Role of bariatric surgery in improving diabetic cardiomyopathy: Molecular mechanisms and therapeutic perspectives (Review)

KE SONG[1,2], DIANYUAN LIANG[1,2], DINGQI XIAO[2], AIJIA KANG[2] and YIXING REN[1-3]

[1]Department of Gastroenterology, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan 637000, P.R. China; [2]Institute of Hepatobiliary Pancreatic Intestinal Diseases, North Sichuan Medical College, Nanchong, Sichuan 637000, P.R. China; [3]Department of General Surgery, Chengdu XinHua Hospital Affiliated to North Sichuan Medical College, Chengdu, Sichuan 610000, P.R. China

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Abstract. Diabetic cardiomyopathy (DCM), a significant complication of diabetes mellitus, is marked by myocardial structural and functional alterations due to chronic hyperglycemia. Despite its clinical significance, optimal treatment strategies are still elusive. Bariatric surgery via sleeve gastrectomy and Roux-en-Y gastric bypass have shown promise in treating morbid obesity and associated metabolic disorders including improvements in diabetes mellitus and DCM. The present study reviews the molecular mechanisms by which bariatric surgery improves DCM, offering insights into potential therapeutic targets. Future research should further investigate the mechanistic links between bariatric surgery and DCM, to evaluate the benefits and limitations of these surgical interventions for DCM treatment. The present study aims to provide a foundation for more effective DCM therapies, contributing to the advancement of patient care.

Contents

Correspondence to: Professor Yixing Ren, Department of Gastroenterology, Affiliated Hospital of North Sichuan Medical College, 1 Maoyuan South Road, Shunqing, Nanchong, Sichuan 637000, P.R. China
E-mail: yixingren@nsmc.edu.cn

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1. Introduction

Diabetes mellitus, an age-related metabolic disorder of escalating global prevalence, is a formidable clinical challenge to public health, with the number of affected individuals expected to reach 783 million by 2045 (1). The chronic nature of diabetes, with the associated insulin resistance and hyperinsulinemia, can precipitate a distinct form of cardiomyopathy, diabetic cardiomyopathy (DCM), that develops independently of traditional risk factors such as coronary artery disease and hypertension (2). As a serious and under-recognized complication of diabetes, the pathogenesis of DCM is complex and multifactorial (3,4). DCM is characterized by an initial phase of myocardial fibrosis and diastolic dysfunction, which may evolve into progressive systolic impairment and, ultimately, heart failure (5,6). Advanced cardiac dysfunction in DCM is a principal determinant of mortality among diabetic patients (7-9).

Bariatric surgery, a transformative metabolic intervention, is a pivotal treatment for severe obesity, which is uniquely capable of inducing sustained weight loss and significantly ameliorating complications (10). This surgical approach surpasses conventional pharmacotherapy in its ability to enhance insulin sensitivity, stabilize blood glucose and lipid levels, and ameliorate diabetes-related complications (2). Mingrone *et al* (11) found that Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion could effectively alleviate DCM. English and Williams (12) found that numerous patients with type 2 diabetes mellitus complicated with other cardiovascular diseases can reduce or completely stop cardiovascular medications after undergoing bariatric surgery. Improvement in left ventricular structure and function, visceral fat and reverse myocardial remodeling after bariatric surgery may be beneficial for the recovery of DCM (13,14). The present review will discuss recent research advances in bariatric surgery to improve DCM (Fig. 1), with the aim to aid the understanding of the pathogenesis of DCM, explore new therapeutic targets and develop more targeted drugs.

2. Bariatric surgery-a procedure originally developed to treat obesity

Bariatric surgery was initially referred termed weight-loss surgery (15). Obesity became increasingly prominent in

the mid-20th century, but strategies to curb this worldwide epidemic were limited (16). At that time, oral medications (such as ephedrine and amphetamine) were often prescribed to help obese patients lose weight, but were usually inadequate to achieve meaningful and sustainable results. By contrast, metabolic and weight-loss surgery is performed only on a small number of eligible patients but has been shown to be the most effective intervention to ensure significant weight loss and amelioration of associated comorbidities (such as diabetes, hypertension, dyslipidemia and cancer) (17-20).

In addition to treating obesity, bariatric surgery is more advantageous than pharmacological treatment alone in terms of glycemic control and reduction of cardiovascular risk factors (21). Moreover, its mechanism is not only limited to the simple reduction of body mass but also includes the improvement of enteric insulin levels, insulin secretion and insulin sensitivity (22,23). Kopp *et al* (24) found that C-reactive protein and interleukin-6 circulating levels decrease almost immediately after RYGB or sleeve gastrectomy (SG), while insulin sensitivity improves. Changes in cardiac structure and function also occur in the months and years after surgery, including mainly a reduction in left ventricular mass. However, this may be unrelated to a decrease in blood pressure (25-30). Rider *et al* (26) performed MRI examinations on 30 obese individuals without cardiac risk factors at baseline and one year after weight loss (bariatric surgery or dieting). Among them, 13 obese patients with left ventricular ejection fraction (LVEF) exceeding 40% showed regression of subclinical abnormalities of myocardial deformability within 6-24 months after bariatric surgery (31). At present, the mechanisms by which bariatric surgery regulates metabolism to improve metabolic diseases is a topic of significant research interest.

3. DCM-the leading cause of heart failure among diabetic patients

In 1972, Rubler *et al* (32) identified a new cardiomyopathy termed DCM in diabetic patients with a history of heart failure in the absence of coronary artery disease, hypertension or heart valve disease. Current diagnostic criteria for DCM include left ventricular diastolic dysfunction and/or reduced LVEF, pathologic left ventricular hypertrophy and interstitial fibrosis (33). DCM is considered one of the major complications of diabetes mellitus and is associated with numerous pathophysiological alterations, such as impaired signaling of cardiac insulin metabolism, mitochondrial dysfunction, increased oxidative stress, impaired calcium handling in the mitochondria and cardiomyocytes, inflammation, endoplasmic reticulum (ER) stress, microvascular dysfunction and cardiac metabolic abnormalities (2,5). All of these collectively promote interstitial fibrosis of the cardiac tissue, cardiac diastolic dysfunction and subsequent systolic dysfunction, ultimately leading to clinical heart failure syndromes (34). There are no specific and targeted treatments for DCM, but some non-specific treatments include lifestyle improvement, glycemic control, lipid lowering, treatment of heart failure and improvement of cardiovascular disease risk factors (35,36).

4. Mechanisms of bariatric surgery to improve DCM

Altered myocardial glucose uptake. Insulin resistance is one of the major pathogenic factors in DCM, and diabetes results in impaired insulin-mediated myocardial glucose uptake (MGU) and glucose utilization, and promotes a shift in substrate toward non-esterified fatty acid oxidation, which can lead to cardiac damage (2,37-39). PI3K/AKT is the central hub of signal transduction in the myocardial insulin signaling pathway (40,41), which receives upstream signals from the insulin substrate receptor family and plays a central role in promoting glucose transporter 4 (GLUT-4) translocation (42). There is still a gap between upstream insulin signaling and downstream GLUT-4 translocation (43,44). However, two novel AKT substrates, glucose metabolism regulator protein 160 and TBC1 domain family member 1 (TBC1D1), are prime candidates for potentially bridging this gap (45). These substrates essentially act as brakes on the cytosolic action of GLUT-4 vesicles and are phosphorylated by AKT in response to insulin, leading to the conversion of some downstream Rab proteins to active GTP-bound forms, thereby triggering GLUT-4 translocation to the cell membrane (45,46). However, studies on the roles of glucose metabolism regulatory proteins 160 and TBC1D1 in DCM are more limited. In a study addressing GLUT-4 translocation, Huang *et al* (37) found that after duodenal-jejunal bypass (DJB), MGU recovered and was involved in the remission of DCM after DJB by promoting GLUT-4 translocation. Furthermore, by assessing the uptake of myocardial energy substrates after bariatric surgery, DJB was found to restore MGU by promoting myocardial GLUT-4 translocation in diabetic rats, and phosphorylation and activation of glucose metabolism-regulating protein 160 was restored after DJB (37). This suggests that DJB alters the activity of the PI3K/AKT pathway by modulating the expression of glucose metabolism-regulating protein 160, thereby playing a key role in the recovery of MGUs (37). The study by Huang *et al* demonstrated that the improvement of MGU defects in diabetic rats by DJB was associated with the promotion of myocardial insulin signaling and GLUT-4 translocation. In addition, Xu *et al* (47) similarly found an improvement in MGU after SG surgery in Wistar rats in which DCM had been induced. This alteration was associated with a significant down-regulation of three MAPKs (phosphorylated p38, phosphorylated c-Jun N-terminal kinase and phosphorylated extracellular signal-regulated kinase 1/2) in the myocardial tissues of Wistar rats (Fig. 2). Although restoration of MGU and improvement of cardiac metabolic homeostasis were shown to be effective in reversing DCM (48), a gap still exists between increased myocardial GLUT-4 at the cell membrane and eventual improvement in cardiac function, and more studies are required to explore the association between the two.

Reduced myocardial fatty acid utilization. In the healthy heart, 50-70% of ATP is produced from fatty acids, however this percentage is higher in patients with obesity or diabetes, reaching 80-90% (49). Although the availability of fatty acids is essential for maintaining cardiac function, this greater reliance on fatty acids may also lead to myocardial lipotoxicity that can eventually result in myocardial dysfunction (49-51).

