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脂肪酸代谢对心力衰竭影响

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摘　要

脂肪酸代谢主要包括脂肪酸氧化(fatty acid oxidation, FAO)和脂肪酸合成，脂肪酸代谢的改变会影响心脏的结构和功能，其作用主要体现在心肌能量供应的改变上。既往研究表明，在心力衰竭状态下，心肌中的能量代谢发生显著变化，其中脂肪酸氧化的变化是研究的重点之一。因此本综述回顾了现有文献，深入探讨脂肪酸代谢与心力衰竭之间的相关性，为其临床防治提供新的线索与思路。

关键词

脂肪酸代谢，心力衰竭，治疗

Effects of Fatty Acid Metabolism on Heart Failure

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Abstract

Fatty acid metabolism mainly includes fatty acid oxidation (FAO) and fatty acid synthesis. The change of fatty acid metabolism will affect the structure and function of the heart, and its effect is mainly reflected in the change of myocardial energy supply. Previous studies have shown that in the state of heart failure, the energy metabolism in the heart muscle changes significantly, among which the change of fatty acid oxidation is one of the key points of the study. Therefore, this paper reviews the existing literature, deeply explores the correlation between fatty acid metabolism and heart

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failure, and provides new clues and ideas for its clinical prevention and treatment.

Keywords

Fatty Acid Metabolism, Heart Failure, Treatment

1. 引言

心力衰竭(Heart Failure, HF)是一种临床综合征，由心脏结构或功能异常导致泵功能失代偿，表现为心衰相关症状和体征。根据最新国际共识，心衰的患者需至少符合以下一项客观证据：利钠肽水平升高或通过影像学或血液动力学测量获得肺循环或体循环淤血的客观证据[1]。流行病学数据显示，全球约有6400 万心衰患者，且随着人口老龄化和心脏疾病患者生存期的延长，心衰的患病率呈上升趋势[2]。

在健康心脏中，心脏必须维持大量三磷酸腺苷(ATP)的产生。ATP 由两种反应产生：线粒体氧化磷酸化和糖酵解，线粒体氧化磷酸化通常占 ATP 产量的 95%，而糖酵解产生剩余的 5% [3] [4]。心脏可以使用各种能量底物，如脂肪酸(fatty acid, FA)、乳酸、葡萄糖、酮和氨基酸来维持 ATP 的产生。在正常情况下，40%~60%的 ATP 生成依赖于 FAs [5] [6]。研究发现，心力衰竭时心肌细胞的能量代谢途径会发生改变，导致心肌功能与结构的异常[7]。正常心肌能够调节不同底物的代谢比例，保持能量供应的动态平衡，从而使 FAO、葡萄糖有氧氧化和糖酵解处于动态平衡状态，以有效维持心肌细胞能量供给。心衰发生时，这种平衡被打破，FAO 比例增加可抑制葡萄糖有氧氧化，而糖酵解比例增加则可同时抑制 FAO 和葡萄糖有氧氧化[8]。心肌细胞对脂肪酸的氧化能力下降，同时伴随着过量脂质的积累，可能引发心脏脂肪毒性，影响心脏功能[9]。脂肪酸代谢是细胞内脂肪酸的合成、分解、转运和利用的复杂过程，对维持生物体的能量平衡和生理功能至关重要。总结最新进展，本综述侧重于脂肪酸代谢在健康、心力衰竭中的作用，以及预期的未来心力衰竭治疗。

