

An Update on the Innovative Mechanistic Modes for the Avoidance of Heart Failure with Preserved Ejection Fraction Using Glucagon Like Peptide 1 Receptor Agonism Particularly in Type 2 Diabetes Mellitus & Metabolic Syndrome: A Review

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Abstract

The aim of this review is to evaluate the manner obesity influences the pathophysiology of Heart failure with preserved ejection fraction (HFpEF) as well as concentrate on innovative mechanistic modes for the avoidance of HFpEF by utilization of glucagon like peptide 1 (GLP-1)-1 receptor agonism (GLP-1RA). Obesity possess the capacity of causing HFpEF via mechanistic modes inclusive of low grade systemic inflammation, accrual of Visceral adipose tissue (VAT) pericardial along with epicardial adipose tissue (EAT), escalated myocardial fat quantities & fibrosis. GLP-1 portrays an incretin glucagon hormone whose liberation takes place from the enteroendocrine L cells of the gut. Continued liberation of GLP-1 occurs from the enteroendocrine cells with lesser baseline quantities in the fasting or interprandial status. GLP-1 controls quantities of blood glucose by stimulating insulin generation, repression of islet α cell working, facilitating proliferation in addition differentiation of β cell, whereas diminishing apoptosis. GLP-1 regulates glycemic differences by escalating liberation of insulin along with diminishing glucagon liberation. Furthermore, slowing of gastric emptying as well as appetite (food consumption) guarantees maximization of nutrients absorption along with restriction of weight accrual. GLP-1RA at present are getting evaluated for efficaciousness in obesity, or metabolic syndrome (MetS) or obese diabetic patients. Recent corroboration have illustrated GLP-1RA might be significantly efficacious in avoidance of HFpEF in patients of obesity, MetS / obese T2D. The modes behind such actions are (protective countercontrolling Renin-Angiotensin system (RAS) along with AMPK/mTOR pathway) or hampering inimical remodeling modes (protein kinase A (PKA)/ Rho/ Rho kinase (ROCK) pathway, aldosterone quantities, or microinflammation.. Nonetheless greater work is required to work out the precise mechanistic modes via which GLP-1R agonists evoke their benefits as well as to generate their long-term safety in addition to the efficaciousness in variable HFpEF populations.

Key words: HFpEF.; GLP-1RA; Renin-Angiotensin system (RAS); EAT; aldosterone; microinflammation.

INTRODUCTION

Obesity along with Heart Failure with Preserved Ejection Fraction (HFpEF)

Heart failure with preserved ejection fraction (HFpEF) portrays an escalating epidemic contributing to 50% of full HF patients as well as represents the commonest reason for hospitalization rates in patients ≥ 65 years age [1]. Escalating prevalence, morbidity in addition to clinical inactivity have prompted retaking into account the pathophysiology of HFpEF at the time of

past years. In contrast to problems in subjects with HF with reduced ($< 40\%$) ejection fraction (HFrEF), HFpEF possesses unique clinical phenotype [1], along with problems of co-morbidities.

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The cornerstone of Heart failure (HF), is left ventricular (LV) remodeling. In the absence of LV remodeling no existence of HF can exist there. In case of HF with reduced (<40%) ejection fraction (HFrEF), systolic impairment results in eccentric hypertrophy as well as myocardial fibrosis. Whereas in HFpEF, propagation of LV thickening results in concentric hypertrophy (LVH) correlated with dysfunctional myocardial relaxation in addition to escalated stiffness that leads to LV diastolic impairment along with HFpEF. Co-morbidities for instance age, obesity, type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, atherosclerosis along with renal impairment robustly aid in LV concentric remodeling.

Unique clinical phenotypes of HFpEF have been acknowledged. Six main phenotypes of HFpEF have been detailed, possessing unique clinical characteristics for instance i) the ageing phenotype ii) the obesity or cardiometabolic phenotype iii) the phenotype correlated with arterial hypertension iv) the pulmonary arterial hypertension phenotype v) the coronary artery disease (CAD) phenotype as well as vi) the phenotype correlated with left atrial myopathy [3]. Complete HFpEF possess variable co-morbidities that are shared. It is infrequent for HFpEF patients to possess only a single co-morbid disorder. For instance the ageing phenotype is usually correlated with i) atrial fibrillation (AF) ii) anaemia iii) chronic obstructive pulmonary disease (COPD) iv) frailty. Conversely, the obesity phenotype is correlated with greater frequency with i) obstructive sleep apnea (OSA) ii), T2DM in addition to iii) chronic kidney disease (CKD) [4]. HFpEF phenotyping aids in customization of the therapeutic avenues for combating making LV concentric remodeling reversible along with ultimately guaranteeing advantageous results. The obese diabetic phenotype of HFpEF is substantially frequent [4], as well as related to bad results [5]. Obesity is the basic guiding force for DM, with 90-95% T2DM patients being obese [6]. There is overlapping amongst obesity in addition to T2DM in the generation along with propagation of HFpEF [7]. The obese diabetic-hypertensive (cardiometabolic phenotype) the commonest phenotype **observed** in clinical scenario, possesses maximum load of mortality along with morbidity [1], as well as cardiac remodeling possesses the main part in reference to its pathophysiology. Obesity, metabolic syndrome (MetS), T2DM, in addition to hypertension are considerably prevalent globally. According to World Health Organization documents 1.28 billion adults at the age of 30-79 are globally hypertensive [8]. During 2016, 3% adults at the age of ≥18 were overweight along with 13% were obese [8]. Furthermore, about 422 million globally are diabetic [8].

MetS prevalence differs worldwide varying from 12.5%-31.4% based on the manner defined [9].

The prevalence of such four disorders has been based on age [10,11]. With ageing escalation of overweight as well as /obese frequency occurs, getting attained to maximum amongst the ages of 50 in addition to 65 years with subsequent tendency of reduction [11]. Noticeably, the prevalence of hypertension in United States of America (USA-2007-2018) escalates with age for instance 22.4% (18-39), 54.5% (40-59) along with 74.5% (≥60) [10]. Such greater prevalence are linked to greater incidence of HFpEF [12]. In reference to efficacious avoidance, in a recent randomized controlled trial (RCT), glucagon like peptide 1 (GLP-1)-1 receptor agonist (GLP-1RA), in case of patients which were previously obese HFpEF patients pointed requirement for acting. Such trial displayed remarkable diminishing of the symptoms along with physical restrictions, greater enhancement of exercise working, in addition to substantially significant diminishing of weight in contrast to placebo [13].