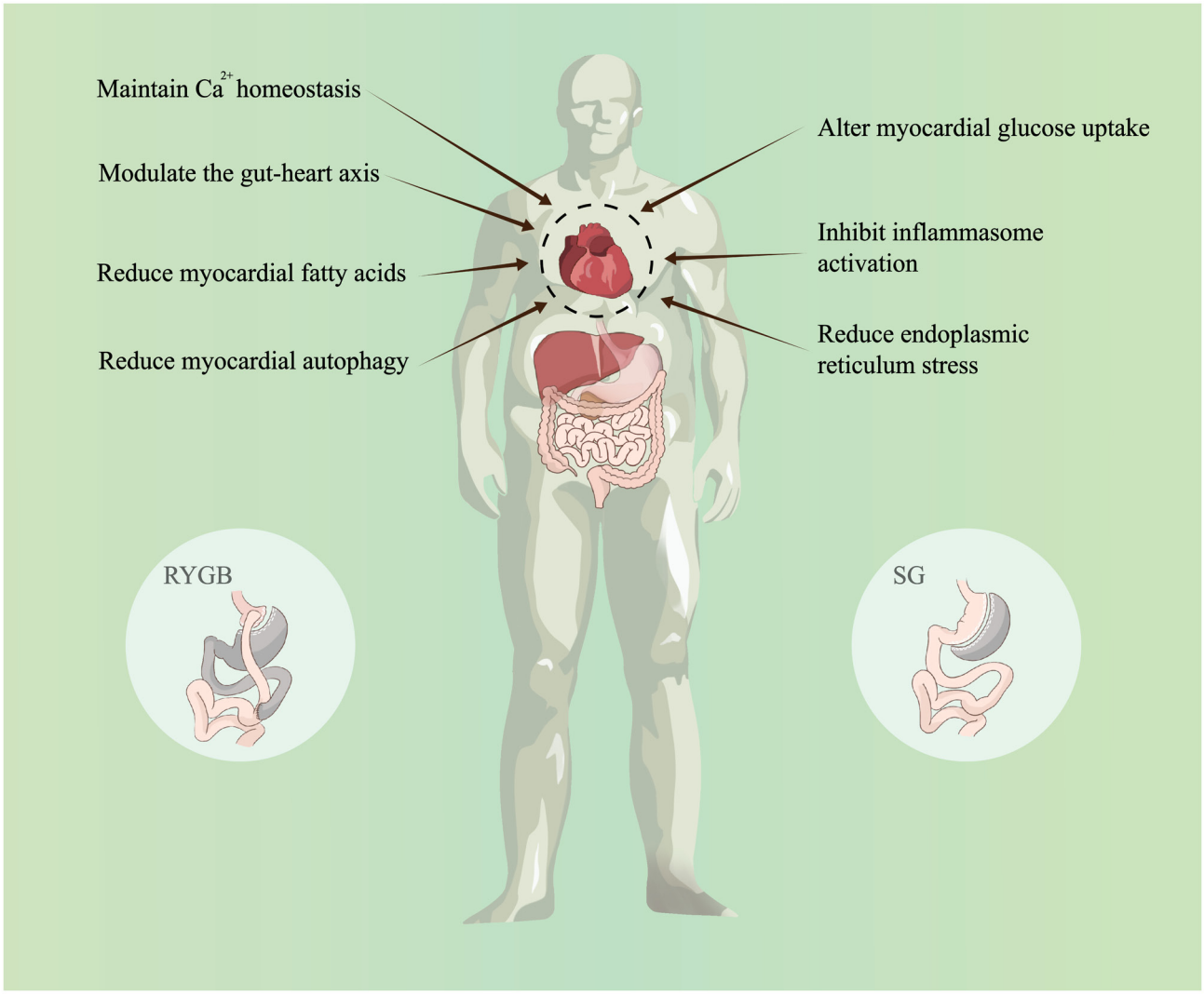

Figure 1. Possible mechanisms by which bariatric surgery improves DCM. Bariatric surgery may improve DCM by maintaining calcium homeostasis, regulating the gut-heart axis, reducing myocardial fatty acid formation, reducing myocardial mitochondrial autophagy, improving myocardial glucose uptake, inhibiting inflammasome activation and reducing endoplasmic reticulum stress. DCM, diabetic cardiomyopathy; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

Studies on animal models have shown that obesity increases myocardial fatty acid metabolism and oxygen consumption, leading to increased oxidative stress, cardiac dysfunction and increased apoptosis (52-55). Owing to disturbed lipid metabolism, excessive fat deposition in the heart creates a lipotoxic environment and induces insulin resistance, which not only impairs pancreatic β-cell function, but also increases myocardial uptake and utilization of fatty acids (56,57). Lin *et al* (58) measured a decrease in myocardial total fatty acid utilization in individuals with a body mass index of >30 kg/m^2 who underwent RYGB and decreased post-surgical left ventricular mass and relatively decreased myocardial total fatty acid oxidation. In addition, reduction in the left ventricular mass was an independent predictor of improvement in myocardial diastolic function, with a significant reduction in left ventricular end-diastolic volume and significant improvement in cardiac function in patients with reduced body mass. Carreau *et al* (59) found that bariatric surgery reduced cardiac fatty acid utilization and enhanced left ventricular function. Existing studies have reported both increases and decreases in fatty acid utilization after bariatric surgery (60,61), with a trend toward decreased fatty acid utilization in the short-term postoperative period (62). In addition, the effect of bariatric surgery on cardiac fatty acid partitioning in patients with type 2 diabetes has also been demonstrated (59), which provides strong evidence for improvement in postoperative DCM. However, more studies are needed to determine the effects of altered fatty acid utilization on cardiac structure and function after bariatric surgery and to determine whether these changes persist over time.

Reducing ER stress. The ER controls the proper folding of polypeptides and proteins through various chaperones and enzymes within the ER organelles (63). The ER folding process is disturbed when the overburdened protein folding exceeds the ER processing capacity, resulting in the accumulation of misfolded/unfolded proteins in the lumen of the ER, a state known as ER stress (63). ER stress plays an important role in the pathogenesis of DCM; furthermore, in diabetic patients, hyperglycemia and insulin resistance lead to an increase in

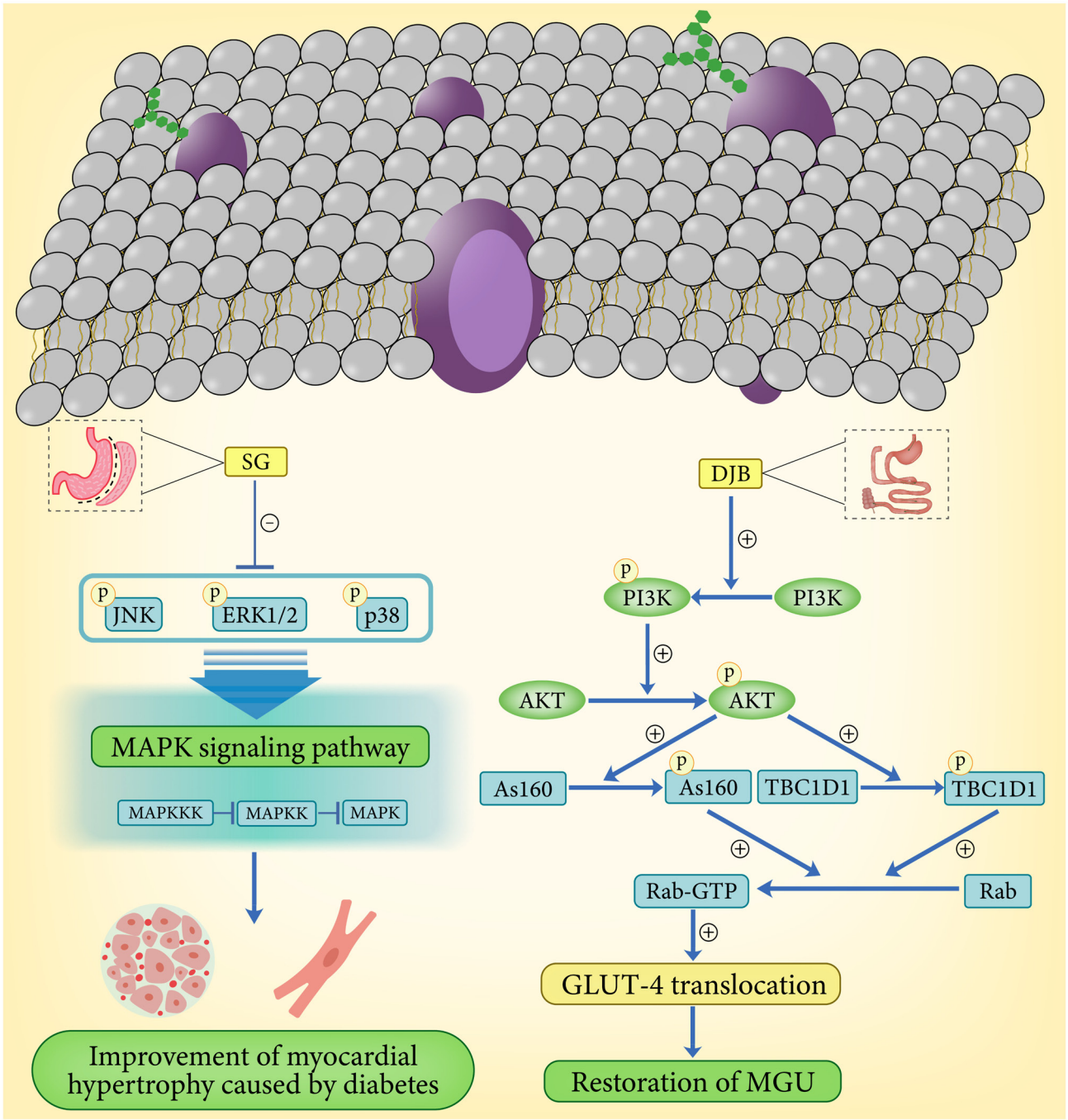

Figure 2. Possible mechanisms of DJB and SG in improving DCM. DJB promotes GLUT-4 translocation and restores MGU by activating the PI3K/AKT signaling pathway and downstream substrates. SG improves diabetes-induced myocardial hypertrophy by inhibiting the MAPK signaling pathway. DJB, duodenal-jejunal bypass; SG, sleeve gastrectomy; DCM, diabetic cardiomyopathy; GLUT-4, glucose transporter 4; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; MGU, myocardial glucose uptake; P, phosphorylated; JNK, c-Jun N-terminal kinase; ERK1/2, extracellular signal-regulated kinase 1/2; TBC1D1, TBC1 domain family member 1.