2. 脂肪酸代谢和心脏调节的机制

FAO 涉及三个主要步骤：FA 进入细胞质；穿过线粒体膜的运输；以及线粒体基质中的氧化，线粒体是线粒体最内层[10]。外源性 FA 要么与血液中的白蛋白结合，要么从乳糜微粒和极低密度脂蛋白(VLDL)中含有的三酰甘油(TG)水解后传递到心脏[11] [12]。FA 通过一个涉及被动“触发”易位的过程在细胞膜上移动，以及通过脂肪酸转位酶(FAT/CD36)和细胞质脂肪酸结合蛋白(fatty acid-binding protein, FABP)的主动运输[12] [13]。一旦进入细胞，FA 被长链酰基辅酶 a 合成酶 1 (ACSL1)转化为酰基辅酶 A (acyl-CoA) [14]。短链和中链 FA 可以直接进入线粒体，而长链需要肉碱棕榈酰转移酶系统[15]。在线粒体内部，acyl-CoA 经过 β 氧化产生乙酰辅酶 A (acetyl-coenzyme A, acetyl-CoA)，进入三羧酸循环最后产生 ATP [16] [17]。超长链 FA 也可能在过氧化物酶体中进行 β 氧化[12]。众所周知，游离 FA 还激活过氧化物酶体增殖物激活受体(PPAR)。过氧化物酶体增殖物激活受体(PPAR: PPARα、γ 和 δ)和雌激素相关受体(ERR: ERRα、β 和 γ)在调节参与 FA 代谢的基因表达方面发挥着关键作用[18]。除了 FA 代谢外，PPAR 和 ERR 还调节参与葡萄糖代谢、脂质合成、细胞增殖和分化[19]。虽然 PPAR 和 ERR 具有重叠的功能，但它们在心脏代谢中也起着不同的作用。

在一项对脂肪特异性 PPARα 的研究中，发现脂肪细胞中 PPARα 信号的丧失会导致胆固醇酯的增加和固醇调节元件结合蛋白-1 (SREBP-1)的激活，导致巨噬细胞极性的转变和脂肪生成增加[20]。最近的研究发现，心脏特异性 PPARα 缺乏的小鼠显示脂肪酸氧化的基因表达减少和加速压力过载引起的心脏功能障碍[21]。此外，在心脏特异性 ERRα 缺乏的小鼠表现出心脏功能障碍、轻度葡萄糖和胰岛素不耐受，并在骨骼肌和白质组织中降低 ERα 基因表达[22]。如上所述，为了有效地产生 ATP 并保持理想的心脏功能，FA 吸收、β-氧化和线粒体氧化磷酸化过程必须顺利、平衡地协同工作。

3. 心力衰竭中的脂肪酸代谢

HF 的关键特征之一是能量代谢受损和代谢失衡，导致这种现象的因素包括线粒体氧化代谢受损、对能量底物偏好的变化以及心脏效率下降[5] [10]。HF 主要分为两种类型：射血分数降低的心力衰竭(HFrEF)和射血分数保留率(HFpEF)的心力衰竭，后者更普遍[23]。HFrEF 和 HFpEF 两种类型中起着不同的作用，并且与心力衰竭的发展密切相关。HFpEF 是一种临床综合征，目前对心血管医学构成根本性挑战。大约 5%的 60 岁以上患者现在患有 HFpEF [24]，对于射血分数降低型心力衰竭(HFrEF)，心肌中脂肪酸供能降低，酮体供能增加。心力衰竭状态下心肌脂肪酸氧化的变化并没有得出一致的结论，这可能主要是由于心力衰竭的严重程度不同，心力衰竭的合并症不同导致。在心力衰竭患者中，脂肪酸氧化的变化与脂肪酸摄取的变化并不总是一致，且在不同类型的心力衰竭中可能有不同的表现[25]。

在射血分数保留型心力衰竭(HFpEF)中，心脏代谢紊乱似乎决定了疾病的进展。心脏代谢性 HFpEF 中间代谢的变化对能量供应和心脏中的许多信号通路都有很大影响。长链脂肪酸(LCFA)是心脏的主要燃料，但过量可能有害，例如脂质副产物的毒性积累。另一方面，短链脂肪酸(SCFA)和酮体(KB)已被提议作为 HFpEF 中潜在的主要替代能源。这些代谢物不仅作为能量来源，还通过蛋白质翻译后修饰和其他形式的信号转导，在 HFpEF 发病机制中具有至关重要的意义[26]。