Earlier we reviewed the different significant etiopathogenesis and role of different antiobesity agents, comprehensively, role of adipocytokines in HFpEF as well as HFrEF, Role of SGLT2 Inhibitors Beyond Glycosuria in Controlling Obesity, NAFLD Treatment, Pancreatic β Cell Protection Besides Therapy for Diabetes Mellitus, CVOT and Renoprotection including MACE with SGLT2 Inhibitors Molecular Modes Implicated in Diastolic Impairment in early HFpEF as well as HFrEF, and epigenetics modifications in diabetic cardiomyopathy (DbCM), with Role of SGLT2 Inhibitors and GLP-1RA in therapy of DbCM [14-31].

The aim of this review is to here concentrate the manner obesity influences the pathophysiology of HFpEF, as well as innovative mechanistic modes for the avoidance of HFpEF by utilization of GLP-1RA in case of patients with obesity, or metabolic syndrome (MetS) or obese diabetic patients particularly tackling the sequelae of obesity on the heart in addition to on HFpEF, the countercontrolling Renin-Angiotensin system (RAS) along with avoidance of cardiovascular injury in such a backdrop. Lastly, GLP-1 axis is detailed in the form of anti diabetic, anti obesity along with anti cardiac remodeling pathway.

METHODS

Here we conducted a narrative review utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like obesity; T2D; Heart failure with preserved ejection fraction (HFpEF); metabolic syndrome (MetS);

Epicardial adipose tissue(EAT); CVD's; glucagon like peptide 1(GLP-1)-1 receptor agonism(GLP-1RA; Renin-Angiotensin system(RAS) PKA ;mTOR; EAT; aldosterone; microinflammation; AMPK;ROCK from 1997 to 2025 till date.

RESULTS

We found a total of 2000 articles out of which we selected 179 articles for this review.No meta-analysis was done.

Sequelae of Obesity on the Heart Along with HFpEF

The areas of the organization of adipose tissue(AT) as well as generation of ectopic fat portray the main etiological factors of metabolic in addition to cardiovascular diseases (CVD[32]. Epicardial adipose tissue(EAT) portrays an ectopic fat with placement amongst the myocardium along with the visceral pericardium in intricate touch with coronary vessels. EAT represents a substantially active endocrine organ, which possesses the remarkably greater capability of liberation of free fatty acids(FFA) [32]. EAT liberates proinflammatory cytokines,causes escalated FA's liberation,escalates mechanical burden on the myocardium,leading to myocardial remodeling[33]. EAT is capable of conferring considerable protection to the nearby myocardium via its dynamic brown fat like thermogenic working, as well as substantially inimical action through paracrine or vasocrine liberation of proinflammatory in addition to profibrotic cytokines[34]. EAT constitutes the main source of adipokines,chemokines along with cytokines which crosstalk with vascular cells as well as myocytes in paracrine or vasocrine fashion . The expression in addition to liberation of proinflammatory cytokines inclusive of interleukin-6(IL-6),IL-1 β , monocyte chemoattractant protein 1(MCP1) as well as tumor necrosis factor alpha(TNF α) are greater in EAT in contrast to subcutaneous(s/c) fat[8]. The exposition for that is partly in view of upregulation of nuclear factor κ B(NF κ B) in addition to c-jun N terminal kinase(JNK) [35]. EAT possesses the capability of manipulating the metabolic milieu of coronary arteries in addition to myocardium along with is correlated with different health disorders inclusive of CAD[33, 34], MetS [35], T2DM[36], COPD[37], sleep apnea,[38], ageing[39], as well as male sex [40]. Such disorders further portray the risk factors of bad prognosis for coronavirus disease(COVID19), as well as such infections are capable of stimulating a systemic inflammatory reactions [41,42]. In case of recent meta-analysis it was **observed** that robust COVID19 group possessed greater EAT estimates in contrast to nonrobust

COVID19 group[42]. Thereby plausability exists that EAT possesses the capability of transmitting inflammation to the heart .

Every metabolic situation is further correlated with atrial fibrillation (AF) in addition to HFpEF is further correlated with an expansion of EAT mass[43]. Obese persons are at substantially greater risk of escalated generating AF along with HFpEF.

Adiponectin as well as leptin portray two adipokines which are capable of manipulating anti inflammatory in addition to proinflammatory actions respectively [44]. Obesity is correlated with escalated leptin amounts which activate cells of the innate along with adaptive immune system[45]. Leptin works in the form of acute phase reactant, escalating the liberation of proinflammatory cytokine IL-6, IL-12 as well as TNF α in the macrophages[46]. In turn this results in escalation of leptin expression in AT in addition to circulating leptin, generating a feedback loop which facilitates the inflammatory status. Obese persons illustrate greater enrichment of macrophages in their AT, pointing that adipocytes along with macrophages, possess a significant part in inflammation in obesity[46]. Escalated leptin amounts in obesity are correlated with cardiac as well as renal fibrosis[47], escalated aldosterone generation [48], in addition to retention of sodium [48,rev by us in ref 25].

Conversely adiponectin, that gets generated only by adipocytes, circulating in plasma possess significant part in escalation of insulin sensitivity actions in humans[12], along with antiinflammatory actions incardiometabolic diseases [49]. Serum amounts of adiponectin possess an inverse association with obesity as well as inflammatory cytokine amounts in T2DM in addition to proinflammatory cytokines diminish expression of adiponectin in adipocytes[49]. Macrophages, treated *in vitro* with adiponectin hampered the proinflammatory cytokine TNF α along with stimulated the expression of anti inflammatory cytokine the IL-10[50]. Additionally, adiponectin stimulated the switching of M1 to M2 macrophages polarization, therefore ameliorating chronic inflammation[49]. Lesser quantities of adiponectin in obesity escalates therisk for CVD[48], while adiponectin quantities are diminished in HFpEF. *In vitro* adiponectin confers protection in a plethora ofmanners i) activation of 5' AMP-activated protein kinase(AMPK) based as well as ii) extracellular signal –regulated kinase (ERK1) signaling in the cardiac myocytes in addition to endothelial cells[51], diminishes hypertrophy along with fibrosis, activation of endothelial nitric oxide synthase (eNOS) as well nitric oxide(NO) generation[52].