intracellular ER stress (64). Lakshmanan *et al* (65) found that ER stress can be induced by a variety of pathological conditions such as ischemia, oxidative stress, hypoxia, hyperglycemia and hyperlipidemia. Hyperglycemia-induced ER stress has been shown to play a major role in the pathology of cardiac dysfunction (66). ER stress-induced C/EBP homologous protein (CHOP) plays an important role in the apoptosis-promoting executive pathway, which is the most described and characterized pathway in ER stress-induced cell death, as well as the downstream signaling pathway of protein kinase R-like endoplasmic reticulum kinase (PERK) (67). The PERK downstream signaling pathway, which produces phosphorylated PERK when phosphorylated, triggers CHOP-induced apoptosis (68). In addition, caspase-12, another apoptotic signaling pathway in the cystatinase cascade reaction, is also closely associated to CHOP (69,70). Zhang *et al* (71) found that, compared with the sham surgery group, the expression of GRP78, PERK, phosphorylated PERK, CHOP and caspase-12 was positively expressed in the bariatric surgery group, indicating that bariatric surgery could alleviate ER

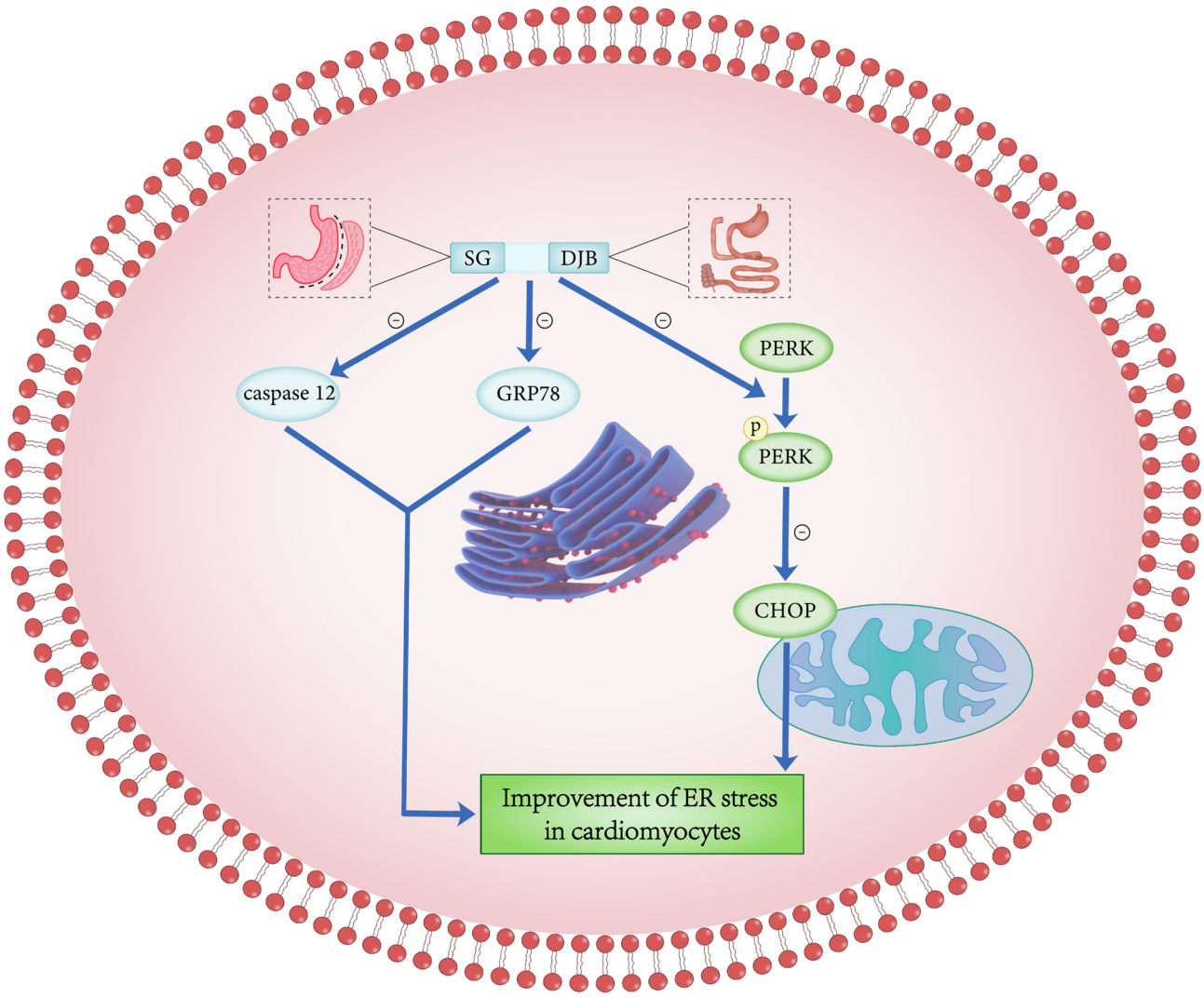

Figure 3. Possible mechanisms by which bariatric surgery improves ER stress in cardiomyocytes. SG and DJB improve ER stress in cardiomyocytes by decreasing signaling molecules related to apoptosis and ER stress in cardiomyocytes such as GRP78, PERK, P-PERK, CHOP and caspase 12. DJB, duodenal-jejunal bypass; SG, sleeve gastrectomy; PERK, protein kinase R-like endoplasmic reticulum kinase; CHOP, C/EBP homologous protein, ER endoplasmic reticulum; P, phosphorylated.

stress by significantly inhibiting CHOP and caspase-12 apoptotic signaling pathways (Fig. 3). ER protein homeostasis is controlled by the unfolded protein response (UPR), which is a signaling pathway that regulates the protein-folding ability of cells to maintain cellular secretory function (72,73). When the adaptive UPR fails to maintain ER homeostasis, maladaptive or terminal UPR is engaged, leading to disruption of the ER integrity and apoptosis (74). Glucose-regulated protein 78 kD (GRP78) is a protective molecular chaperone that binds to the UPR during initial ER stress, and GRP78 is a negative regulator of the UPR in a variety of models (75,76). Zhang *et al* (71) found that compared with the sham surgery group, the expression of GRP78 in the bariatric surgery group was significantly decreased, confirming that bariatric surgery could reduce ER stress in cardiomyocytes.

Altered myocardial autophagic flux and inhibition of NLRP3 inflammasome activation. Autophagy is a tightly regulated lysosomal degradation mechanism that plays an important role in maintaining intracellular homeostasis as well as coping with intracellular stress (77). During the development of diabetes mellitus, intracellular stress (such as ER stress) can activate autophagy, and the overactivation of autophagy in DCM cardiomyocytes can lead to self-digestion and increased reactive oxygen species generation (78). Huang *et al* (79) used chloroquine to determine myocardial autophagic flux through the expression of autophagy-related proteins. The results showed that autophagosome formation was weakened after SG and DJB, and that cardiomyocyte hypertrophy in the rats of the SG and DJB groups was also significantly ameliorated, and the degree of interstitial and perivascular fibrosis was lower than that of the sham-operated group. However, obesity in turn inhibits autophagy activation (80), and the effect of reduced fat load on autophagy after bariatric surgery should not be ignored. It has been reported that RYGB significantly activates hepatic autophagy and may be associated with altered glucagon-like peptide-1 (GLP-1) levels after surgery (81). Similarly, in cardiomyocytes, enhanced autophagy contributes to the amelioration of diabetes-induced cardiac injury (82,83) (Fig. 4). In summary, autophagy plays a dual role in DCM, and