由于人口老龄化，以及肥胖、糖尿病和高血压等 HFpEF 主要风险因素的患病率增加[27]-[29]。其患病率正在迅速增长[30]。HFpEF 是一种病态和致命的综合征：平均而言，一半以上的 HF 住院率涉及 HFpEF 患者[31]，2 年的全因死亡率和 HF 住院率为 35%，2 年死亡率为 14% [32]。目前对 HFpEF 心脏中发生的代谢改变的了解仍然有限。研究表明，HFpEF 心脏表现出葡萄糖氧化受损和脂肪酸氧化增加，而 β-羟基丁酸(β-OHB)的氧化减少，且 β-OHB 在 HFpEF 中控制线粒体功能和心肌生物功能，通过 β-羟基丁酰化(Kbhb)影响线粒体中的酶活性[33]。

针对 HFrEF 和 HFpEF 的最新研究显示，钠–葡萄糖共转运蛋白 2 抑制剂(sodium-glucose cotransporter 2 inhibitors, SGLT2i)在治疗 HFpEF 方面取得了突破性进展，EMPEROR-Preserved 和 DELIVER 研究均显示 SGLT2i 能够降低心血管死亡或首次心衰住院的复合终点风险[34]。此外，2023 年的中国专家委员会制定并发表的《心力衰竭 SGLT2 抑制剂临床应用的中国专家共识》推荐使用 SGLT2i 来降低心力衰竭住院或心血管死亡复合终点事件风险，并推荐使用沙库巴曲缬沙坦，尤其是对于 LVEF 相对较低的 HFpEF 患者，以降低心力衰竭住院风险。射血分数保留的心力衰竭诊断与治疗中国专家共识 2023 尽管如此，到目前为止，HFpEF 的有效治疗方法数量非常有限。

4. 治疗

在心脏上测试的一个策略是通过甲嘧啶(TMZ)、依托莫昔和 perhexiline 等药物来抑制 FAO，这些药物在动物模型和人类研究中显示出希望，主要适用于缺血–再灌注和慢性 HF [35]-[37]。这种方法抑制了 FAO 且提高氧气效率，并恢复糖酵解和葡萄糖氧化之间的耦合[38]。另一种方法是使用 PPARα 激动剂，通过增加其在心外组织中的利用率来减少 FA 的心肌供应[39]。PPARα 激动剂治疗在缺血–再灌注损伤

期间具有心脏保护作用，但临床试验显示新发 HF 的风险呈阴性[40]。此外，广泛使用的策略是抑制丙二酰辅酶 A 脱羧酶(MCD)，该脱羧酶是脂肪酸氧化的主要调节因子，催化丙二酰辅酶 A (malonyl-CoA)脱羧[41]。大鼠 HF 模型中对 MCD 的抑制导致心肌丙二酰辅酶 A 水平升高，心脏 FAO 率下降，从而阻止了 HF 的发展[35]。最近，SGLT2i 主要以通过促进尿葡萄糖排泄来管理糖尿病而闻名，被发现表现出额外的心血管益处[42]。在小鼠和猪模型中，最近发现 SGLT2 抑制会增加心脏酮氧化[42] [43]，这种改变被认为可以缓解心脏的代谢压力和炎症，可能有助于改善心脏功能[44]。尽管有相关证据，但因为 FAO 已经受损，所以抑制 FAO 在 HF 中可能无效，葡萄糖氧化减少并转向生物合成途径[45]-[47]。因此，HF 的治疗方法可能需要专注于恢复所有有贡献的代谢途径的平衡，而不是仅仅减少心脏中的 FAO。

5. 结论

综上所述，针对心肌脂肪酸代谢的治疗策略正在不断发展，通过调节脂肪酸代谢来改善心脏病患者的心肌能量代谢，已经成为心脏病治疗中的一个有前景的研究方向。这些治疗方法的有效性和安全性仍需通过大规模的临床试验来验证。未来的研究和临床应用将继续探索这一领域的新策略和新药物。

参考文献

[1] Bozkurt, B., Coats, A.J.S., Tsutsui, H., *et al.* (2021) Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *Journal of Cardiac Failure*, **27**, 387-413.

