 501-505. https://doi.org/10.1161/01.hyp.36.4.501

[58] Dong, F., Zhang, X. and Ren, J. (2006) Leptin Regulates Cardiomyocyte Contractile Function through Endothelin-1 Receptor-NADPH Oxidase Pathway. *Hypertension*, **47**, 222-229. https://doi.org/10.1161/01.hyp.0000198555.51645.f1

[59] Theodorakis, N. and Nikolaou, M. (2025) Leptin and Heart Failure: The Chicken or the EGG? *Heart Failure Reviews*, **30**, 749-757. https://doi.org/10.1007/s10741-025-10501-6

[60] Rubio, B., Pintado, C., Mazuecos, L., Benito, M., Andrés, A. and Gallardo, N. (2024) Central Actions of Leptin Induce an Atrophic Pattern and Improves Heart Function in Lean Normoleptinemic Rats via PPARβ/δ Activation. *Biomolecules*, **14**, Article No. 1028. https://doi.org/10.3390/biom14081028

[61] Anaszewicz, M., Wawrzeńczyk, A., Czerniak, B., Banaś, W., Socha, E., Lis, K., *et al*. (2019) Leptin, Adiponectin, Tumor Necrosis Factor A, and Irisin Concentrations as Factors Linking Obesity with the Risk of Atrial Fibrillation among Inpatients with Cardiovascular Diseases. *Kardiologia Polska*, **77**, 1055-1061. https://doi.org/10.33963/kp.14989

[62] Zhu, T., Chen, M., Wang, M., Wang, Z., Wang, S., Hu, H., *et al*. (2021) Association between Adiponectin-to-Leptin Ratio and Heart Rate Variability in New-Onset Paroxysmal Atrial Fibrillation: A Retrospective Cohort Study. *Annals of Noninvasive Electrocardiology*, **27**, e12896. https://doi.org/10.1111/anec.12896

[63] Li, G. and Liu, T. (2009) The Therapeutic Strategies of Enhancing Adiponectin and Lowering Leptin May Be Benefit to Controlling Atrial Fibrillation. *Medical Hypotheses*, **73**, Article No. 122. https://doi.org/10.1016/j.mehy.2009.02.005

[64] López-Canoa, J.N., Couselo-Seijas, M., Baluja, A., González-Melchor, L., Rozados, A., Llorente-Cortés, V., *et al*. (2020) Sex-Related Differences of Fatty Acid-Binding Protein 4 and Leptin Levels in Atrial Fibrillation. *EP Europace*, **23**, 682-690. https://doi.org/10.1093/europace/euaa284