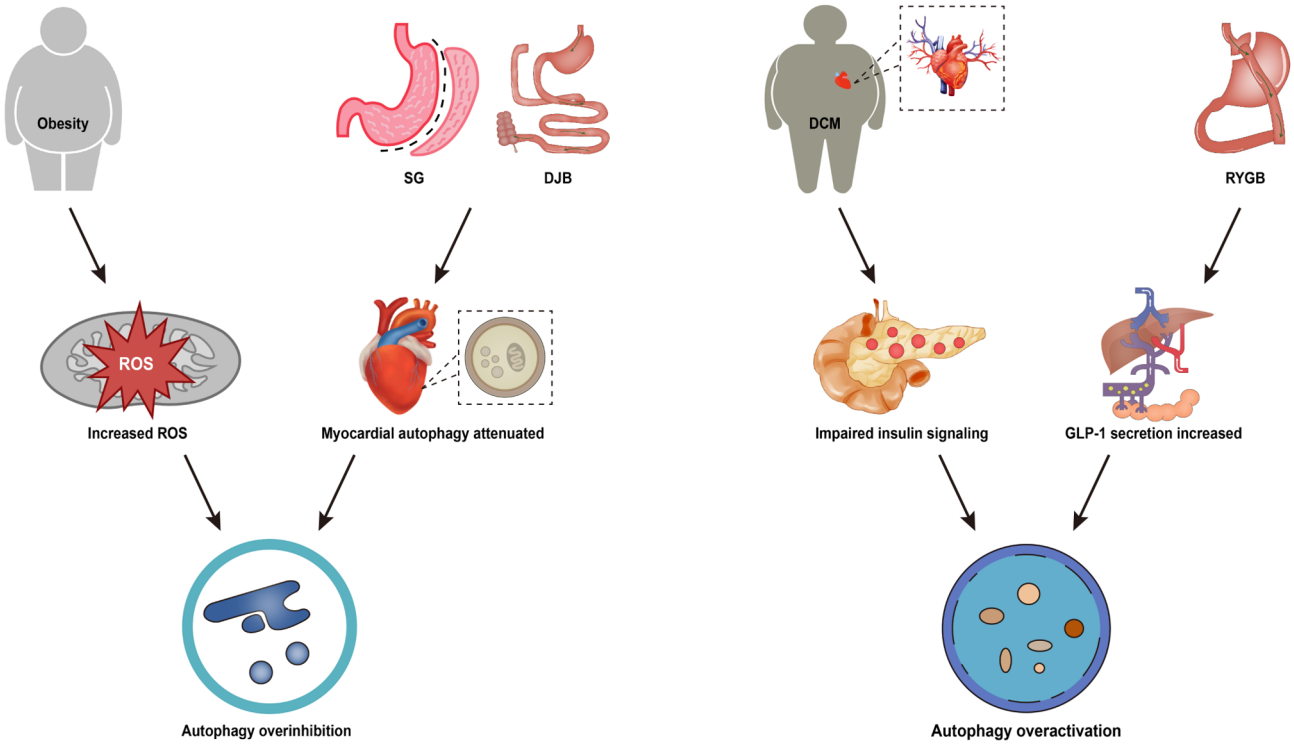

Figure 4. Schematic representation of the formation of autophagy inhibition/activation. Obesity or diabetic cardiomyopathy leads to over inhibition/activation of myocardial autophagy, which can be ameliorated by bariatric surgery. SG, sleeve gastrectomy; DJB, duodenal-jejunal bypass; RYGB, Roux-en-Y gastric bypass; ROS, reactive oxygen species; DCM, diabetic cardiomyopathy; GLP-1, glucagon-like peptide-1.

both inhibition and over-activation of myocardial autophagy can have pathological effects on DCM.

Evidence from several studies supports that the NLRP3 inflammasome is closely associated with the development of DCM (84-88). Bariatric surgery has been found to inhibit NLRP3 activation in pancreatic islets, hepatocytes and adipose tissue, and consequently exert anti-apoptotic and anti-inflammatory effects (89-92). Recently, Li *et al* (93) observed NLRP3 inflammatory vesicle-mediated inactivation of cardiomyocyte pyroptosis in SG mice. Reactive oxygen species play an important role in the pathogenesis of type 2 diabetes mellitus, and the overproduction of reactive oxygen species is considered to be a mechanism involved in the activation of NLRP3 inflammatory vesicles (84). Thus, the use of reactive oxygen species scavengers significantly reduced the expression of NLRP3. Reactive oxygen species are important regulators of NLRP3 inflammatory vesicles in cardiomyocytes (93). It has been shown that chloride efflux acts downstream of mitochondrial reactive oxygen species production and activates the NLRP3 inflammatory vesicles in macrophages (93). In addition, inhibition of volume-sensitive chloride currents reduces cell death and reverses the contractile dysfunction in cardiomyopathy (94). Myocardial NLRP3-mediated pyroptosis restored by high glucose stimulation was observed after administration of chloride channel blockers to SG rats, suggesting that chloride efflux may act as a messenger to regulate the NLRP3 assembly and activation, either directly or indirectly (93). It is therefore clear that cardiac remodeling in DCM rats can be significantly reversed by reducing reactive oxygen/chlorine ion efflux-mediated NLRP3 inflammatory vesicle activation after SG. However, Yang *et al* (95) found that metformin could inhibit the expression of the NLRP3 inflammasome by activating autophagy in DCM cardiomyocytes, which seemed to be in contrast to the results of Huang *et al* (79) in terms of exerting cardioprotective function. It is evident that bariatric surgery still has a great potential to be investigated in terms of the regulation of myocardial autophagy.

Restoration of mitochondrial homeostasis. Mitochondrial homeostasis is important for maintaining cellular metabolism and function (96). Calcium ions play an important role in mitochondrial synthesis (97). In diabetic cardiomyocytes, the decline in cardiomyocyte function is partly mediated by abnormal mitochondrial calcium handling and decreased free matrix calcium levels (98). The diminished mitochondrial capacity for Ca^{2+} uptake leads to reduced ATP production (99-101) and favors reactive oxygen species generation (102). Therefore, improper mitochondrial Ca^{2+} handling is considered a key factor in DCM cell dysfunction (103). Huang *et al* (79) performed SG, DJB and sham operations on male Sprague-Dawley rats that had been induced with DCM, and subsequently assessed the ventricular diastolic function and Ca^{2+} homeostasis by echocardiography and calcium fluorescent probe, respectively. The results showed that both systolic and diastolic functions of the heart were improved in the SG and DJB groups of rats after surgery, as well as myoplasmic reticulum Ca^{2+} release and Ca^{2+} decay. In addition, mitochondrial dysfunction was also improved by inactivation of nuclear receptor family group 4A member 1 (NR4A1) (104). NR4A1 causes disruption of mitochondrial homeostasis by promoting mitochondrial rupture and decreasing the mitochondrial membrane potential (105,106).

The inactivation of NR4A1 is closely associated with the AMPK pathway (107). It has been found that SG activates the AMPK signaling pathway, inhibits NR4A1 and corrects mitochondrial dysfunction *in vivo*, thus contributing to the improvement of DCM in terms of morphology and cardiac function (108). Under the pathological conditions of DCM, activation of silent information regulator 1 (SIRT1) and phosphorylation of AMPK can promote the clearance of dysfunctional mitochondria and peroxisomal enzymes to reverse cardiomyopathy development (109).

Regulation of the gut-heart axis. There is a bidirectional communication network between the gut and the heart, known as the 'gut-heart axis' (110). GLP-1 is secreted after meals, lowering glucose levels by enhancing insulin secretion and inhibiting glucagon release (111). Bariatric surgery not only increases postprandial GLP-1 release but also alters the gastrointestinal microbiota and bile acid profile cycle with beneficial effects (112,113). Bariatric surgery may alter the gut-heart axis through one or more mechanisms to obtain benefits in terms of improved cardiac function (114). GLP-1 analogs may exert cardiovascular protection by reducing inflammation (115), and increased levels of GLP-1 after bariatric surgery may reverse endothelial dysfunction and restore the endothelial-protective properties of high-density lipoproteins (116). Bile acids are considered to be important regulators of systemic metabolism, producing effects on obesity prevention and improving insulin resistance and hyperglycemia (117,118). Thus, alterations in bile acid levels and composition after gastric bypass may help to improve glucose and lipid metabolism in patients, which in turn modulates the gut-heart axis, protects the myocardium and improves myocardial fibrosis in terms of decreasing apoptosis, increasing glucose uptake, and reversing DCM (119). Alterations in gut flora after bariatric surgery have also been repeatedly reported in recent years, indicating that changes in intestinal flora after bariatric surgery may be related to improvements in glucose tolerance and insulin sensitivity, and may also regulate non-alcoholic fatty liver disease from multiple aspects such as the production of short-chain fatty acids and the regulation of one-carbon metabolism (120-125). Chaudhari *et al* (126) found that changes in the composition of the intestinal microbial community in mice after bariatric surgery may up-regulate the expression of bile acid-7-sulphate, thereby regulating the gut-heart axis. As the intestinal flora and its metabolites play an important regulatory role in cardiovascular disease, imbalance of the intestinal flora has been suggested to be an important pathological mechanism in the development of cardiovascular diseases (127,128). In summary, changes in GLP-1 release, bile acid levels and gut flora composition after bariatric surgery may facilitate improvements in DCM by exerting an effect on the gut-heart axis.

5. Potential novel therapeutic targets

Researchers have explored the molecular mechanisms underlying the improvements in DCM after bariatric surgery, but some potential therapeutic targets need further investigation. CD36 is a fatty acid transporter that is related to cardiac fatty acid uptake (129). Wang *et al* (130) hypothesized that the loss of the Takeda G protein-coupled receptor 5 (TGR5) promoted the localization of CD36 on the plasma membrane through aspartate-histidine-histidine-cysteine4 (DHHC4)-mediated CD36 palmitoylation, resulting in enhanced cardiac fatty acid uptake and lipid accumulation, indicating that the TGR5-DHHC4 pathway regulates cardiac fatty acid uptake and may be a potential target for the treatment of DCM. Ion channels play an important role in the pathogenesis of DCM, including changes in cation channels such as calcium, potassium and sodium, as well as anion channels (131). Studying the functional changes of calcium channels, sodium channels and potassium channels may provide new strategies for the treatment of DCM. In addition, based on the aforementioned effects of NR4A1 on mitochondria, studies have found that AMPK can further downregulate NR4A1 by activating SIRT1, thereby correcting mitochondrial dysfunction and enhancing myocardial energy production, and improving myocardial remodeling (132,133). Therefore, bariatric surgery restores mitochondrial homeostasis and alleviates DCM morphologically and functionally by maintaining myocardial Ca^{2+} homeostasis and downregulating NR4A1 expression (79,108). The decline in cardiomyocyte function is partly mediated by abnormal mitochondrial calcium handling and decreased free matrix calcium levels, which may be a good target for new therapeutic interventions (98,99,103).