In case of young adults who are obese, plasma leptin quantities were 2.6 fold greater in addition to GLP-1 quantities were 90% greater in contrast to those with a lean phenotype. Additionally, the homeostatic assessment of insulin resistance (HOMA-IR) meant for the determination of the insulin resistance (IR), was displayed to be 5 fold greater in such a population[53]. Obese persons possessed 100% greater plasma leptin quantities, 2.7 times greater HOMA-IR index ($p < 0.001$) as well as 20% lesser adiponectin amounts ($p = 0.003$) in contrast to lean compatriots[54]. Obesity treatment possesses the capability of causing alteration in such hormone quantities. Subsequent to bariatric surgery, a newer systematic review **observed** that leptin quantities diminished subsequent to maximum bariatric surgeries[55]. The exposition for that might be resultant secondary to restoration of leptin resistance that gets escalated in obesity[55]. Conversely adiponectin has been demonstrated to result in avoidance of obesity, with the escalation of quantities subsequent to weight reduction, along with the aforementioned systematic review, same was found in maximum bariatric surgeries[55]. **Observational** as well as community dependent cohorts have documented correlation amongst obesity, in addition to LV concentric remodeling[56]. Corroboration of the central part of obesity in the LV concentric remodeling along with diminishing of LV mass[57], as well as further amongst diminishing of weight, LVH size regressing in addition to BP further got validated subsequent to bariatric surgeries [58]. Obesity has the capacity of resulting in dysfunctional LV diastolic working, the mechanistic modes separate from escalated cardiac pre as well as afterload[1], in addition to acknowledged risk factor for incident HFpEF[47,59].

Intriguingly HFpEF associates greater intricately with visceral adipose tissue (VAT) mass in contrast to body mass index (BMI) [60,61], along with peak aerobic capability is inversely as well as autonomously associated with intraabdominal fat. VAT is anticipative of hospitalization in case of HFpEF patients[62,63]. In case of Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial, 71% of HFpEF patients possessed a BMI $> 26.5 \text{ kg/m}^2$ [64]. In reference to RELAX Trial 55% of HFpEF patients possessed a BMI $> 35 \text{ kg/m}^2$ [65]. Prevalence of BMI $> 30 \text{ kg/m}^2$ was **observed** in five recent clinical trials amongst 34-68%[64,65]. Obesity aids in generating HFpEF by renal tubular sodium reabsorption as well as expansion of plasma volume i) with over generation of aldosterone via 2 pathways i) activation of Renin-Angiotensin-System (RAS) ii) in addition to escalation of liberation of aldosterone from adrenal cortex as well as adipocytes along with iib)

directly stimulating leptin from adrenal cortical cells [66]. Natriuretic peptides (NP) have been established to diminish aldosterone quantities. Nonetheless, noticeably in obesity patients, neprilysin actions are capable of causing metabolism of NP in diminishing escalated aldosterone liberation[67]. Hyperaldosteronism further stimulates accrual of inflammation of EAT, resulting in escalated local in addition to systemic inflammation[47].

Obesity, Low Grade Systemic Inflammation, Injury Along With Hfpef

Sustenance of adipocyte homeostasis gets attained via the manipulation of proinflammatory along with anti inflammatory cytokines. Obesity, facilitates the escalated proinflammatory cytokines as well as decontrolling of adipokines. AT acts in the form of a critical endocrine organ by liberation of a lot of adipocytokines, in addition to obesity stimulated adipocyte impairment results in modifications of adipokine quantities[68], facilitating LV remodeling along with HFpEF[69].

AT storage takes place in variable chambers with subcutaneous (s/c) attributing for around 80%, whereas the rest 20%, organization is in visceral in addition to other chambers for instance perivascular, epicardium, liver, renal, pancreas along with skeletal muscles[70]. Visceral adipose tissue (VAT) portrays fat accrual in the abdominal cavity inclusive of mesentery as well as omentum. Its determination is feasible by the utilization of single slice computed tomography (CT) or multiple slice magnetic resonance imaging (MRI) [71]. Escalated weight, results in AT accrual via escalated fat cell size (or hypertrophy) or number (or hyperplasia). VAT expansion results in impairment along with inflammation that in turn stimulates the low grade systemic inflammation) [72]. Escalated BMI is escalating quantities of circulating inflammatory markers for instance vascular cell adhesion molecule (VCAM1), C-reactive protein (CRP), plasminogen activator inhibitor -1 (PAI-1), IL-6, P-selectin as well as TNF α [73,74].

Subsequent to adipocytes hypertrophy or hyperplasia VAT transits from anti inflammatory status facilitate the angiogenesis, in addition to lipid storage towards a proinflammatory status. such transition gets portrayed by liberation of MCP1, C-X-C motif chemokine ligand 12 (CXCL12), leukotriene 4s (LTs), Colony-Stimulating Factor 1, facilitate the proliferation of activated macrophages along with infiltration of AT by macrophages[75]. Additionally, in case of escalated accessibility of nutrients, storage of variable lipid species (spp) takes place in the form of lipid droplet (LDs), which escalate in size at a substantially fast pace outreaching diffusion restriction

of oxygen[76]. Thereby hypoxia portrays the significant guiding force of the earlier AT reaction to escalated dietary lipids[76]. Subsequent to high fat diet(HFD), adipocytes hypoxia gets stimulated early enough by 1 to 3 days[77]. Hypoxia at the time of AT expansion stimulates stress signaling which promotes angiogenesis, stimulates infiltration of inflammatory cells, as well as stimulates remodeling of structured extracellular matrix(ECM) for stimulating proper AT expansion[76]. Adipogenesis impact the event of AT remodeling, whereas hypoxia stimulates angiogenesis, ECM remodeling, in addition to inflammation[76-78].