[2] James, S.L., Abate, D., Abate, K.H., Abay, S.M., Abbafati, C., Abbasi, N., *et al.* (2018) Global, Regional, and National Incidence, Prevalence, and Years Lived with Disability for 354 Diseases and Injuries for 195 Countries and Territories, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study 2017. *The Lancet*, **392**, 1789-1858. https://doi.org/10.1016/s0140-6736(18)32279-7

[3] Saddik, M. and Lopaschuk, G.D. (1991) Myocardial Triglyceride Turnover and Contribution to Energy Substrate Utilization in Isolated Working Rat Hearts. *Journal of Biological Chemistry*, **266**, 8162-8170. https://doi.org/10.1016/s0021-9258(18)92956-x

[4] Wisneski, J.A., Stanley, W.C., Neese, R.A. and Gertz, E.W. (1990) Effects of Acute Hyperglycemia on Myocardial Glycolytic Activity in Humans. *Journal of Clinical Investigation*, **85**, 1648-1656. https://doi.org/10.1172/jci114616

[5] Karwi, Q.G., Uddin, G.M., Ho, K.L. and Lopaschuk, G.D. (2018) Loss of Metabolic Flexibility in the Failing Heart. *Frontiers in Cardiovascular Medicine*, **5**, Article 68. https://doi.org/10.3389/fcvm.2018.00068

[6] Murashige, D., Jang, C., Neinast, M., Edwards, J.J., Cowan, A., Hyman, M.C., *et al.* (2020) Comprehensive Quantification of Fuel Use by the Failing and Nonfailing Human Heart. *Science*, **370**, 364-368. https://doi.org/10.1126/science.abc8861

[7] 邱泽平, 王芝嫣, 金玮. 从心肌能量代谢角度浅谈心力衰竭药物治疗进展[J]. 中华心力衰竭和心肌病杂志(中英文), 2021, 5(1): 74-78.

[8] Zhao, X.L. and Yang, J.F. (2022) Research Progress on the Relationship between Myocardial Energetic Metabolism and Heart Failure. *Chinese Journal of Cardiovascular Diseases*, **50**, 404-409.

[9] Wang, H., Wang, J., Cui, H., Fan, C., Xue, Y., Liu, H., *et al.* (2024) Inhibition of Fatty Acid Uptake by TGR5 Prevents Diabetic Cardiomyopathy. *Nature Metabolism*, **6**, 1161-1177. https://doi.org/10.1038/s42255-024-01036-5

[10] Bertero, E. and Maack, C. (2018) Metabolic Remodelling in Heart Failure. *Nature Reviews Cardiology*, **15**, 457-470. https://doi.org/10.1038/s41569-018-0044-6

[11] Lopaschuk, G.D., Ussher, J.R., Folmes, C.D.L., Jaswal, J.S. and Stanley, W.C. (2010) Myocardial Fatty Acid Metabolism in Health and Disease. *Physiological Reviews*, **90**, 207-258. https://doi.org/10.1152/physrev.00015.2009

[12] Chen, Z., Jin, Z., Cai, J., Li, R., Deng, K., Ji, Y., *et al.* (2022) Energy Substrate Metabolism and Oxidative Stress in Metabolic Cardiomyopathy. *Journal of Molecular Medicine*, **100**, 1721-1739. https://doi.org/10.1007/s00109-022-02269-1

[13] Øie, E., Ueland, T., Dahl, C.P., Bohov, P., Berge, C., Yndestad, A., *et al.* (2011) Fatty Acid Composition in Chronic Heart Failure: Low Circulating Levels of Eicosatetraenoic Acid and High Levels of Vaccenic Acid Are Associated with Disease Severity and Mortality. *Journal of Internal Medicine*, **270**, 263-272.

