运动改善糖尿病性心肌病的机制研究进展

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摘要 糖尿病性心肌病(diabetic cardiomyopathy, DC)是由糖尿病性机体稳态失调引起的一类心肌疾病, 其病理特征主要表现为心脏结构损伤和功能紊乱, 这是导致糖尿病病人死亡的主要原因之一。DC的发病机制复杂多样, 涉及到多种机制, 如代谢失调、线粒体功能障碍、Ca^{2+}稳态失衡、心肌细胞过度凋亡和纤维化等。近年来, 多项研究证明运动训练对糖尿病的预防和治疗具有显著效果。运动除了对糖尿病恢复有益外, 还可以改善DC的多种代谢紊乱特征。一方面, 运动时机体产生的高收缩活动可加快心脏代谢和加速心源性结构损伤的修复, 从而直接改善DC造成的心脏损伤。另一方面, 运动可通过降低体内血液循环中的糖和脂肪含量, 增加胰岛素敏感性, 从而间接缓解DC的病理发展。目前对于运动如何介导DC病症恢复的分子机理仍未完全清楚。该文对运动缓解DC及其目前已知的分子作用机制进行综述, 以期为运动缓解DC和开发新的治疗策略提供重要信息和线索。

关键词 运动; 糖尿病性心肌病; Ca^{2+}稳态; 代谢失调

The Research Progress on Ameliorating Diabetic Cardiomyopathy via Exercises

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Abstract DC (diabetic cardiomyopathy) is a myocardial disease caused by diabetic homeostasis disorder, which is one of the main causes of death in diabetic patients. Its pathological features are heart structural damage and dysfunction, which lead to heart failure. The pathogenesis of DC is complex, including a variety of mechanisms, such as metabolic disorders, mitochondrial dysfunction, Ca^{2+} homeostasis imbalance, and excessive apoptosis and fibrosis of cardiac myocytes. In recent years, several studies have proved that physical training has significant effects on the prevention and treatment of diabetes. In addition to the beneficial effects on systemic changes associated with diabetes recovery, exercise ameliorates multiple metabolic dysfunctions in DC. On the one hand, high systolic activity of the organism during exercise can directly recover cardiac injury caused by DC through accelerating cardiac metabolism and cardiogenic structural damage repairment. On the other hand, exercise can indirectly alleviate the pathological development of DC by reducing circulating blood sugar and fat as well as increasing insulin sensitivity. However, the molecular mechanism of how exercise mediates DC recovery remains unknown. To provide a clue for the development of new therapeutic strategies, this study reviewed the current molecular mechanisms on alleviating DC by exercises.

Keywords exercise; diabetic cardiomyopathy; Ca^{2+} homeostasis; metabolic disorders

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随着生活方式的改变, 糖尿病的发病率逐年增加, 给人民的健康和社会经济带来巨大负担。糖尿病是一种由于胰岛素分泌缺陷或其生物作用受损而导致血糖过高的慢性代谢疾病, 主要包括1型糖尿病(type 1 diabetes, T1D)和2型糖尿病(type 2 diabetes, T2D)[1]。已有临床证据表明, 糖尿病的发生与治疗不当会导致严重的并发症, 例如心血管疾病、中风、肾衰竭、失明和神经损伤, 其中心血管疾病是导致糖尿病病人死亡的主要原因。糖尿病除了会增加高血压和心血管疾病的发病率外, 也有发展成为一种特定的糖尿病性心肌病(diabetic cardiomyopathy, DC)的风险[2-3]。DC的发展与糖尿病引起的多种生理变化相关, 包括心脏代谢失调、线粒体功能障碍、Ca^{2+}稳态失衡、心肌细胞过度凋亡和纤维化等[2,4-8]。DC的最初病理特征是心肌纤维化、功能重构, 随后心脏收缩功能出现障碍, 最终发展成为临床心衰[9-10]。目前, DC的主要治疗方法是通过使用改善心肌功能为主的药物, 包括利用血管紧张素转换酶抑制剂、钙通道阻滞剂、α1-受体阻滞剂、他汀类药物等进行降压和降血脂治疗[11-12]。然而, 目前临床治疗方案只能暂时缓解DC的病症, 无法从根源上逆转DC的进程。众所周知, 运动是预防和治疗糖尿病和肥胖的一种低成本策略[13-14]。运动可以提高心肌耐力, 其对于糖尿病/肥胖症患者心脏的有益作用已经被广泛报道[15-18]。其中, 一项临床研究对24名T2D患者进行6个月时期的运动训练, 发现相比未运动的T2D患者, 运动的T2D患者心脏峰值摄氧量明显改善, 静息心率降低, DC病症得到缓解[19]。同时, KARJALAINEN等[20]对539名T2D患者进行长达2年的运动训练随访, 发现其DC病理进程得到明显缓解。此项研究强调了长期运动更能预防和缓解心血管疾病的发展。不同的运动可以通过一系列相应的分子机制起到心脏保护作用, 如改善代谢底物利用率、调节线粒体功能、平衡Ca^{2+}稳态、减少心肌细胞凋亡和纤维化等[19]。然而, 运动如何改善心脏功能、缓解DC病症发展的机制尚未完全清楚。因此, 研究运动改善DC病症发生的方法和理解运动影响DC的生理机制有利于临床DC治疗的发展。