Inflammatory VAT generates reactive oxygen species(ROS) along with lesser quantities of NO, resulting in mitochondrial impairment as well as activation of nucleotide-binding domain, leucine-rich-repeat containing family, pyrin domain-containing (NLRP3) inflammasome [79], that acts in the form of an objective activation of caspase1 resulting in processing of the proinflammatory cytokines into, IL-1 β , IL-18 along with gasdermin (GSDMD) modulated cell demise[78]. Such cell demise portrays the main pathway of inflammation[80]. Low grade systemic inflammation escalates the inimicality of cardiovascular working [81]. This potentiates the inflammatory reactions in case of coronary microvasculature[82], that causes modifications of the elasticity of cardiomyocytes as well as their working, escalating myocardial collagen getting deposited, causes dysfunctional myocardial relaxation resulting in diastolic impairment in addition to HFpEF[83]. Inflammation of microvasculature with macrophages along with liberation of transforming growth factor beta(TGF- β) causes greater tensile collagen getting deposited [84]. Escalated myocardial collagen (myocardial fibrosis) escalates the LV stiffness as well as results in diastolic impairment. This causes tough passive inflow leading to backwards diastolic flow, which further causes dysfunctional early filling [85]. In reference to this a direct association exists amongst myocardial collagen, LV stiffness as well as pulmonary wedge capillaries pressure[86]. Furthermore, microvascular rarefaction(alias the lessening of density of tissue) as well as deficiency in endothelial cells metabolic reprogramming in addition to angiogenesis, that is based on the Sirtuin 3 (SIRT3), influences propagation of perivascular along with myocardial fibrosis in HFpEF also[87].

VAT along with HFpEF

The accrual of VAT possesses a part in generation along with propagation of cardiometabolic disorders. In case of T2DM, VAT is robustly anticipative of IR [88], as well as escalates cardiometabolic risk[89]. The body's incapability

of regulating unlimited energy consumption causes VAT expansion, that is implicated in modulating maximum of negative actions of obesity on clinical results. The Multi-ethnic Study of Atherosclerosis (MESA) **observed** that maximum patients with escalated VAT possessed a 2.2 times greater incident hospitalization in view of HFpEF. Incident hospitalization of the Jackson Heart Study were significantly correlated with VAT in addition to EAT, however not with subcutaneous(s/c) AT[90]. The single significant variable anticipator, that was related to all cause mortality was EAT. A tendency to escalated "all cause mortality" was **observed** in case of escalated VAT, however no significant tendency was **observed** in case of s/c AT[90].

Accrual of VAT was correlated with LV diastolic impairment, escalated LV mass, sphericity, lesser end diastolic volume in patients with obesity along with HFpEF[61,91]. Furthermore, the actions of VAT are gender particular, with women possessing greater proportion of VAT at the baseline along with maximum inimical haemodynamics in HFpEF[92]. Women with escalated VAT as well as HFpEF further demonstrated exercise stimulated LV filling pressure[92].

The Pericardial/EAT along with HFpEF

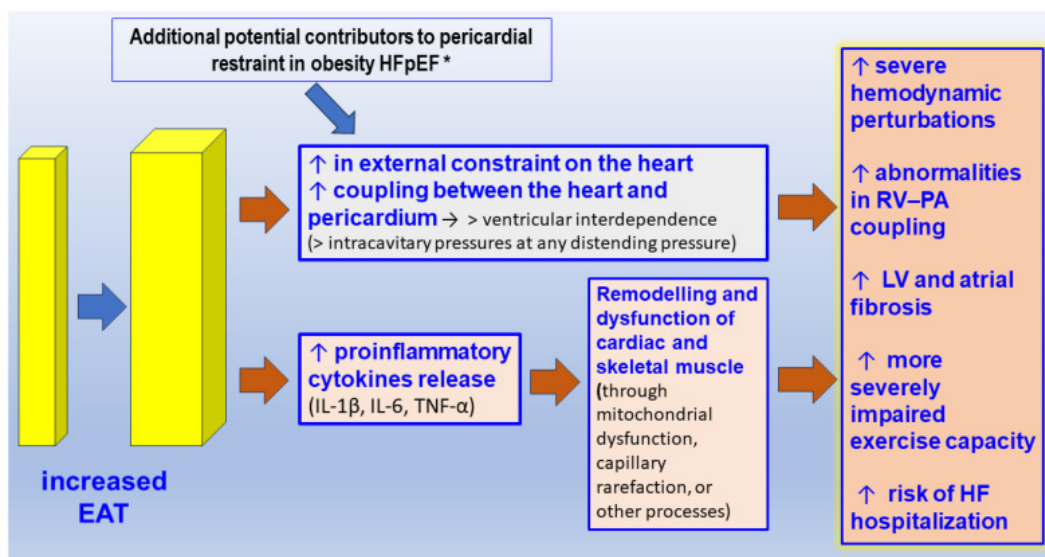
Obesity, along with type 2 diabetes mellitus (T2DM) are autonomously correlated with escalated pericardial/EAT[93]. EAT, a constituent of VAT with placement in heart, possesses metabolic, mechanical as well as thermogenic part[15]. EAT possesses double the metabolic actions in contrast to normal White adipose tissue (WAT) as well as has a significant part in lipolysis in addition to liberation of free fatty acids(FFA) [94]. It results in escalated quantities of the circulating FFA, leading to diminished cardiac lipid getting deposited. In view of EAT has direct placement over myocardium, FFA liberation by it might directly have actions on myocytes in addition to coronaries in view of absence of a fibrous fascial layer amongst the two of them. Substantially greater liberation of FFA might cause cardiac lipotoxicity[41]. Greater intriguingly, in a study constituted of 33 patients having CVD going via open cardiac surgery had evaluation of expression of GLP-1R along with glucose-dependent insulinotropic polypeptide receptor (GIPR), glucagon receptor (GCGR), which **observed** that expression of GLP-1R, GIPR as well as GCGR in human EAT at analogous quantities at the level of the mRNA in addition to protein in macrophages in addition to partly in adipocytes[95], pointing that such G- protein coupled receptor(GPCR) might get targeted at the level of plethora of receptors, novel latest agents having cardiometabolic advantages

further than their actions takes place on glucose along with body weight[95].