6. Conclusion

DCM is one of the most serious complications of diabetes mellitus, and while its etiology involves the synergistic effect of multiple molecular mechanisms, the specific underlying pathogenesis is still unclear (101). Hence, the lack of specificity in DCM treatment is one of the reasons why a clinical cure is challenging. Currently, the mainstream treatment includes intensive glucose control, traditional Chinese medicine intervention and corresponding symptomatic treatment, but none of these approaches can further improve patient prognosis (134). Therefore, it is particularly important to explore new treatment modalities. Relevant basic experiments have proved that bariatric surgery can effectively alleviate or even reverse DCM-induced cardiomyopathy, but the specific mechanism of the therapeutic effect of bariatric surgery has not been fully elucidated (37,47,71). The present review summarized the latest advances in the treatment of DCM with bariatric surgery. It is critical to study the underlying mechanisms of cardiac microstructural changes after bariatric surgery to develop more effective therapeutic strategies. Furthermore, research should focus on the association between signaling pathways, and studies with clear experimental results should be shifted to clinical studies to guide the use of future medication, research and the development of new drugs. By elucidating the molecular and physiological responses to bariatric surgery, the present review aimed to enhance the understanding of DCM, identify new targets for intervention and advance the development of more efficacious and personalized treatment options. This research direction is pivotal for the advancement of clinical strategies that can effectively address the multifaceted challenges posed by DCM, ultimately improving patient care and outcomes.

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Authors' contributions

KS and YR conceived the subject of the review, performed the investigation, and wrote and edited the original draft. DL, DX and AK wrote, reviewed, and edited the manuscript and contributed to the figures. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ahmad E, Lim S, Lamptey R, Webb DR and Davies MJ: Type 2 diabetes. Lancet 400: 1803-1820, 2022.
2. Jia G, DeMarco VG and Sowers JR: Insulin resistance and hyperinsulinemia in diabetic cardiomyopathy. Nat Rev Endocrinol 12: 144-153, 2016.
3. Qiu Y, Buffonge S, Ramnath R, Jenner S, Fawaz S, Arkill KP, Neal C, Verkade P, White SJ, Hezzell M, *et al*: Endothelial glycocalyx is damaged in diabetic cardiomyopathy: Angiopoietin 1 restores glycocalyx and improves diastolic function in mice. Diabetologia 65: 879-894, 2022.
4. Khokhlova A, Myachina T, Volzhaninov D, Butova X, Kochurova A, Berg V, Gette I, Moroz G, Klinova S, Minigalieva I, *et al*: Type 1 diabetes impairs cardiomyocyte contractility in the left and right ventricular free walls but preserves it in the interventricular septum. Int J Mol Sci 23: 1719, 2022.
5. Tan Y, Zhang Z, Zheng C, Wintergerst KA, Keller BB and Cai L: Mechanisms of diabetic cardiomyopathy and potential therapeutic strategies: Preclinical and clinical evidence. Nat Rev Cardiol 17: 585-607, 2020.
6. Marfella R, Sardu C, Mansueto G, Napoli C and Paolisso G: Evidence for human diabetic cardiomyopathy. Acta Diabetol 58: 983-988, 2021.
7. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, *et al*: 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 41: 255-323, 2020.
8. Bellary S, Kyrou I, Brown JE and Bailey CJ: Type 2 diabetes mellitus in older adults: Clinical considerations and management. Nat Rev Endocrinol 17: 534-548, 2021.
9. Kelsey MD, Nelson AJ, Green JB, Granger CB, Peterson ED, McGuire DK and Pagidipati NJ: Guidelines for cardiovascular risk reduction in patients with type 2 diabetes: JACC guideline comparison. J Am Coll Cardiol 79: 1849-1857, 2022.
10. Arterburn DE, Telem DA, Kushner RF and Courcoulas AP: Benefits and risks of bariatric surgery in adults: A review. JAMA 324: 879-887, 2020.
11. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Nanni G, Castagneto M, Bornstein S and Rubino F: Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 Year follow-up of an open-label, single-centre, randomised controlled trial. Lancet 386: 964-973, 2015.
12. English WJ and Williams DB: Metabolic and bariatric surgery: An effective treatment option for obesity and cardiovascular disease. Prog Cardiovasc Dis 61: 253-269, 2018.
13. Sorimachi H, Obokata M, Omote K, Reddy YNV, Takahashi N, Koepp KE, Ng ACT, Rider OJ and Borlaug BA: Long-term changes in cardiac structure and function following bariatric surgery. J Am Coll Cardiol 80: 1501-1512, 2022.
14. Heidenreich P: Weight loss and cardiac reverse remodeling. J Am Coll Cardiol 80: 1513-1515, 2022.
15. Zhang H, Pu Y, Chen J, Tong W, Cui Y, Sun F, Zheng Z, Li Q, Yang T, Meng C, *et al*: Gastrointestinal intervention ameliorates high blood pressure through antagonizing overdrive of the sympathetic nerve in hypertensive patients and rats. J Am Heart Assoc 3: e000929, 2014.
16. Cao L, Qin X, Peterson MR, Haller SE, Wilson KA, Hu N, Lin X, Nair S, Ren J and He G: CARD9 knockout ameliorates myocardial dysfunction associated with high fat diet-induced obesity. J Mol Cell Cardiol 92: 185-195, 2016.
17. Martin M, Beekley A, Kjorstad R and Sebesta J: Socioeconomic disparities in eligibility and access to bariatric surgery: A national population-based analysis. Surg Obes Relat Dis 6: 8-15, 2010.
18. Nguyen N, Champion JK, Ponce J, Quebbemann B, Patterson E, Pham B, Raum W, Buchwald JN, Segato G and Favretti F: A review of unmet needs in obesity management. Obes Surg 22: 956-966, 2012.
19. Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, Barakat HA, deRamon RA, Israel G, Dolezal JM, *et al*: Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg 222: 339-352, 1995.
20. Phillips BT and Shikora SA: The history of metabolic and bariatric surgery: Development of standards for patient safety and efficacy. Metabolism 79: 97-107, 2018.
21. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, Thomas S, Abood B, Nissen SE and Bhatt DL: Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med 366: 1567-1576, 2012.
22. Pareek M, Schauer PR, Kaplan LM, Leiter LA, Rubino F and Bhatt DL: Metabolic surgery: Weight loss, diabetes, and beyond. J Am Coll Cardiol 71: 670-687, 2018.
23. Ferraz-Bannitz R, Kashyap S and Patti ME: Bariatric surgery: It's not just incretins! J Clin Endocrinol Metab 107: e883-e885, 2022.
24. Kopp HP, Kopp CW, Festa A, Krzyzanowska K, Kriwanek S, Minar E, Roka R and Schernthaner G: Impact of weight loss on inflammatory proteins and their association with the insulin resistance syndrome in morbidly obese patients. Arterioscler Thromb Vasc Biol 23: 1042-1047, 2003.
25. Leichman JG, Aguilar D, King TM, Mehta S, Majka C, Scarborough T, Wilson EB and Taegtmeyer H: Improvements in systemic metabolism, anthropometrics, and left ventricular geometry 3 months after bariatric surgery. Surg Obes Relat Dis 2: 592-599, 2006.
26. Rider OJ, Francis JM, Ali MK, Petersen SE, Robinson M, Robson MD, Byrne JP, Clarke K and Neubauer S: Beneficial cardiovascular effects of bariatric surgical and dietary weight loss in obesity. J Am Coll Cardiol 54: 718-726, 2009.
27. Ikonomidis I, Mazarakis A, Papadopoulos C, Patsouras N, Kalfarentzos F, Lekakis J, Kremastinos DT and Alexopoulos D: Weight loss after bariatric surgery improves aortic elastic properties and left ventricular function in individuals with morbid obesity: A 3-year follow-up study. J Hypertens 25: 439-447, 2007.