1 DC的病理发生

心脏代谢网络是一个多功能系统, 能够利用多种碳氢化合物以产生能量, 其中葡萄糖和脂肪酸(fatty acids, FAs)是心脏能量代谢反应的主要底物[21]。正常心脏的一个重要特征是对代谢底物利用的多样性和ATP产生的高速率性, 其底物代谢紊乱和ATP产生速率的失调被认为是DC(包括心脏衰竭)发展的根本原因, 但其具体机制仍不清楚[9]。同时, 高血糖也是促进DC发展的重要危险因素, 患者血浆葡萄糖水平升高将通过调节厌氧葡萄糖通路参与DC发展[22]。

心脏活动高度依赖于线粒体氧化磷酸化(oxidative phosphorylation, OxPhos), 人们认为线粒体功能障碍在DC的发病机制中具有核心作用。线粒体OxPhos与ATP水解速率密切相关, 而能量可用性和需求之间的不平衡将导致心脏能量利用效率降低, 从而导致心脏起搏功能下降[23]。据报道, 糖尿病性心脏的线粒体质量、面积和数量增加, 可能作为一种适应机制, 以克服受损的线粒体呼吸能力[24]。值得注意的是, 细胞内Ca^{2+}响应的改变也被认为是导致糖尿病患者心室功能障碍的一个重要因素。在细胞水平上, 糖尿病性心肌细胞的Ca^{2+}瞬态变化具有较低的振幅和较慢的衰减率, 其与受损的肌浆网(sarcoplasmic reticulum, SR)相关[2]。近期研究发现, 活化的转化生长因子β(transforming growth factor beta, TGF-β)将导致心脏纤维化, 进而通过Smad依赖和独立的途径诱导DC[25]。 另外, 血糖过高将会增加心脏中氧自由基的含量, 促进心肌细胞发生氧化应激, 进而导致其过度凋亡。因此, 心肌细胞的凋亡也被认定为是引起其病理发展的重要原因[26]。

总体来说, DC的病理发展与糖尿病的病理特征紧密相关, 然而其发病机制尚未完全明确。近年来, DC的病理变化已逐渐被证明可通过运动来改善, 因此, 运动有望成为未来一种更自然、健康和廉价的DC病症恢复方案。

2 运动改善DC病理发展的机制

多项临床调查报告显示, 多种运动, 如水上运动、北欧漫步、特定的健身活动、瑜伽、普拉提、太极和舞蹈活动等, 对糖尿病以及DC的恢复具有积极效应[27-33]。然而, 目前运动如何改善DC的病理进程仍不清楚。一系列预临床试验初步揭示了运动可通过改善心脏代谢失调、线粒体功能障碍、Ca^{2+}稳态失衡、心肌细胞过度凋亡和纤维化等多方面延缓DC的发展(表1), 为运动改善DC病理进程提供了理论基础。