Cases having greater escalated EAT possess greater LV mass index(LVMI), bigger left atrial size in addition to, greater E/e' velocity (The ratio of mitral peak velocity of the early filling (E) to early diastolic mitral annular velocity (e'), termed the E/e' ratio, was calculated as a measure of diastolic cardiac function mainly echocardiographic E/e' ratio) . HFpEF was considered likely in patients with an E/e' ratio ≥ 13 and a mean e' septal and lateral wall < 9 cm/s; either/or tricuspid regurgitation velocity > 2.8 m/s.) [96,97]. The correlation of EAT, as well as LV working criterion continue to be significant despite adjustment for the obesity biomarkers in addition to, canonical factors[98].

EAT might result in escalated myocardial fat quantities along with interstitial fibrosis that possesses the capacity of diminishing myocardial diastolic working as well as contractility, the manner witnessed by longitudinal strain[99]. In cases possessing considerable obesity along with cardiomegaly in addition to epicardial fat volume, extra stretching of pericardial sac takes place to abrupt

pressure- volume correlation as well as escalated diastolic ventricular crosstalk along with pericardial constraint [100]. This evokes exacerbated compressive force on heart leading to greater left to right sided filling pressure, to any magnitude of left ventricular(LV) as well as diastolic volume- actual LV preload [101]. In a study on HFpEF patients, 28 in number inclusive of 17 women, having BMI $> 37 \pm 7$ kg/m², at age 70 ± 6 yrs) epicardial fat, was robustly associated with LV eccentricity index, that corroborate with an inimical cardiomechanical crosstalk[101]. LV eccentricity was not associated with BMI, s/c in addition to visceral fat, or pulmonary vascular resistance along with exercise were not capable of influencing modifications in cardiomechanical crosstalk in this study [101]. Patients which had diastolic impairment along with escalated EAT demonstrated greater predominant diastolic failure working as well as inimical structured remodeling[102]. Although kindred morphological properties, patients with greater EAT, demonstrate significant cardiac working impairment, specifically in the atria, pointing to escalated EAT at site directly stimulates atrial working failure[102](see Figure1) [rev in ref103].



Legend for Figure 1

Courtesy reference no-103- Mechanical and paracrine effects of increased epicardial adipose tissue (EAT) on myocardial structure and function (adapted from [100,104,105]).* = Additional potential contributors to pericardial restraint in obesity HFpEF: increased LV and RV volumes, increased left and right atrial volumes, blood volume expansion, mediastinal/abdominal extrinsic restraint, pulmonary hypertension with abnormal RV-PA coupling). Abbreviations: LV = left ventricle, RV = right ventricle, PA = pulmonary artery, IL = interleukin, TNF = tumor necrosis factor, HF = heart failure

Recently, it has been demonstrated that HFpEF patients epicardial adiposity correlated with haemodynamic signs of pericardial restraint [105], in addition to 73% of those possessed a square root sign[105]. Escalated epicardial fat further leads to lesser peak VO₂ utilization along with

peripheral extraction of oxygen in patients of HFpEF, pointing to greater inimical haemodynamic profile[106]. In reference to MESA study it was **observed** that the escalated EAT volume associated with two time greater HFpEF incidence in women as well as 53% in men ($p < 0.001$)

without association with greater HFrEF incidence[107]. In epicardial adipose samples HFpEF patients, differentially expressed circRNAs, were commensurate with genes basically implicated in cellular in addition to metabolic events[108].

The Association of Obesity, T2DM along with HFpEF

Apart from T2DM macrovascular complications, T2DM possesses direct actions on the myocardium, for instance LV hypertrophy[109,110], complicated myocardial impairment acknowledged as diabetic cardiomyopathy(that leads to aberrant systolic along with diastolic working) [111], Heart failure[112], as well as continued ventricular hyperpolarization[113].

T2DM cases along with HFpEF escalated t-tubule density in addition to type 1 collagen getting deposited in contrast to HFrEF patients. Additionally, they possess dysfunctional Ca^{2+} io lesser sarcoplasmic / endoplasmic reticulum calcium Ca^{2+} homeostasis -ATPase(SERCA2)-actions, pointing to separate pathophysiological events in contrast to non T2DM HFrEF [114]. Cases having HFrEF along with T2DM generally possess greater BMI in contrast to non T2DM HFrEF cases [46,115]. Furthermore, they possess tendency of greater robust manifestation, greater hospitalization rates, greater LV hypertrophy, greater filling pressures along with tendency greater LV mass as well as cardiac fibrosis, in the manner n found in cardiac magnetic resonance imaging (CMRI) [116].

Intolerance at the time of exercise is a frequent characteristics T2DM along with HFpEF, in view of dysfunctional cardiac working [117], in addition to skeletal muscles metabolism or blood flow, [118]. In reference to HFpEF, Obesity as well as T2DM aid in exercise intolerance. Obesity stimulated sarcopenia, escalates muscle mass elimination in view of ageing or exercise intolerance [119]. T2DM diminishes exercise capability via dysfunctional cardiac energetics in addition to skeletal muscles extraction of oxygen along with metabolism[120]. Intolerance at the time of exercise is capable of diminishing quality of life (QOL), commoner rehospitalization rates as well as mortality in cases of T2DM along with HFpEF[120]. Thereby, attempting to revert exercise intolerance is needed in the form of a therapeutic target for T2DM along with HFpEF cases obesity as well as T2DM are capable of working as summated risk factors in cases of T2DM along with HFpEF. Obesity directly influence the robustness of both T2DM in addition to HFpEF along with deleteriousness of T2DM. IR leads to escalated generation of insulin from the pancreatic β cells, that are incapable of taking care of glycemic needs. Accrual of ectopic fat in pancreas further

aids in impairment of β cells, that in turn results in T2DM generation[121]. Therefore, treatment in obese diabetic-HFpEF phenotype needs to concentrate on tackling obesity as well as T2DM.