28. Willens HJ, Chakko SC, Byers P, Chirinos JA, Labrador E, Castrillon JC and Lowery MH: Effects of weight loss after gastric bypass on right and left ventricular function assessed by tissue Doppler imaging. Am J Cardiol 95: 1521-1524, 2005.
29. Garza CA, Pellikka PA, Somers VK, Sarr MG, Collazo-Clavell ML, Korenfeld Y and Lopez-Jimenez F: Structural and functional changes in left and right ventricles after major weight loss following bariatric surgery for morbid obesity. Am J Cardiol 105: 550-556, 2010.
30. Shah RV, Murthy VL, Abbasi SA, Eng J, Wu C, Ouyang P, Kwong RY, Goldfine A, Bluemke DA, Lima J and Jerosch-Herold M: Weight loss and progressive left ventricular remodelling: The multi-ethnic study of atherosclerosis (MESA). Eur J Prev Cardiol 22: 1408-1418, 2015.
31. Di Bello V, Santini F, Di Cori A, Pucci A, Talini E, Palagi C, Delle Donne MG, Marsili A, Fierabracci P, Valeriano R, *et al*: Effects of bariatric surgery on early myocardial alterations in adult severely obese subjects. Cardiology 109: 241-248, 2008.
32. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW and Grishman A: New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol 30: 595-602, 1972.
33. Avagimyan A, Popov S and Shalnova S: The pathophysiological basis of diabetic cardiomyopathy development. Curr Probl Cardiol 47: 101156, 2022.
34. Jia G, Whaley-Connell A and Sowers JR: Diabetic cardiomyopathy: A hyperglycaemia- and insulin-resistance-induced heart disease. Diabetologia 61: 21-28, 2018.
35. Pappachan JM, Varughese GI, Sriraman R and Arunagirinathan G: Diabetic cardiomyopathy: Pathophysiology, diagnostic evaluation and management. World J Diabetes 4: 177-189, 2013.
36. Nakamura K, Miyoshi T, Yoshida M, Akagi S, Saito Y, Ejiri K, Matsuo N, Ichikawa K, Iwasaki K, Naito T, *et al*: Pathophysiology and treatment of diabetic cardiomyopathy and heart failure in patients with diabetes mellitus. Int J Mol Sci 23: 3587, 2022.
37. Huang X, Wu D, Cheng Y, Zhang X, Liu T, Liu Q, Xia P, Zhang G, Hu S and Liu S: Restoration of myocardial glucose uptake with facilitated myocardial glucose transporter 4 translocation contributes to alleviation of diabetic cardiomyopathy in rats after duodenal-jejunal bypass. J Diabetes Investig 10: 626-638, 2019.
38. Bugger H and Abel ED: Molecular mechanisms of diabetic cardiomyopathy. Diabetologia 57: 660-671, 2014.
39. Zhou Z, Mahdi A, Tratsiakovich Y, Zahorán S, Kövamees O, Nordin F, Uribe Gonzalez AE, Alvarsson M, Östenson CG, Andersson DC, *et al*: Erythrocytes from patients with type 2 diabetes induce endothelial dysfunction via arginase I. J Am Coll Cardiol 72: 769-780, 2018.
40. Xiao H, Sun X, Lin Z, Yang Y, Zhang M, Xu Z, Liu P, Liu Z and Huang H: Gentiopicroside targets PAQR3 to activate the PI3K/AKT signaling pathway and ameliorate disordered glucose and lipid metabolism. Acta Pharm Sin B 12: 2887-2904, 2022.
41. Alaaeldin R, Abdel-Rahman IAM, Hassan HA, Youssef N, Allam AE, Abdelwahab SF, Zhao QL and Fathy M: Carpachromene ameliorates insulin resistance in HepG2 cells via modulating IR/IRS1/PI3k/Akt/GSK3/FoxO1 pathway. Molecules 26: 7629, 2021.
42. Zhang N, Liu X, Zhuang L, Liu X, Zhao H, Shan Y, Liu Z, Li F, Wang Y and Fang J: Berberine decreases insulin resistance in a PCOS rats by improving GLUT4: Dual regulation of the PI3K/AKT and MAPK pathways. Regul Toxicol Pharmacol 110: 104544, 2020.
43. Ruze R, Xu Q, Liu G, Li Y, Chen W, Cheng Z, Xiong Y, Liu S, Zhang G, Hu S and Yan Z: Central GLP-1 contributes to improved cognitive function and brain glucose uptake after duodenum-jejunum bypass on obese and diabetic rats. Am J Physiol Endocrinol Metab 321: E392-E409, 2021.
44. Wang N, Zhang S, Yuan Y, Xu H, Defossa E, Matter H, Besenius M, Derdau V, Dreyer M, Halland N, *et al*: Molecular basis for inhibiting human glucose transporters by exofacial inhibitors. Nat Commun 13: 2632, 2022.
45. Mafakheri S, Chadt A and Al-Hasani H: Regulation of RabGAPs involved in insulin action. Biochem Soc Trans 46: 683-690, 2018.
46. Lee KD, Ilavenil S, Karnan M, Yang CJ, Kim D and Choi KC: Novel bacillus ginsengihumi CMRO6 inhibits adipogenesis via p38MAPK/Erk44/42 and stimulates glucose uptake in 3T3-L1 pre-adipocytes through Akt/AS160 signaling. Int J Mol Sci 23: 4727, 2022.
47. Xu Q, Ding H, Li S, Dong S, Li L, Shi B, Zhong M and Zhang G: Sleeve gastrectomy ameliorates diabetes-induced cardiac hypertrophy correlates with the MAPK signaling pathway. Front Physiol 12: 785799, 2021.
48. Belke DD, Larsen TS, Gibbs EM and Severson DL: Altered metabolism causes cardiac dysfunction in perfused hearts from diabetic (db/db) mice. Am J Physiol Endocrinol Metab 279: E1104-E1113, 2000.
49. Lopaschuk GD, Ussher JR, Folmes CD, Jaswal JS and Stanley WC: Myocardial fatty acid metabolism in health and disease. Physiol Rev 90: 207-258, 2010.
50. Lopaschuk GD and Ussher JR: Evolving concepts of myocardial energy metabolism: More than just fats and carbohydrates. Circ Res 119: 1173-1176, 2016.
51. Carpentier AC: Abnormal myocardial dietary fatty acid metabolism and diabetic cardiomyopathy. Can J Cardiol 34: 605-614, 2018.
52. Zhou YT, Grayburn P, Karim A, Shimabukuro M, Higa M, Baetens D, Orci L and Unger RH: Lipotoxic heart disease in obese rats: Implications for human obesity. Proc Natl Acad Sci USA 97: 1784-1789, 2000.
53. Listenberger LL, Ory DS and Schaffer JE: Palmitate-induced apoptosis can occur through a ceramide-independent pathway. J Biol Chem 276: 14890-14895, 2001.
54. Aasum E, Hafstad AD, Severson DL and Larsen TS: Age-dependent changes in metabolism, contractile function, and ischemic sensitivity in hearts from db/db mice. Diabetes 52: 434-441, 2003.
55. Vincent HK, Powers SK, Dirks AJ and Scarpace PJ: Mechanism for obesity-induced increase in myocardial lipid peroxidation. Int J Obes Relat Metab Disord 25: 378-388, 2001.
56. Lopaschuk GD, Karwi QG, Tian R, Wende AR and Abel ED: Cardiac energy metabolism in heart failure. Circ Res 128: 1487-1513, 2021.
57. Wali JA, Jarzebska N, Raubenheimer D, Simpson SJ, Rodionov RN and O'Sullivan JF: Cardio-metabolic effects of high-fat diets and their underlying mechanisms-a narrative review. Nutrients 12: 1505, 2020.
58. Lin CH, Kurup S, Herrero P, Schechtman KB, Eagon JC, Klein S, Dávila-Román VG, Stein RI, Dorn GW II, Gropler RJ, *et al*: Myocardial oxygen consumption change predicts left ventricular relaxation improvement in obese humans after weight loss. Obesity (Silver Spring) 19: 1804-1812, 2011.
59. Carreau AM, Noll C, Blondin DP, Frisch F, Nadeau M, Pelletier M, Phoenix S, Cunnane SC, Guérin B, Turcotte EE, *et al*: Bariatric surgery rapidly decreases cardiac dietary fatty acid partitioning and hepatic insulin resistance through increased intra-abdominal adipose tissue storage and reduced spillover in type 2 diabetes. Diabetes 69: 567-577, 2020.
60. Middleton ALO, Byrne JP and Calder PC: The influence of bariatric (metabolic) surgery on blood polyunsaturated fatty acids: A systematic review. Clin Nutr ESPEN 48: 121-140, 2022.
61. Moreland AM, Santa Ana CA, Asplin JR, Kuhn JA, Holmes RP, Cole JA, Odstrcil EA, Van Dinter TG Jr, Martinez JG and Fordtran JS: Steatorrhea and hyperoxaluria in severely obese patients before and after Roux-en-Y gastric bypass. Gastroenterology 152: 1055-1067.e3, 2017.
62. Verna EC and Berk PD: Role of fatty acids in the pathogenesis of obesity and fatty liver: Impact of bariatric surgery. Semin Liver Dis 28: 407-426, 2008.
63. Ajoolabady A, Lebeaupin C, Wu NN, Kaufman RJ and Ren J: ER stress and inflammation crosstalk in obesity. Med Res Rev 43: 5-30, 2023.
64. Liang B, Chen SW, Li YY, Zhang SX and Zhang Y: Comprehensive analysis of endoplasmic reticulum stress-related mechanisms in type 2 diabetes mellitus. World J Diabetes 14: 820-845, 2023.
65. Lakshmanan AP, Harima M, Suzuki K, Soetikno V, Nagata M, Nakamura T, Takahashi T, Sone H, Kawachi H and Watanabe K: The hyperglycemia stimulated myocardial endoplasmic reticulum (ER) stress contributes to diabetic cardiomyopathy in the transgenic non-obese type 2 diabetic rats: A differential role of unfolded protein response (UPR) signaling proteins. Int J Biochem Cell Biol 45: 438-447, 2013.
66. Yu H, Zhen J, Yang Y, Gu J, Wu S and Liu Q: Ginsenoside Rg1 ameliorates diabetic cardiomyopathy by inhibiting endoplasmic reticulum stress-induced apoptosis in a streptozotocin-induced diabetes rat model. J Cell Mol Med 20: 623-631, 2016.
67. Hu H, Tian M, Ding C and Yu S: The C/EBP homologous protein (CHOP) transcription factor functions in endoplasmic reticulum stress-induced apoptosis and microbial infection. Front Immunol 9: 3083, 2018.
68. B'Chir W, Maurin AC, Carraro V, Averous J, Jousse C, Muranishi Y, Parry L, Stepien G, Fafournoux P and Bruhat A: The eIF2α/ATF4 pathway is essential for stress-induced autophagy gene expression. Nucleic Acids Res 41: 7683-7699, 2013.