表1 多种运动方式促进DC心脏功能恢复的机制

Table 1 Multiple exercise modes promote cardiac function recovery in DC

运动处方 Exercise prescription	研究对象 Object	研究设计 Design	研究结果 Result	参考文献 Reference
Moderate-intensity training	STZ induced diabetic rat	Metabolic regulation	GLUT4 up-regulation	[34]
Long-term exercise training	ZDF rat	Metabolic regulation	AMPK activation	[35]
High-intensity training	Diet-induced obesity mice	Metabolic regulation	Oxidation of glucose increasing	[21]
High-intensity training	STZ induced diabetic rat	Metabolic regulation	Glucose oxidation and glycolysis rates increasing	[36]
High-intensity training	Diet-induced obesity mice	Mitochondrial regulation	Mitochondrial proton leakage compensating	[21]
Long-term exercise training	STZ induced diabetic rat	Mitochondrial regulation	Mitochondrial ultrastructure improvement	[40]
Long-term exercise training	db/db mice	Mitochondrial regulation	PGC-1α and AKT signaling activation	[41]
Long-term exercise training	STZ/diet-induced obesity mice	Mitochondrial regulation	Mitochondrial OxPhos levels and membrane potential increasing	[42]
Moderate-intensity training	STZ induced diabetic mice	Oxidative stress regulation	*Mst1* inhibition	[43]
Moderate-intensity training	Diet-induced obesity rat	Ca^{2+} homeostasis regulation	Ca^{2+} sensitivity increasing	[15]
Moderate-intensity training	STZ induced diabetic rat	Ca^{2+} homeostasis regulation	SR Ca^{2+} leakage recovery	[48]
Aerobic interval training	db/db mice	Ca^{2+} homeostasis regulation	Type-1 Ca^{2+} channel recovery, transverse (T)-tubule density increasing	[49]
Moderate-intensity training	db/db mice	Apoptosis decreasing	Cytochrome leakage decreasing	[53]
Long-term exercise training	STZ induced diabetic rat	Apoptosis decreasing	Phosphorylation of C-Jun *N*-terminal kinase decreasing	[55]
Low-intensity training	STZ induced diabetic rat	Apoptosis decreasing	Propylene glycol decreasing as well as SOD, GSH-Px and catalase increasing	[56]
Long-term exercise training	STZ induced diabetic rat	Apoptosis decreasing	Endoplasmic reticulum stress inhibition	[57]
Low-intensity training	STZ induced diabetic rat	Fibrosis decreasing	Blood pressure improvement	[58]
High-intensity training	Diet-induced obesity mice	Fibrosis decreasing	Mmp2 level and collagen degradation increasing	[21]
High-intensity training	Diet-induced obesity mice	Fibrosis decreasing	Blood glucose and myocardial glycogen deposition decreasing	[60]
High-intensity training	Alloxan-induced diabetic rat	Fibrosis decreasing	Myocardial hypertrophy and collagen deposition decreasing	[61]

STZ (streptozocin); GLUT4 (glucose transporter-4); ZDF (zucker diabetic fatty); AMPK (AMP-activated protein kinase); PGC-1α (peroxisome proliferator-activated receptor gamma co-stimulatory factor-1α); OxPhos (oxidative phosphorylation); SR (sarcoplasmic reticulum); SOD (superoxide dismutase); GSH-Px (glutathione peroxidase); MMP2 (matrix metalloproteinase-2).

2.1 运动通过调节代谢状态改善DC

DC的心肌结构和功能异常通常是因为葡萄糖和脂肪的代谢失调, 其伴随着相关代谢信号通路的改变, 最终加剧心肌性疾病的发展[5]。葡萄糖载体4(glucose transporter-4, GLUT-4)是一种受胰岛素信号调控的膜上蛋白, 其可通过调控心肌细胞内葡萄糖的转运和摄取来参与能量代谢。在高糖的病理环境下, 心肌细胞膜上GLUT-4的含量减少, 葡萄糖转运和利用受阻, 从而导致心脏无法有效获取能量[34]。运动可促进GLUT-4水平升高, 从而恢复细胞内葡萄糖运输和能量代谢[35]。研究表明, 运动也可通过促进AMP活化蛋白激酶(AMP-activated protein kinase, AMPK)的表达来促进胰岛素介导的葡萄糖转运[36]。除了调节葡萄糖转运外, 在饮食诱导的糖尿病小鼠中, 进行高强度跑步运动也可增加心肌葡萄糖氧化, 改善心肌底物利用速率[22]。在链脲霉素(streptozotocin, STZ)诱导的糖尿病大鼠中, 运动训练可增加葡萄糖氧化和糖酵解率, 从而有效预防心肌糖代谢的降低[37]。运动对于恢复糖尿病性心脏中增加的非氧化葡萄糖途径也具有重要作用, 其可诱发机体产生自愈效应[38]。由于运动