Present Efficacious therapeutics in patients having obese- HFpEF phenotype

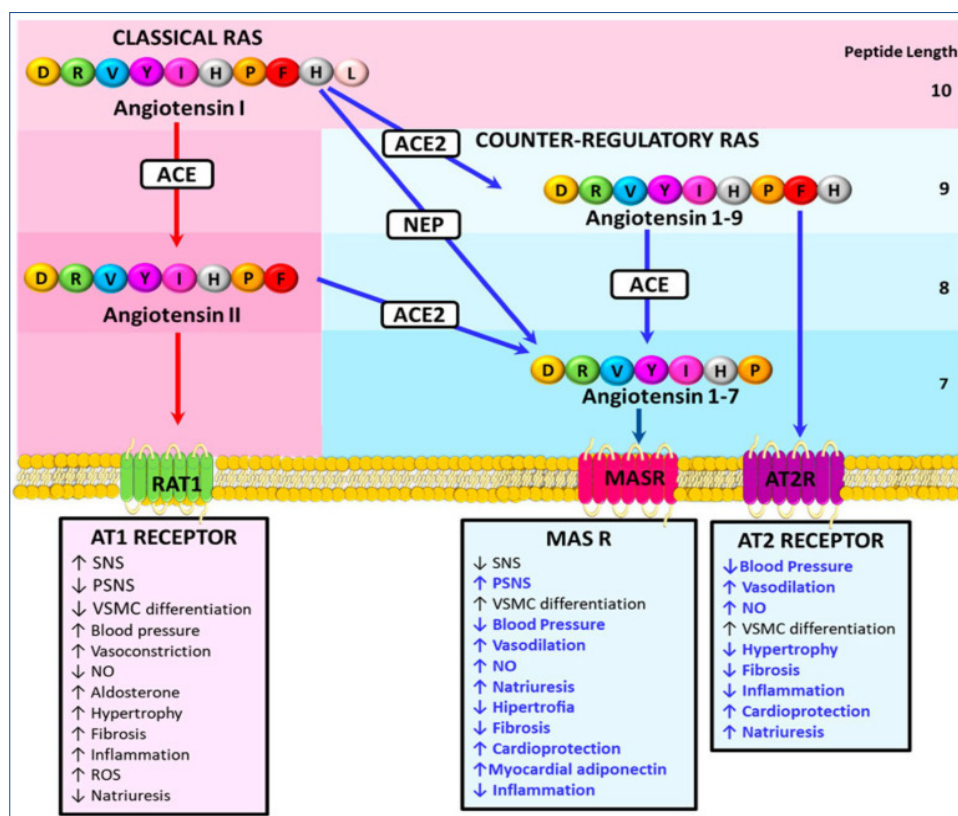
A systematic review and meta-analysis performed recently by Launbo et al.[122], validated that exercise, diet, bariatric surgery or pharmaceutical intervening had the capability of diminishing cardiac AT volume[122]. According to Packer M[43], a significant pooled action size for diminishing in the EAT volume was found subsequent to intervening for weight reduction in contrast to intervening in controls (ES-0.89, 95%CI:-1.23 to 55, $p < 0.001$). Significant weight reduction was capable of diminishing epicardial adiposity in addition to improvement of generation of atrial fibrillation (AF) as well as HFpEF[43]. One systematic review and meta-analysis performed recently by Anagnostopoulos et al. [123], illustrated that EAT encompassing left atria quantification performed by utilization of the CT was anticipative of AF recurrence subsequent to catheter ablation[123]. According to studies, it got illustrated that weight reduction possesses the capability of positively affecting the clinical time period of HF patients, specifically in cases of HFpEF. Such patients feel improvement of dynamics of diastolic filling, their symptoms along with exercise intolerance[43]. In an open label randomized controlled 6mth study, 95 T2DM patients (BMI $> 27 \text{ kg/m}^2$, with glycated haemoglobin A1c (HbA1c) $> 8\%$) that were getting metformin monotherapy, got randomized for getting GLP-1-receptor agonist (GLP-1RA), Liraglutide, / to continue getting metformin monotherapy. A significant reduction of EAT thickness took place from 9.6 to 6.8 as well as 6.26 mm at the time period of 3 in addition to 6 mths respectively following Liraglutide use[129]. Compared to that no reduction occurred in group of patients getting only metformin. Furthermore, Liraglutide group illustrated BMI along with HbA1c getting improved [124]. Cardiac magnetic resonance (CMR) was performed recently in study prior to as well as following bariatric surgery. In terms of mean the patients illustrated 38.9% accelerated weight reduction in 212 days in addition to 64.7% in 1030 days maximum abdominal VAT reduction along with EAT reduction occurred amongst the initial 212 days (43% as well as 14% respectively $p < 0.0001$) non significant reduction in following time period[104]. Presently bariatric surgery portrays maximum efficacious therapy in reference to accessibility weight reduction in addition to possesses the autonomous advantages for epicardial adipose depots, that might be advantageous with regards to pericardial restraint[100].

Positive outcomes obtained in reference to HFrEF treatments have illustrated diminishing mortality rates the for HFpEF. In case of In TOPCAT trial. Obesity as well as T2DM cases witnessed maximum advantages from the mineralocorticoid receptor blocker spironolactone[125]. The primary end point inclusive of all cause mortality in addition to hospitalization, maximization of the BMI diminished in patients that had (BMI>33kg/m²[126]. Elkholey et al.[126], **observed** that maximum efficacy was with spironolactone in patients which possesses the greater waist circumference(WC) pointing to escalated VAT Furthermore, 6 studies which 5201 patients **observed** that sacubitril/valsartan diminished hospitalization rates in HF in contrast to angiotensin converting enzyme(ACEs), angiotensin II receptor antagonists(ARBs), (relative riskto,95%CI: 0.65 to0.85, p=0.001) [127]. 2 randomized controlled trial(RCT), have illustrated the advantages of Sodium -glucose cotransporter 2(SGLT2) - hampering agents[128,129], in contrast to placebo in case of HFpEF as well as NYHA HF classes II-IV symptoms , structural heart (left atrial / left ventricular(LV) hypertrophy)

hospitalization recently, escalated quantities of brain natriuretic peptide (BNP) along with EF >40% [130]. These studies illustrated that SGLT2) - hampering agents led to 18% to 21%hospitalization rates secondary to HF/ cardiovascular (CV) demise[130].