69. Belali OM, Ahmed MM, Mohany M, Belali TM, Alotaibi MM, Al-Hoshani A and Al-Rejaie SS: LCZ696 Protects against diabetic cardiomyopathy-induced myocardial inflammation, ER stress, and apoptosis through inhibiting AGEs/NF-κB and PERK/CHOP signaling pathways. Int J Mol Sci 23: 1288, 2022.
70. Meng Y, Xu X, Niu D, Xu Y, Qiu Y, Zhu Z, Zhang H and Yin D: Organophosphate flame retardants induce oxidative stress and Chop/Caspase 3-related apoptosis via Sod1/p53/Map3k6/Fkbp5 in NCI-1975 cells. Sci Total Environ 819: 153160, 2022.
71. Zhang X, Liu S, Zhang G, Zhong M, Liu T, Wei M, Wu D, Huang X, Cheng Y, Wu Q and Hu S: Bariatric surgery ameliorates diabetic cardiac dysfunction by inhibiting ER stress in a diabetic rat model. Obes Surg 27: 1324-1334, 2017.
72. Hetz C, Zhang K and Kaufman RJ: Mechanisms, regulation and functions of the unfolded protein response. Nat Rev Mol Cell Biol 21: 421-438, 2020.
73. Ron D and Walter P: Signal integration in the endoplasmic reticulum unfolded protein response. Nat Rev Mol Cell Biol 8: 519-5, 2007.
74. Ren J, Bi Y, Sowers JR, Hetz C and Zhang Y: Endoplasmic reticulum stress and unfolded protein response in cardiovascular diseases. Nat Rev Cardiol 18: 499-521, 2021.
75. Zhu G and Lee AS: Role of the unfolded protein response, GRP78 and GRP94 in organ homeostasis. J Cell Physiol 230: 1413-1420, 2015.
76. Elfiky AA, Baghdady AM, Ali SA and Ahmed MI: GRP78 targeting: Hitting two birds with a stone. Life Sci 260: 118317, 2020.
77. Kitada M and Koya D: Autophagy in metabolic disease and ageing. Nat Rev Endocrinol 17: 647-661, 2021.
78. Dewanjee S, Vallamkondu J, Kalra RS, John A, Reddy PH and Kandimalla R: Autophagy in the diabetic heart: A potential pharmacotherapeutic target in diabetic cardiomyopathy. Ageing Res Rev 68: 101338, 2021.
79. Huang X, Liu S, Wu D, Cheng Y, Han H, Wang K, Zhang G and Hu S: Facilitated Ca^{2+} homeostasis and attenuated myocardial autophagy contribute to alleviation of diabetic cardiomyopathy after bariatric surgery. Am J Physiol Heart Circ Physiol 315: H1258-H1268, 2018.
80. Packer M: SGLT2 inhibitors produce cardiorenal benefits by promoting adaptive cellular reprogramming to induce a state of fasting mimicry: A paradigm shift in understanding their mechanism of action. Diabetes Care 43: 508-511, 2020.
81. He B, Liu L, Yu C, Wang Y and Han P: Roux-en-Y gastric bypass reduces lipid overaccumulation in liver by upregulating hepatic autophagy in obese diabetic rats. Obes Surg 25: 109-118, 2015.
82. Rodríguez-Hernández A, Cordero MD, Salviati L, Artuch R, Pineda M, Briones P, Gómez Izquierdo L, Cotán D, Navas P and Sánchez-Alcázar JA: Coenzyme Q deficiency triggers mitochondria degradation by mitophagy. Autophagy 5: 19-32, 2009.
83. Russo SB, Baicu CF, Van Laer A, Geng T, Kasiganesan H, Zile MR and Cowart LA: Ceramide synthase 5 mediates lipid-induced autophagy and hypertrophy in cardiomyocytes. J Clin Invest 122: 3919-3930, 2012.
84. Sun Y and Ding S: NLRP3 inflammasome in diabetic cardiomyopathy and exercise intervention. Int J Mol Sci 22: 13228, 2021.
85. Zheng Y, Xu L, Dong N and Li F: NLRP3 inflammasome: The rising star in cardiovascular diseases. Front Cardiovasc Med 9: 927061, 2022.
86. Zhang L, Ai C, Bai M, Niu J and Zhang Z: NLRP3 inflammasome/pyroptosis: A key driving force in diabetic cardiomyopathy. Int J Mol Sci 23: 10632, 2022.
87. Ding K, Song C, Hu H, Yin K, Huang H and Tang H: The Role of NLRP3 inflammasome in diabetic cardiomyopathy and its therapeutic implications. Oxid Med Cell Longev 2022: 3790721, 2022.
88. Sun X, Sun X, Meng H, Wu J, Guo X, Du L and Wu H: Krill oil inhibits NLRP3 inflammasome activation in the prevention of the pathological injuries of diabetic cardiomyopathy. Nutrients 14: 368, 2022.
89. Mocanu AO, Mulya A, Huang H, Dan O, Schauer PR, Dinischiotu A, Brethauer SA and Kirwan JP: Effect of Roux-en-Y gastric bypass on the NLRP3 inflammasome in pancreatic islets from zucker diabetic fatty rats. Obes Surg 26: 3076-3081, 2016.
90. Mocanu AO, Mulya A, Huang H, Dan O, Shimizu H, Batayyah E, Brethauer SA, Dinischiotu A and Kirwan JP: Effect of Roux-en-Y gastric bypass on the NLRP3 inflammasome in adipose tissue from obese rats. PLoS One 10: e0139764, 2015.
91. Sun K, Wang J, Lan Z, Li L, Wang Y, Li A, Liu S and Li Y: Sleeve gastroplasty combined with the NLRP3 inflammasome inhibitor CY-09 reduces body weight, improves insulin resistance and alleviates hepatic steatosis in mouse model. Obes Surg 30: 3435-3443, 2020.
92. Wu D, Yan ZB, Cheng YG, Zhong MW, Liu SZ, Zhang GY and Hu SY: Deactivation of the NLRP3 inflammasome in infiltrating macrophages by duodenal-jejunal bypass surgery mediates improvement of beta cell function in type 2 diabetes. Metabolism 81: 1-12, 2018.
93. Li S, Dong S, Shi B, Xu Q, Li L, Wang S, Zhang W, Zhong M, Zhu J, Cheng Y, *et al*: Attenuation of ROS/chloride efflux-mediated NLRP3 inflammasome activation contributes to alleviation of diabetic cardiomyopathy in rats after sleeve gastrectomy. Oxid Med Cell Longev 2022: 4608914, 2022.
94. Zhou R, Yazdi AS, Menu P and Tschopp J: A role for mitochondria in NLRP3 inflammasome activation. Nature 469: 221-225, 2011.
95. Yang F, Qin Y, Wang Y, Meng S, Xian H, Che H, Lv J, Li Y, Yu Y, Bai Y and Wang L: Metformin inhibits the NLRP3 inflammasome via AMPK/mTOR-dependent effects in diabetic cardiomyopathy. Int J Biol Sci 15: 1010-1019, 2019.
96. Li R and Chen J: Salidroside protects dopaminergic neurons by enhancing PINK1/parkin-mediated mitophagy. Oxid Med Cell Longev 2019: 9341018, 2019.
97. Yang Y, Zhao J, Qiu J, Li J, Liang X, Zhang Z, Zhang X, Fu H, Korantzopoulos P, Letsas KP, *et al*: Xanthine oxidase inhibitor allopurinol prevents oxidative stress-mediated atrial remodeling in alloxan-induced diabetes mellitus rabbits. J Am Heart Assoc 7: e008807, 2018.
98. Zhang N, Yu H, Liu T, Zhou Z, Feng B, Wang Y, Qian Z, Hou X and Zou J: Bmal1 downregulation leads to diabetic cardiomyopathy by promoting Bcl2/IP3R-mediated mitochondrial Ca^{2+} overload. Redox Biol 64: 102788, 2023.
99. Gutiérrez T, Parra V, Troncoso R, Pennanen C, Contreras-Ferrat A, Vasquez-Trincado C, Morales PE, Lopez-Crisosto C, Sotomayor-Flores C, Chiong M, *et al*: Alteration in mitochondrial Ca(2+) uptake disrupts insulin signaling in hypertrophic cardiomyocytes. Cell Commun Signal 12: 68, 2014.
100. Luptak I, Sverdlov AL, Panagia M, Qin F, Pimentel DR, Croteau D, Siwik DA, Ingwall JS, Bachschmid MM, Balschi JA and Colucci WS: Decreased ATP production and myocardial contractile reserve in metabolic heart disease. J Mol Cell Cardiol 116: 106-114, 2018.
101. Dillmann WH: Diabetic cardiomyopathy. Circ Res 124: 1160-1162, 2019.
102. Zamora M and Villena JA: Contribution of impaired insulin signaling to the pathogenesis of diabetic cardiomyopathy. Int J Mol Sci 20: 2833, 2019.
103. Dia M, Gomez L, Thibault H, Tessier N, Leon C, Chouabe C, Ducreux S, Gallo-Bona N, Tubbs E, Bendridi N, *et al*: Reduced reticulum-mitochondria Ca^{2+} transfer is an early and reversible trigger of mitochondrial dysfunctions in diabetic cardiomyopathy. Basic Res Cardiol 115: 74, 2020.
104. Mohan HM, Aherne CM, Rogers AC, Baird AW, Winter DC and Murphy EP: Molecular pathways: The role of NR4A orphan nuclear receptors in cancer. Clin Cancer Res 18: 3223-3228, 2012.
105. Zhou H, Wang J, Zhu P, Zhu H, Toan S, Hu S, Ren J and Chen Y: NR4A1 aggravates the cardiac microvascular ischemia reperfusion injury through suppressing FUNDC1-mediated mitophagy and promoting Mff-required mitochondrial fission by CK2α. Basic Res Cardiol 113: 23, 2018.
106. Wang D, Yin Y, Wang S, Zhao T, Gong F, Zhao Y, Wang B, Huang Y, Cheng Z, Zhu G, *et al*: $FGF1^{\Delta HBS}$ prevents diabetic cardiomyopathy by maintaining mitochondrial homeostasis and reducing oxidative stress via AMPK/Nur77 suppression. Signal Transduct Target Ther 6: 133, 2021.
107. Zheng Y, Tao Y, Zhan X and Wu Q: Nuclear receptor 4A1 (NR4A1) silencing protects hepatocyte against hypoxia-reperfusion injury in vitro by activating liver kinase B1 (LKB1)/AMP-activated protein kinase (AMPK) signaling. Bioengineered 13: 8349-8359, 2022.
108. Li S, Dong S, Xu Q, Shi B, Li L, Zhang W, Zhu J, Cheng Y, Zhang G and Zhong M: Sleeve gastrectomy-induced AMPK activation attenuates diabetic cardiomyopathy by maintaining mitochondrial homeostasis via NR4A1 suppression in rats. Front Physiol 13: 837798, 2022.
109. Meier JJ: GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 8: 728-742, 2012.