训练也会增加心肌葡萄糖氧化, 因此这可能是一种有助于碳从厌氧葡萄糖途径中转移的机制[22]。

2.2 运动通过调节线粒体改善DC

线粒体作为细胞能量代谢的中心, 在DC的发病机制中起关键作用。研究表明, 线粒体功能障碍主要是通过引起能量供需失衡从而诱发心肌功能失调的[39-40]。通过透射电镜观察发现, DC的线粒体形态变大、数量增加、其内外膜结构出现损伤, 而运动可减轻糖尿病大鼠心肌组织超微结构变化[41]。研究表明, 运动可调控线粒体相关蛋白, 如过氧化物酶体增殖物激活受体γ共刺激因子-1α(peroxisome proliferator-activated receptor gamma co-stimulatory factor-1α, PGC-1α), 从而激活AKT信号通路。因此, 运动可以增强线粒体相关基因表达, 维持线粒体稳态平衡[42]。实验证明运动可提高线粒体OxPhos水平、增加线粒体膜电位、降低活性氧水平, 从而改善糖尿病小鼠心脏的血压和收缩功能障碍[43]。耐力训练被证明可诱导线粒体适应弥补线粒体轻度质子泄漏, 并保持ATP合成的效率[22]。近年来, ZHAO等[44]研究发现, 有氧运动可通过抑制*Mst1*激活减轻糖尿病小鼠心肌的氧化应激、减少线粒体活性氧的形成、减轻线粒体肿胀、促进线粒体三磷酸腺苷的形成和提高线粒体膜电位的水平。

2.3 运动通过维持钙离子稳态改善DC

钙是骨骼肌细胞功能和特定细胞信号转导的重要媒介, 其参与的生理过程包括细胞收缩、纤维分化和能量生产。细胞内Ca^{2+}稳态失调是DC的主要标志之一, 可以影响心肌收缩功能, 直接导致DC的发展[45-46]。T2D患者心肌细胞钠钙离子交换受到抑制, 而肌浆网Ca^{2+}泵正常, Ca^{2+}逐渐集中在肌浆网[47-48]。在T2D模型中, 运动可调控细胞膜内外Ca^{2+}稳态, 通过影响心肌收缩和舒张来促进DC病理恢复[15]。此外, 运动锻炼使db/db小鼠和STZ大鼠心肌细胞中糖尿病性的Ca^{2+} SR泄漏正常化, 其与CaMKII活性正常化所导致的磷酸化状态有关[49]。此外, STOLEN等[50]报道, 长期有氧运动可促进因T2D引起的心肌Ca^{2+}通道损伤修复, 恢复SR中Ca^{2+}释放, 从而促进Ca^{2+}泄露相关的心脏收缩功能提高。

2.4 运动改善高血糖引起的心肌细胞凋亡

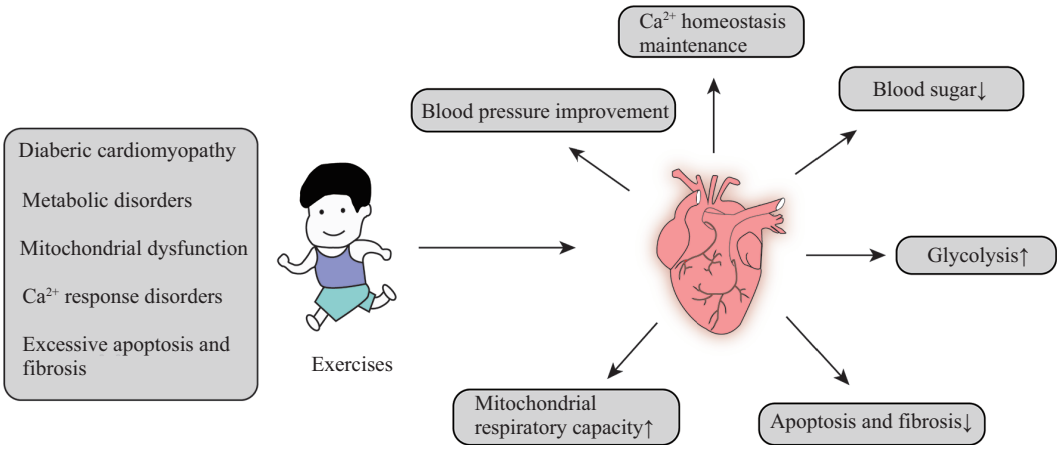
高血糖状态下, DC的病理特征常表现为心肌细胞过度凋亡。研究表明, 高血糖可增加细胞质内细胞色素C的含量, 从而启动Caspase-3相关的内源性凋亡程序, 进而导致心肌细胞损伤[51-52]。这种损伤如果不被限制, 将最终引起心肌衰竭[53]。运动促进db/db小鼠的心肌线粒体膜电位恢复, 从而降低胞质内细胞色素C的含量, 减少内源性凋亡的发生[54]。C-Jun N-端激酶是一种丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK), 可通过增加细胞内活化Caspase-9的含量, 促进线粒体细胞色素C的释放, 从而启动内源性凋亡途径[55]。研究表明, 运动可减弱糖尿病模型大鼠心肌中C-Jun N-端激酶的活化, 从而减少心肌细胞过度凋亡。适当运动可提高抑凋亡蛋白Bcl-2的表达水平, 最终对糖尿病小鼠心肌细胞起抗凋亡作用[56]。KANTER等[57]发现, 低强度运动可降低糖尿病大鼠心脏组织丙二醇含量, 增加抗氧化酶类物质如超氧化物歧化酶(Superoxide dismutase, SOD)、谷胱甘肽过氧化物酶(Glutathione peroxidase, GSH-Px)和过氧化氢酶的含量, 从而减少心脏组织凋亡。最近的一项研究表明, 运动似乎可以通过抑制内质网应激诱导的糖尿病大鼠的心肌凋亡来改善DC, 且其方式呈强度依赖性[58]。