Counter- Controlling Regulatory Renin-Angiotensin -Systemin Along with Avoidance of CV Injury

Chronic activation of the canonical renin angiotensin system (RAS) facilitates CV injury, an action antagonized by constituents of the conventional counter- controlling RAS . Counter- controlling RAS axis -gets constituted by angiotensin1-7 (Ang 1-7), angiotensin1-9 (Ang 1-9), ACE2, type 2 Angiotensin II receptor (AT2R), protooncogene Mas receptor (MasR) in addition to receptor related G-protein coupled receptor member D[131]. Constituents of the counter- controlling RAS are inclusive of Ang 1-7, Ang 1-9,that confer protection in variable CVD 's inclusive of hypertension, as well as heart failure (HF) [131 (see Figure 2)].



Legend for Figure 2

Courtesy reference no-103- Preventive effects of the counter-regulatory renin angiotensin system (non-classic reninangiotensin pathway) on obese HFpEF. Activation of the AT2R and the MASR with angiotensin 1-9 and angiotensin 1-7, respectively, achieves protective effects on obese HFpEF by counteracting the classic effects of the RAS pathway activation. Additionally, GLP-1 RA also promotes activation of the counter-regulatory renin angiotensin system. Abbreviations: ACE = angiotensin converting enzyme1, ACE2 = angiotensin converting enzyme 2, NEP = neutral endopeptidase, AT1R = angiotensin receptor type 1, AT2R = angiotensin receptor type 2, MASR = G-protein-coupled receptor Mas, SNS = sympathetic nervous system

Of the canonical renin angiotensin system (RAS) angiotensinogen cleavage gets obtained by renin for the generation of angiotensin I, which gets hydrolyzed by ACE to form Angiotensin II (AngII), whose binding takes place with Angiotensin II receptor type 1 (AT1R) along with 2 (AT2R). Activation of AT1R escalated generation of aldosterone as well as antidiuretic hormone (ADH), sympathetic nervous system (SNS) tone, BP, vasoconstriction, cardiac hypertrophy, fibrosis, inflammation, dedifferentiation of vascular smooth muscle in addition to escalated generation of ROS along with concomitantly diminishes tone of the parasympathetic nervous system (PSNS), baroreflex sensitivity, generation of NO as well as natriuresis [131]. AngI cleavage further might be obtained by ACE2, as well as neprilysin for the generation of Ang 1-9 in addition to Ang 1-7. Ang 1-9 causes activation of AT2R, for stimulation of natriuresis along with generation of NO, facilitating vasodilatory actions as well as diminishing BP. Ang 1-9 confers protection to heart, ameliorates cardiac hypertrophy, fibrosis, as well as inflammation [85]. Binding of AngI occurs with Mas receptor (MasR) diminishes BP in addition to liberation of noradrenaline in hypertensive rodents [86]. MasR activation uses escalated generation of NO, natriuresis, PSNS tone along with baroreflex sensitivity. AngI further might be obtained by AngII cleavage by ACE2 as well as possesses the capacity of further metabolized to alamandine [131].

A plethora of studies have illustrated the beneficial actions of the counter- controlling RAS. Nonetheless, studies corroborating such findings are restricted. It has been found prehypertensive cases possessed greater ACE2 actions in contrast to hypertensive persons [132]. regarding HF patients, ACE2 actions are robustly associated with diagnosis of HF, inimical LVEF, escalated BNP quantities as well as inimicality of HF [133].

The counter- controlling RAS illustrates inverse association amongst AngII with Ang 1-9 in addition to ACE2 quantities [131]. Nonetheless, existence of restricted accessibility of human results on the protection conferred to heart by Ang 1-9 as well as ACE2 in T2DM, MetS along with HF. Plasma AngII quantities were 29% greater in case of stable T2DM patients in contrast to control ($p < 0.05$) [134]. In case of HF persons plasma Ang 1-9 quantities were 86% lesser in addition to AngII quantities were 30% greater in contrast to control ($p < 0.05$) [135]. At present there is no existence of extra results regarding Ang 1-9 in humans. A short study constituted of 11 patients with CKD as well as T2DM plasma AngII quantities were escalated by 2.3 time subsequent to empagliflozin treatment [136]. Nevertheless, no existence of results regarding Ang 1-7, Ang 1-9, Ang 1-7 in addition to ACE2 / aldosterone

quantities have been described in patients with T2DM, along with MetS regarding GLP-1RA for conferring protection in case of cardiac phenotype.

El-Sayed Moustafa et al. [136], demonstrated in a meta-analysis that diminished ACE2 expression in humans particularly abdominal subcutaneous (s/c) fat were correlated with plethora of inimical cardio-metabolic health indices. They were inclusive of T2DM, status of obesity, escalated fasting serum insulin quantities as well as BMI, in addition to diminished HDL quantities [136]. Particularly persons with cardio-metabolic characteristics possess lesser ACE2 expression, as well as diminished percentage of microvascular endothelial cells however escalated macrophages [137]. Therefore diminished ACE2 expression in AT might possess a part in the generation of cardio-metabolic conditions along with implications for escalated risk in COVID-19.

in the obese adolescents Ang 1-7 quantities possessed an inverse association amongst weight, BMI, leptin amounts, systolic in addition to diastolic blood pressure (BP) [138], along with skinfolds, waist:hip ratio, leptin as well as arm circumference. Plasma AngI quantities were greater in obese group in contrast to the normal weight group, AngII quantities were corresponding in both groups [138], pointing that Ang 1-7 portrays an innovative biomarker in childhood obesity.