https://doi.org/10.1111/j.1365-2796.2011.02384.x

[14] Glatz, J.C. and Luiken, J.F.P. (2018) Dynamic Role of the Transmembrane Glycoprotein CD36 (SR-B2) in Cellular Fatty Acid Uptake and Utilization. *Journal of Lipid Research*, **59**, 1084-1093. https://doi.org/10.1194/jlr.r082933

[15] Goldenberg, J.R., Wang, X. and Lewandowski, E.D. (2016) Acyl Coa Synthetase-1 Links Facilitated Long Chain Fatty Acid Uptake to Intracellular Metabolic Trafficking Differently in Hearts of Male versus Female Mice. *Journal of Molecular and Cellular Cardiology*, **94**, 1-9. https://doi.org/10.1016/j.yjmcc.2016.03.006

[16] Schlaepfer, I.R. and Joshi, M. (2020) Cpt1a-mediated Fat Oxidation, Mechanisms, and Therapeutic Potential. *Endocrinology*, **161**, bqz046. https://doi.org/10.1210/endocr/bqz046

[17] Marin, W., Marin, D., Ao, X. and Liu, Y. (2020) Mitochondria as a Therapeutic Target for Cardiac Ischemia-Eperfusion Injury (Review). *International Journal of Molecular Medicine*, **47**, 485-499. https://doi.org/10.3892/ijmm.2020.4823

[18] Northam, C. and LeMoine, C.M.R. (2019) Metabolic Regulation by the PGC-1α and PGC-1β Coactivators in Larval Zebrafish (Danio Rerio). *Comparative Biochemistry and Physiology Part A*: *Molecular & Integrative Physiology*, **234**, 60-67. https://doi.org/10.1016/j.cbpa.2019.04.011

[19] Montaigne, D., Butruille, L. and Staels, B. (2021) PPAR Control of Metabolism and Cardiovascular Functions. *Nature Reviews Cardiology*, **18**, 809-823. https://doi.org/10.1038/s41569-021-00569-6

[20] Hinds, T.D., Kipp, Z.A., Xu, M., Yiannikouris, F.B., Morris, A.J., Stec, D.F., *et al.* (2021) Adipose-Specific PPARα Knockout Mice Have Increased Lipogenesis by PASK-SREBP1 Signaling and a Polarity Shift to Inflammatory Macrophages in White Adipose Tissue. *Cells*, **11**, Article 4. https://doi.org/10.3390/cells11010004

[21] Wang, X., Zhu, X., Jiao, S., Qi, D., Yu, B., Xie, G., *et al.* (2021) Cardiomyocyte Peroxisome Proliferator-Activated Receptor α Is Essential for Energy Metabolism and Extracellular Matrix Homeostasis during Pressure Overload-Induced Cardiac Remodeling. *Acta Pharmacologica Sinica*, **43**, 1231-1242. https://doi.org/10.1038/s41401-021-00743-z

[22] Softic, S., Meyer, J.G., Wang, G., Gupta, M.K., Batista, T.M., Lauritzen, H.P.M.M., *et al.* (2019) Dietary Sugars Alter Hepatic Fatty Acid Oxidation via Transcriptional and Post-Translational Modifications of Mitochondrial Proteins. *Cell Metabolism*, **30**, 735-753.e4. https://doi.org/10.1016/j.cmet.2019.09.003

[23] Snipelisky, D., Chaudhry, S. and Stewart, G.C. (2019) The Many Faces of Heart Failure. *Cardiac Electrophysiology Clinics*, **11**, 11-20. https://doi.org/10.1016/j.ccep.2018.11.001

[24] van Riet, E.E.S., Hoes, A.W., Wagenaar, K.P., Limburg, A., Landman, M.A.J. and Rutten, F.H. (2016) Epidemiology of Heart Failure: The Prevalence of Heart Failure and Ventricular Dysfunction in Older Adults over Time. A Systematic Review. *European Journal of Heart Failure*, **18**, 242-252. https://doi.org/10.1002/ejhf.483