110. Du Z, Wang J, Lu Y, Ma X, Wen R, Lin J, Zhou C, Song Z, Li J, Tu P and Jiang Y: The cardiac protection of Baoyuan decoction via gut-heart axis metabolic pathway. Phytomedicine 79: 153322, 2020.
111. Chambers AP, Jessen L, Ryan KK, Sisley S, Wilson-Pérez HE, Stefater MA, Gaitonde SG, Sorrell JE, Toure M, Berger J, *et al*: Weight-independent changes in blood glucose homeostasis after gastric bypass or vertical sleeve gastrectomy in rats. Gastroenterology 141: 950-958, 2011.
112. Ryan KK, Tremaroli V, Clemmensen C, Kovatcheva-Datchary P, Myronovych A, Karns R, Wilson-Pérez HE, Sandoval DA, Kohli R, Bäckhed F and Seeley RJ: FXR is a molecular target for the effects of vertical sleeve gastrectomy. Nature 509: 183-188, 2014.
113. Ding H, Zhang Y, Ma X, Zhang Z, Xu Q, Liu C, Li B, Dong S, Li L, Zhu J, *et al*: Bariatric surgery for diabetic comorbidities: A focus on hepatic, cardiac and renal fibrosis. Front Pharmacol 13: 1016635, 2022.
114. Helmstädter J, Frenis K, Filippou K, Grill A, Dib M, Kalinovic S, Pawelke F, Kus K, Kröller-Schön S, Oelze M, *et al*: Endothelial GLP-1 (glucagon-like peptide-1) receptor mediates cardiovascular protection by liraglutide in mice with experimental arterial hypertension. Arterioscler Thromb Vasc Biol 40: 145-158, 2020.
115. Osto E, Doytcheva P, Corteville C, Bueter M, Dörig C, Stivala S, Buhmann H, Colin S, Rohrer L, Hasballa R, *et al*: Rapid and body weight-independent improvement of endothelial and high-density lipoprotein function after Roux-en-Y gastric bypass: Role of glucagon-like peptide-1. Circulation 131: 871-881, 2015.
116. Lee CJ, Sears CL and Maruthur N: Gut microbiome and its role in obesity and insulin resistance. Ann NY Acad Sci 1461: 37-52, 2020.
117. Castellanos-Jankiewicz A, Guzmán-Quevedo O, Fénelon VS, Zizzari P, Quarta C, Bellocchio L, Tailleux A, Charton J, Fernandois D, Henricsson M, *et al*: Hypothalamic bile acid-TGR5 signaling protects from obesity. Cell Metab 33: 1483-1492.e10, 2021.
118. Fuchs CD and Trauner M: Role of bile acids and their receptors in gastrointestinal and hepatic pathophysiology. Nat Rev Gastroenterol Hepatol 19: 432-450, 2022.
119. Tu J, Wang Y, Jin L and Huang W: Bile acids, gut microbiota and metabolic surgery. Front Endocrinol (Lausanne) 13: 929530, 2022.
120. Stefura T, Zapała B, Gosiewski T, Krzysztofik M, Skomarovska O and Major P: Relationship between bariatric surgery outcomes and the preoperative gastrointestinal microbiota: a cohort study. Surg Obes Relat Dis 17: 889-899, 2021.
121. Coimbra VOR, Crovesy L, Ribeiro-Alves M, Faller ALK, Mattos F and Rosado EL: Gut microbiota profile in adults undergoing bariatric surgery: A systematic review. Nutrients 14: 4979, 2022.
122. Anhê FF, Zlitni S, Zhang SY, Choi BS, Chen CY, Foley KP, Barra NG, Surette MG, Biertho L, Richard D, *et al*: Human gut microbiota after bariatric surgery alters intestinal morphology and glucose absorption in mice independently of obesity. Gut 72: 460-471, 2023.
123. Martínez-Montoro JI, Kuchay MS, Balaguer-Román A, Martínez-Sánchez MA, Frutos MD, Fernández-García JC and Ramos-Molina B: Gut microbiota and related metabolites in the pathogenesis of nonalcoholic steatohepatitis and its resolution after bariatric surgery. Obes Rev 23: e13367, 2022.
124. Debédat J, Le Roy T, Voland L, Belda E, Alili R, Adriouch S, Bel Lassen P, Kasahara K, Hutchison E, Genser L, *et al*: The human gut microbiota contributes to type-2 diabetes non-resolution 5-years after Roux-en-Y gastric bypass. Gut Microbes 14: 2050635, 2022.
125. Gutiérrez-Repiso C, Moreno-Indias I, Martín-Núñez GM, Ho-Plagaro A, Ocaña-Wilhelmi L, Fernández García D, Gonzalo Marín M, Moreno-Ruiz FJ, García-Fuentes E and Tinahones FJ: Influence of factors altering gastric microbiota on bariatric surgery metabolic outcomes. Microbiol Spectr 9: e0053521, 2021.
126. Chaudhari SN, Luo JN, Harris DA, Aliakbarian H, Yao L, Paik D, Subramaniam R, Adhikari AA, Vernon AH, Kiliç A, *et al*: A microbial metabolite remodels the gut-liver axis following bariatric surgery. Cell Host Microbe 29: 408-424.e7, 2021.
127. Wang J, Chen P, Cao Q, Wang W and Chang X: Traditional Chinese medicine ginseng dingzhi decoction ameliorates myocardial fibrosis and high glucose-induced cardiomyocyte injury by regulating intestinal flora and mitochondrial dysfunction. Oxid Med Cell Longev 2022: 9205908, 2022.
128. Bastin M and Andreelli F: The gut microbiota and diabetic cardiomyopathy in humans. Diabetes Metab 46: 197-202, 2020.
129. Shu H, Peng Y, Hang W, Nie J, Zhou N and Wang DW: The role of CD36 in cardiovascular disease. Cardiovasc Res 118: 115-129, 2022.
130. Wang H, Wang J, Cui H, Fan C, Xue Y, Liu H, Li H, Li J, Li H, Sun Y, *et al*: Inhibition of fatty acid uptake by TGR5 prevents diabetic cardiomyopathy. Nat Metab 6: 1161-1177, 2024.
131. Cesario DA, Brar R and Shivkumar K: Alterations in ion channel physiology in diabetic cardiomyopathy. Endocrinol Metab Clin North Am 35: 601-610, ix-x, 2006.
132. Ming Y, Yin Y and Sun Z: Interaction of nuclear receptor subfamily 4 group A member 1 (Nr4a1) and liver linase B1 (LKB1) mitigates type 2 diabetes mellitus by activating monophosphate-activated protein kinase (AMPK)/sirtuin 1 (SIRT1) axis and inhibiting nuclear factor-kappa B (NF-κB) activation. Med Sci Monit 26: e920278, 2020.
133. Liu M, Chen H, Dai H, Wang Y, Li J, Tian F, Li Z and Ge RS: Effects of bis (2-butoxyethyl) phthalate on adrenocortical function in male rats in puberty partially via down-regulating NR5A1/NR4A1/NR4A2 pathways. Environ Toxicol 37: 2419-2433, 2022.
134. Huynh K, Bernardo BC, McMullen JR and Ritchie RH: Diabetic cardiomyopathy: Mechanisms and new treatment strategies targeting antioxidant signaling pathways. Pharmacol Ther 142: 375-415, 2014.