2.5 运动通过减少心肌纤维化改善DC

DC最显著的临床病理特征是心脏组织纤维化, 其主要包括心肌糖原积累和胶原过剩、心肌间质细胞和血管纤维化, 进而发展为心脏正常起搏功能的失调[59-60]。多项研究表明, 运动可通过减少血糖含量和降低血压水平, 改善心肌代谢功能, 降低心肌糖原积累和胶原过剩导致的纤维化, 从而恢复心脏正常生理结构并改善其收缩功能[54,59]。基质金属蛋白酶-2(matrix metalloproteinase-2, Mmp2)是一种促进胶原降解的蛋白, 其表达受运动影响, 研究发现适当运动可促进MMP2的表达, 从而抑制心肌纤维化的形成[22]。除了降低血糖和血压水平外, 运动还可通过增加葡萄糖转运和摄取相关的蛋白改变心肌代谢状态, 减少糖原积累和胶原过剩, 从而降低心肌间质细胞和血管的纤维化[61]。NOVOA等[62]的研究表明, 高强度的慢性运动对心脏重构有积极的影响, 表现为心肌细胞肥大减少、胶原沉积减少、心肌纤维化改善。

3 结语与展望

近年来, 糖尿病患病率在全球范围内日益增加, 而DC是导致糖尿病患者死亡的主要原因。运动可改善糖尿病相关的多个病症, 包括胰岛素抵抗、血



图中向上箭头代表促进, 向下箭头代表抑制。

The upward arrow represents promotion and the downward arrow represents inhibition.

图1 DC的病理特征和运动促进DC恢复的机制

Fig.1 Pathological features of DC and the mechanism by which exercise promotes DC recovery

糖血脂失衡和炎症紊乱等, 并对心脏功能恢复具有显著效果。多项研究揭示运动训练可通过不同分子机制改善DC病理发展, 包括改善心脏代谢、线粒体功能障碍、Ca^{2+}稳态失衡、心肌细胞过度凋亡和纤维化等(图1)。值得注意的是, 心脏在不同的运动反应中有明显不同的分子途径, 如何深刻理解运动所产生的生物学效应对于靶向改善心脏功能是关键。例如, 在运动的适应性反应中, 心脏很可能存在短暂的时间依赖性变化, 不同的运动模式、持续时间和强度的训练方案可能导致治疗结果之间的差异[22]。另外, 由于DC发展的复杂性, 如何根据DC的病症发展制定不同的运动训练方案是至关重要的。然而, 运动训练有益作用背后的分子机制尚未被完全阐明。因此, 预临床和临床研究的进展可为未来新的运动治疗策略的推广提供更好的理论基础。

参考文献 (References)

[1] AMERICAN DIABETES A. 2. classification and diagnosis of diabetes: standards of medical care in diabetes-2021 [J]. Diabetes Care, 2021, 44: S15-33.

[2] DILLMANN W H. Diabetic cardiomyopathy [J]. Circ Res, 2019, 124: 1160-2.

[3] 张雄慧, 郭浩, 米卓卓, 等. 糖尿病心肌病发病机制研究进展[J]. 现代医药卫生(ZHANG X H, GUO H, MI Z Z, et al. Advances in the pathogenesis of diabetic cardiomyopathy [J]. Mod Med Heal), 2021, 37: 3850-4.

[4] RITCHIE R H, ABEL E D. Basic mechanisms of diabetic heart disease [J]. Circ Res, 2020, 126: 1501-25.

[5] FILLMORE N, MORI J, LOPASCHUK G D. Mitochondrial fatty acid oxidation alterations in heart failure, ischaemic heart disease and diabetic cardiomyopathy [J]. Br J Pharmacol, 2014, 171: 2080-90.

[6] ZHU C, ZHANG H, WEI D, et al. Silencing lncRNA GAS5 alleviates apoptosis and fibrosis in diabetic cardiomyopathy by targeting miR-26a/b-5p [J]. Acta Diabetol, 2021, 58: 1491-501.

[7] DIA M, GOMEZ L, THIBAULT H, et al. Reduced reticulum-mitochondria Ca^{2+} transfer is an early and reversible trigger of mitochondrial dysfunctions in diabetic cardiomyopathy [J]. Basic Res Cardiol, 2020, 115: 74.