[25] Lopaschuk, G.D., Karwi, Q.G., Tian, R., Wende, A.R. and Abel, E.D. (2021) Cardiac Energy Metabolism in Heart Failure. *Circulation Research*, **128**, 1487-1513. https://doi.org/10.1161/circresaha.121.318241

[26] Capone, F., Sotomayor-Flores, C., Bode, D., Wang, R., Rodolico, D., Strocchi, S., *et al.* (2022) Cardiac Metabolism in HFpEF: From Fuel to Signalling. *Cardiovascular Research*, **118**, 3556-3575. https://doi.org/10.1093/cvr/cvac166

[27] Sidney, S., Go, A.S., Jaffe, M.G., Solomon, M.D., Ambrosy, A.P. and Rana, J.S. (2019) Association between Aging of the US Population and Heart Disease Mortality from 2011 to 2017. *JAMA Cardiology*, **4**, 1280-1286. https://doi.org/10.1001/jamacardio.2019.4187

[28] Flegal, K.M., Kruszon-Moran, D., Carroll, M.D., Fryar, C.D. and Ogden, C.L. (2016) Trends in Obesity among Adults in the United States, 2005 to 2014. *JAMA*, **315**, 2284-2291. https://doi.org/10.1001/jama.2016.6458

[29] Mills, K.T., Stefanescu, A. and He, J. (2020) The Global Epidemiology of Hypertension. *Nature Reviews Nephrology*, **16**, 223-237. https://doi.org/10.1038/s41581-019-0244-2

[30] Dunlay, S.M., Roger, V.L. and Redfield, M.M. (2017) Epidemiology of Heart Failure with Preserved Ejection Fraction. *Nature Reviews Cardiology*, **14**, 591-602. https://doi.org/10.1038/nrcardio.2017.65

[31] Sax, D.R., Rana, J.S., Mark, D.G., Huang, J., Collins, S.P., Liu, D., *et al.* (2021) Outcomes among Acute Heart Failure Emergency Department Patients by Preserved vs. Reduced Ejection Fraction. *ESC Heart Failure*, **8**, 2889-2898. https://doi.org/10.1002/ehf2.13364

[32] Lam, C.S.P., Gamble, G.D., Ling, L.H., Sim, D., Leong, K.T.G., Yeo, P.S.D., *et al.* (2018) Mortality Associated with Heart Failure with Preserved vs. Reduced Ejection Fraction in a Prospective International Multi-Ethnic Cohort Study. *European Heart Journal*, **39**, 1770-1780. https://doi.org/10.1093/eurheartj/ehy005

[33] Wang, R., Capone, F., Capone, F., Luo, L., L, L., Keller, D., *et al.* (2024) Ketone-based Metabolism and Signalling in Heart Failure with Preserved Ejection Fraction (HFpEF). *Cardiovascular Research*, **120**, cvae088.096. https://doi.org/10.1093/cvr/cvae088.096

[34] Anker, S.D., Butler, J., Filippatos, G., Ferreira, J.P., Bocchi, E., Böhm, M., *et al.* (2021) Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *New England Journal of Medicine*, **385**, 1451-1461. https://doi.org/10.1056/nejmoa2107038

[35] Wang, W., Zhang, L., Battiprolu, P.K., Fukushima, A., Nguyen, K., Milner, K., *et al.* (2019) Malonyl CoA Decarboxylase Inhibition Improves Cardiac Function Post-Myocardial Infarction. *JACC*: *Basic to Translational Science*, **4**, 385-400. https://doi.org/10.1016/j.jacbts.2019.02.003

[36] Knottnerus, S.J.G., Mengarelli, I., Wüst, R.C.I., Baartscheer, A., Bleeker, J.C., Coronel, R., *et al.* (2020) Electrophysiological Abnormalities in VLCAD Deficient hiPSC-Cardiomyocytes Can Be Improved by Lowering Accumulation of Fatty Acid Oxidation Intermediates. *International Journal of Molecular Sciences*, **21**, Article 2589. https://doi.org/10.3390/ijms21072589