[8] 刘辉, 段佳琪, 任晓梅, 等. 2型糖尿病患者心肌间充质细胞基因表达变化及相关环境化学物的筛选[J]. 中国医学科学院学报(LIU H, DUAN J Q, REN X M, et al. Changes in gene expression and related environmental chemicals in myocardial mesenchymal cells of patients with type 2 diabetes mellitus [J]. Acta Academiae Medicinae Sinicae), 2020, 42: 37-46.

[9] JIA G, HILL M A, SOWERS J R. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity [J]. Circ Res, 2018, 122: 624-38.

[10] PETERSON L R, GROPLER R J. Metabolic and molecular imaging of the diabetic cardiomyopathy [J]. Circ Res, 2020, 126: 1628-45.

[11] TAN Y, ZHANG Z, ZHENG C, et al. Mechanisms of diabetic cardiomyopathy and potential therapeutic strategies: preclinical and clinical evidence [J]. Nat Rev Cardiol, 2020, 17: 585-607.

[12] 佟红娜, 张晨阳, 韩美欣, 等. 糖尿病心肌病的发病机制及药物干预研究进展[J]. 中国实验方剂学杂志(TONG H N, ZHANG C Y, HAN M X, et al. Research progress on pathogenesis and drug intervention of diabetic cardiomyopathy [J]. Chin J Exp Tradit Med Form), 2022, 28: 257-65.

[13] PAN B, GE L, XUN Y Q, et al. Exercise training modalities in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis [J]. Int J Behav Nutr Phys Act, 2018, 15: 72.

[14] 刘得锐, 常凤, 罗财, 等. 运动干预糖尿病前期的机制与应用研究进展[J]. 辽宁体育科技(LIU D R, CHANG F, LUO C, et al. Research progress on mechanism and application of exercise intervention in prediabetes [J]. Liaoning Sport Science and Technology), 2020, 42: 49-53,7.

[15] EPP R A, SUSSER S E, MORISSETTE M P, et al. Exercise training prevents the development of cardiac dysfunction in the

low-dose streptozotocin diabetic rats fed a high-fat diet [J]. Can J Physiol Pharmacol, 2013, 91: 80-9.

[16] 郑东波. 运动干预联合二甲双胍治疗糖尿病前期患者的临床效果研究[J]. 临床医学工程(ZHENG D B. Clinical effect of exercise intervention combined with metformin in the treatment of prediabetic patients [J]. Clinical Medical & Engineering), 2021, 28: 957-8.

[17] 刘映云, 胡素恒, 黎洁银. 有氧运动结合抗阻训练应用于2型糖尿病患者临床效果分析[J]. 白求恩医学杂志(LIU Y Y, HU S H, LI J Y. Clinical effect analysis of aerobic exercise combined with resistance training in patients with type 2 diabetes [J]. Journal of Bethune Military Medical College), 2020, 18: 574-6.

[18] 常翠青. 2型糖尿病患者的个体化运动处方[J]. 中国医学科学院学报(CHANG C Q. Individualized exercise prescription for type 2 diabetes [J]. Acta Academiae Medicinae Sinicae), 2011, 33: 248-52.

[19] SACRE J W, JELLIS C L, JENKINS C, et al. A six-month exercise intervention in subclinical diabetic heart disease: effects on exercise capacity, autonomic and myocardial function [J]. Metabolism, 2014, 63: 1104-14.

[20] KARJALAINEN J J, KIVINIEMI A M, HAUTALA A J, et al. Effects of physical activity and exercise training on cardiovascular risk in coronary artery disease patients with and without type 2 diabetes [J]. Diabetes Care, 2015, 38: 706-15.

[21] CORTASSA S, CACERES V, TOCCHETTI C G, et al. Metabolic remodelling of glucose, fatty acid and redox pathways in the heart of type 2 diabetic mice [J]. J Physiol, 2020, 598: 1393-415.

[22] HAFSTAD A D, LUND J, HADLER-OLSEN E, et al. High- and moderate-intensity training normalizes ventricular function and mechanoenergetics in mice with diet-induced obesity [J]. Diabetes, 2013, 62: 2287-94.

[23] DORN G W 2nd, VEGA R B, KELLY D P. Mitochondrial biogenesis and dynamics in the developing and diseased heart [J]. Genes Dev, 2015, 29: 1981-91.

[24] AON M A, TOCCHETTI C G, BHATT N, et al. Protective mechanisms of mitochondria and heart function in diabetes [J]. Antioxid Redox Signal, 2015, 22: 1563-86.

[25] YUE Y, MENG K, PU Y, et al. Transforming growth factor beta (TGF-beta) mediates cardiac fibrosis and induces diabetic cardiomyopathy [J]. Diabetes Res Clin Pract, 2017, 133: 124-30.

[26] FRUSTACI A, KAJSTURA J, CHIMENTI C, et al. Myocardial cell death in human diabetes [J]. Circ Res, 2000, 87: 1123-32.

[27] CUGUSI L, MANCA A, BASSAREO P P, et al. Supervised aquatic-based exercise for men with coronary artery disease: a meta-analysis of randomised controlled trials [J]. Eur J Prev Cardiol, 2020, 27: 2387-92.

[28] CUGUSI L, MANCA A, BERGAMIN M, et al. Zumba fitness and women's cardiovascular health: a systematic review [J]. J Cardiopulm Rehabil Prev, 2019, 39: 153-60.

[29] CUGUSI L, MANCA A, YEO T J, et al. Nordic walking for individuals with cardiovascular disease: a systematic review and meta-analysis of randomized controlled trials [J]. Eur J Prev Cardiol, 2017, 24: 1938-55.

[30] NUHU J M, MAHARAJ S S. Influence of a mini-trampoline rebound exercise program on insulin resistance, lipid profile and central obesity in individuals with type 2 diabetes [J]. J Sports Med Phys Fitness, 2018, 58: 503-9.

[31] REES J L, JOHNSON S T, BOULE N G. Aquatic exercise for adults with type 2 diabetes: a meta-analysis [J]. Acta Diabetol, 2017, 54: 895-904.

[32] THIND H, LANTINI R, BALLETTO B L, et al. The effects of yoga among adults with type 2 diabetes: a systematic review and meta-analysis [J]. Prev Med, 2017, 105: 116-26.

[33] ZHOU Z, ZHOU R, LI K, et al. Effects of tai chi on physiology, balance and quality of life in patients with type 2 diabetes: a systematic review and meta-analysis [J]. J Rehabil Med, 2019, 51: 405-17.

[34] GARVEY W T, HARDIN D, JUHASZOVA M, et al. Effects of diabetes on myocardial glucose transport system in rats: implications for diabetic cardiomyopathy [J]. Am J Physiol, 1993, 264: H837-44.

[35] NAKAI N, MIYAZAKI Y, SATO Y, et al. Exercise training increases the activity of pyruvate dehydrogenase complex in skeletal muscle of diabetic rats [J]. Endocr J, 2002, 49: 547-54.

[36] POLD R, JENSEN L S, JESSEN N, et al. Long-term AICAR administration and exercise prevents diabetes in ZDF rats [J]. Diabetes, 2005, 54: 928-34.

[37] BRODERICK T L, POIRIER P, GILLIS M. Exercise training restores abnormal myocardial glucose utilization and cardiac function in diabetes [J]. Diabetes Metab Res Rev, 2005, 21: 44-50.

[38] MEDFORD H M, PORTER K, MARSH S A. Immediate effects of a single exercise bout on protein O-GlcNAcylation and chromatin regulation of cardiac hypertrophy [J]. Am J Physiol Heart Circ Physiol, 2013, 305: H114-23.

[39] CROSTON T L, THAPA D, HOLDEN A A, et al. Functional deficiencies of subsarcolemmal mitochondria in the type 2 diabetic human heart [J]. Am J Physiol Heart Circ Physiol, 2014, 307: H54-65.

[40] VASQUEZ-TRINCADO C, GARCIA-CARVAJAL I, PENNANEN C, et al. Mitochondrial dynamics, mitophagy and cardiovascular disease [J]. J Physiol, 2016, 594: 509-25.

[41] SEARLS Y M, SMIRNOVA I V, FEGLEY B R, et al. Exercise attenuates diabetes-induced ultrastructural changes in rat cardiac tissue [J]. Med Sci Sports Exerc, 2004, 36: 1863-70.

[42] WANG H, BEI Y, LU Y, et al. Exercise prevents cardiac injury and improves mitochondrial biogenesis in advanced diabetic cardiomyopathy with PGC-1alpha and Akt activation [J]. Cell Physiol Biochem, 2015, 35: 2159-68.

[43] WANG S Y, ZHU S, WU J, et al. Exercise enhances cardiac function by improving mitochondrial dysfunction and maintaining energy homoeostasis in the development of diabetic cardiomyopathy [J]. J Mol Med, 2020, 98: 245-61.

[44] ZHAO H X, ZHANG Z, ZHOU H L, et al. Exercise training suppresses Mst1 activation and attenuates myocardial dysfunction in mice with type 1 diabetes [J]. Can J Physiol Pharmacol, 2020, 98: 777-84.