[37] Beadle, R.M., Williams, L.K., Kuehl, M., Bowater, S., Abozguia, K., Leyva, F., *et al.* (2015) Improvement in Cardiac Energetics by Perhexiline in Heart Failure Due to Dilated Cardiomyopathy. *JACC*: *Heart Failure*, **3**, 202-211. https://doi.org/10.1016/j.jchf.2014.09.009

[38] Palm, C.L., Nijholt, K.T., Bakker, B.M. and Westenbrink, B.D. (2022) Short-Chain Fatty Acids in the Metabolism of Heart Failure—Rethinking the Fat Stigma. *Frontiers in Cardiovascular Medicine*, **9**, Article 915102. https://doi.org/10.3389/fcvm.2022.915102

[39] Khuchua, Z., Glukhov, A.I., Strauss, A.W. and Javadov, S. (2018) Elucidating the Beneficial Role of PPAR Agonists in Cardiac Diseases. *International Journal of Molecular Sciences*, **19**, Article 3464. https://doi.org/10.3390/ijms19113464

[40] Kim, N.H. and Kim, S.G. (2020) Fibrates Revisited: Potential Role in Cardiovascular Risk Reduction. *Diabetes & Metabolism Journal*, **44**, 213-221. https://doi.org/10.4093/dmj.2020.0001

[41] Yang, C., Li, Q., Lin, Y., Wang, Y., Shi, H., Huang, L., *et al.* (2023) MCD Inhibits Lipid Deposition in Goat Intramuscular Preadipocytes. *Genes*, **14**, Article 440. https://doi.org/10.3390/genes14020440

[42] Santos-Gallego, C.G., Requena-Ibanez, J.A., San Antonio, R., Ishikawa, K., Watanabe, S., Picatoste, B., *et al.* (2019) Empagliflozin Ameliorates Adverse Left Ventricular Remodeling in Nondiabetic Heart Failure by Enhancing Myocardial Energetics. *Journal of the American College of Cardiology*, **73**, 1931-1944. https://doi.org/10.1016/j.jacc.2019.01.056

[43] Verma, S., Rawat, S., Ho, K.L., Wagg, C.S., Zhang, L., Teoh, H., *et al.* (2018) Empagliflozin Increases Cardiac Energy Production in Diabetes: Novel Translational Insights into the Heart Failure Benefits of SGLT2 Inhibitors. *JACC*: *Basic to Translational Science*, **3**, 575-587. https://doi.org/10.1016/j.jacbts.2018.07.006

[44] Chen, S., Coronel, R., Hollmann, M.W., Weber, N.C. and Zuurbier, C.J. (2022) Direct Cardiac Effects of SGLT2 Inhibitors. *Cardiovascular Diabetology*, **21**, Article No. 45. https://doi.org/10.1186/s12933-022-01480-1

[45] Umbarawan, Y., Syamsunarno, M.R.A.A., Koitabashi, N., Obinata, H., Yamaguchi, A., Hanaoka, H., *et al.* (2018) Myocardial Fatty Acid Uptake through CD36 Is Indispensable for Sufficient Bioenergetic Metabolism to Prevent Progression of Pressure Overload-Induced Heart Failure. *Scientific Reports*, **8**, Article No. 12035. https://doi.org/10.1038/s41598-018-30616-1

[46] Nabben, M., Luiken, J.J.F.P. and Glatz, J.F.C. (2018) Metabolic Remodelling in Heart Failure Revisited. *Nature Reviews Cardiology*, **15**, 780-780. https://doi.org/10.1038/s41569-018-0115-8

[47] Shao, D., Kolwicz, S.C., Wang, P., Roe, N.D., Villet, O., Nishi, K., *et al.* (2020) Increasing Fatty Acid Oxidation Prevents High-Fat Diet-Induced Cardiomyopathy through Regulating Parkin-Mediated Mitophagy. *Circulation*, **142**, 983-997. https://doi.org/10.1161/circulationaha.119.043319