[45] JAQUENOD DE GIUSTI C, PALOMEQUE J, MATTIAZZI A. Ca^{2+} mishandling and mitochondrial dysfunction: a converging road to prediabetic and diabetic cardiomyopathy [J]. Pflugers Arch, 2022, 474: 33-61.

[46] JI L, LIU F, JING Z, et al. MICU1 alleviates diabetic cardiomyopathy through mitochondrial Ca^{2+}-dependent antioxidant response [J]. Diabetes, 2017, 66: 1586-600.

[47] MAIUOLO J, CARRESI C, GLIOZZI M, et al. Effects of bergamot polyphenols on mitochondrial dysfunction and sarcoplasmic reticulum stress in diabetic cardiomyopathy [J]. Nutrients, 2021, 13.

[48] DHALLA N S, RANGI S, ZIEROTH S, et al. Alterations in sarcoplasmic reticulum and mitochondrial functions in diabetic cardiomyopathy [J]. Exp Clin Cardiol, 2012, 17: 115-20.

[49] SHAO C H, WEHRENS X H, WYATT T A, et al. Exercise training during diabetes attenuates cardiac ryanodine receptor dysregulation [J]. J Appl Physiol, 2009, 106: 1280-92.

[50] STOLEN T O, HOYDAL M A, KEMI O J, et al. Interval training normalizes cardiomyocyte function, diastolic Ca^{2+} control, and SR Ca^{2+} release synchronicity in a mouse model of diabetic cardiomyopathy [J]. Circ Res, 2009, 105: 527-36.

[51] REN B C, ZHANG Y F, LIU S S, et al. Curcumin alleviates oxidative stress and inhibits apoptosis in diabetic cardiomyopathy via Sirt1-Foxo1 and PI3K-Akt signalling pathways [J]. J Cell Mol Med, 2020, 24: 12355-67.

[52] GE Q, ZHAO L, REN X M, et al. LCZ696, an angiotensin receptor-neprilysin inhibitor, ameliorates diabetic cardiomyopathy by inhibiting inflammation, oxidative stress and apoptosis [J]. Exp Biol Med, 2019, 244: 1028-39.

[53] OUYANG C, YOU J, XIE Z. The interplay between autophagy and apoptosis in the diabetic heart [J]. J Mol Cell Cardiol, 2014, 71: 71-80.

[54] VEERANKI S, GIVVIMANI S, KUNDU S, et al. Moderate intensity exercise prevents diabetic cardiomyopathy associated contractile dysfunction through restoration of mitochondrial function and connexin 43 levels in db/db mice [J]. J Mol Cell Cardiol, 2016, 92: 163-73.

[55] ZHOU Y Y, LI Y, JIANG W Q, et al. MAPK/JNK signalling: a potential autophagy regulation pathway [J]. Biosci Rep, 2015, 35.

[56] CHENG S M, HO T J, YANG A L, et al. Exercise training enhances cardiac IGFI-R/PI3K/Akt and Bcl-2 family associated pro-survival pathways in streptozotocin-induced diabetic rats [J]. Int J Cardiol, 2013, 167: 478-85.

[57] KANTER M, AKSU F, TAKIR M, et al. Effects of low intensity exercise against apoptosis and oxidative stress in streptozotocin-induced diabetic rat heart [J]. Exp Clin Endocrinol Diabetes, 2017, 125: 583-91.

[58] CHENGJI W, XIANJIN F. Exercise protects against diabetic cardiomyopathy by the inhibition of the endoplasmic reticulum stress pathway in rats [J]. J Cell Physiol, 2019, 234: 1682-8.

[59] SILVA E, NATALI A J, SILVA M F, et al. Ventricular remodeling in growing rats with experimental diabetes: the impact of swimming training [J]. Pathol Res Pract, 2013, 209: 618-26.

[60] EVANGELISTA I, NUTI R, PICCHIONI T, et al. Molecular dysfunction and phenotypic derangement in diabetic cardiomyopathy [J]. Int J Mol Sci, 2019, 20(13): 3264.

[61] LUND J, HAFSTAD A D, BOARDMAN N T, et al. Exercise training promotes cardioprotection through oxygen-sparing action in high fat-fed mice [J]. Am J Physiol Heart Circ Physiol, 2015, 308: H823-9.

[62] NOVOA U, ARAUNA D, MORAN M, et al. High-intensity exercise reduces cardiac fibrosis and hypertrophy but does not restore the nitroso-redox imbalance in diabetic cardiomyopathy [J]. Oxid Med Cell Longev, 2017, 2017: 7921363.