Glucagon like peptide 1 (GLP-1)- axis: an Innovative Anti Diabetic, Anti Obesity Along with Anti Cardiac Remodeling Pathway

Glucagon like peptide 1 (GLP-1)- portrays an incretin glucagon hormone whose liberation takes place from the enteroendocrine L cells of the gut. Continued liberation of GLP-1 in addition to, GLP-2 occurs from the enteroendocrine cells with lesser baseline quantities in the fasting or interprandial status. Thereby paces escalation of circulating quantities of these peptides occur amongst minutes (min) of food consumption [139]. GLP-1 regulates glycemic differences by escalating liberation of insulin along with diminishing glucagon liberation. Furthermore, slowing of gastric emptying as well as food consumption guarantees maximization of nutrients absorption along with restriction of weight accrual. Modulation of such actions get brought about by GLP-1 receptor (GLP-1R). Initial identification of GLP-1R occurred in the β cell islets along with central nervous system (CNS). Following that it was **observed in** islets as well as pancreatic exocrine cells in addition to autonomic nervous system (ANS) along with enteric nervous system (ENS), blood vessels, Brunner's glands, as well as sinoatrial nodes [139]. At present therapeutic utilization

occurs in T2DM, MetS in addition to obesity [140]. *In vivo*, it possesses substantially short half life of under 2 min, gets broken down by Dipeptidyl Peptidase -4 (DPP-4) [141], along with depletion occurs by the kidneys [142]. GLP-1 controls quantities of blood glucose by stimulating insulin generation, repression of islet α cell working, facilitating proliferation in addition differentiation of β cell, whereas diminishing apoptosis [143,144]. Furthermore, GLP-1 along with its agonists have been illustrated to facilitate protection conferring actions to CVS subsequent to acute myocardial infarction (MI), congestive heart failure (CHF), as well as ischaemia in addition to protection conferring actions to variable CVD along with situations, for instance hypertension, atherosclerosis as well as myocardial hypertrophy [144].

GLP-1 actions on glucose controlling ,Obesity along with T2DM

Due to obese HFpEF, VAT as well as EAT, work in the form of guiding force for LV remodeling, belligerent weight reduction therapies would be advantageous in HFpEF patients having obesity along with T2DM [1]. As per recommendations by Food and Drug Administration (FDA) 5 therapies inclusive of combination therapies HFpEF for instance i) Qysmia (topiramate/phentermine)/ii) Contrave (Bupropion SR/Naltrexone SR) iii) orlistat as well as 2 GLP-1RA's iv) liraglutide in addition to, v) semaglutide [145, rev by us in ref 14,15]. Every GLP-1RA's possesses the capability of stimulating liberation of insulin along with diminishing glucagon liberation, diminishing glucose, however they possess variable structure, leading to variation in time period of effects, dosaging, formulation, inimical sequelae, weight reduction as well as conformity [146]. Other than semaglutide, delivery of each GLP-1RA gets done by s/c route. Short acting s GLP-1RA's possess tendency of resulting in greater prominent actions on postprandial (PP) hyperglycemia as well as slowing of gastric emptying in addition to, lesser actions on fasting glucose in contrast to GLP-1RA's that are long acting. delivery of long acting GLP-1RA's for instance liraglutide in addition to, oral semaglutide gets done/day, whereas dulaglutide, exenatide extended release, subcutaneous (s/c) semaglutide delivery with gets done once weekly. maximum efficacy of diminishing glucose gets attained by s/c semaglutide delivery dulaglutide, liraglutide, along with exenatide in that order [146].

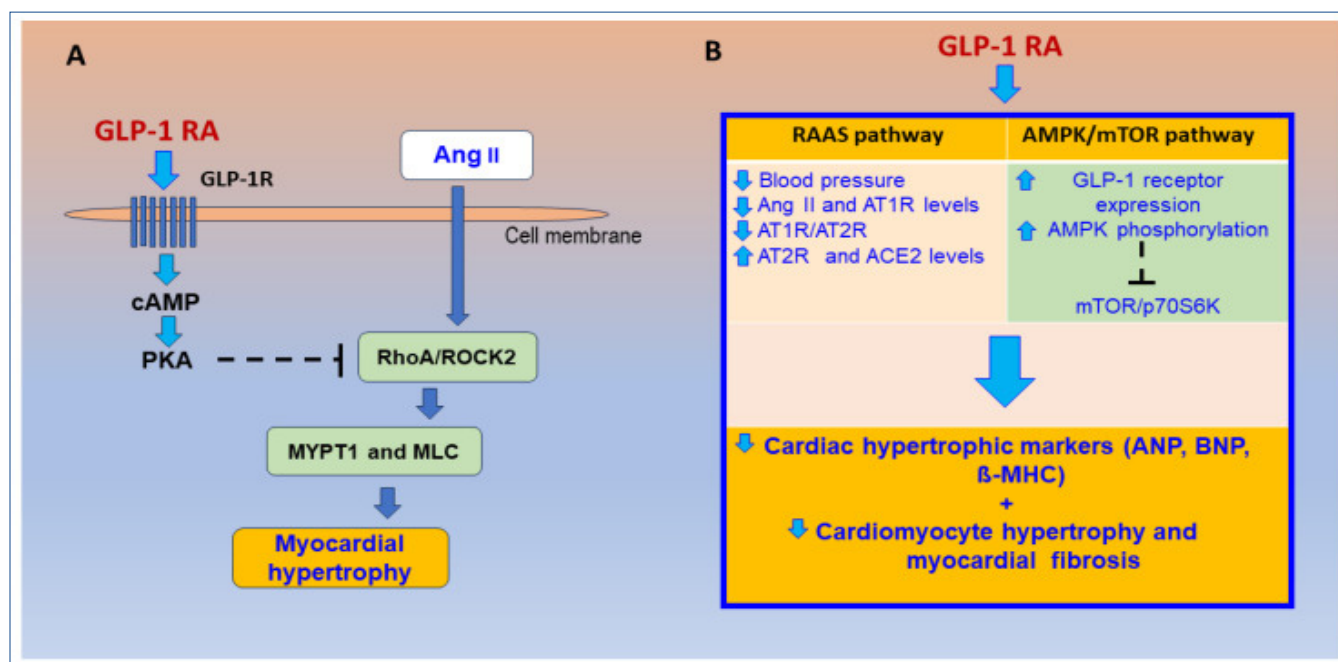
GLP-1 agonistic actions on RAS, cardiac remodeling pathways along with HFpEF mechanistic modes

Existence of certain findings is there in reference to association amongst GLP-1 Ragonism in addition to RAS. Activation of GLP-1R possesses the plausibility of crosstalk

with RAS actions [147]. GLP-1R activation by exendin-4 in case of mice diminished intrarenal RAS actions along with AngII modulated TGF- β 1/Smad3 signaling pathway [148]. In reference to spontaneously hypertensive rats (SHR), liraglutide as well as alogliptin significantly diminished circulating quantities of AngII along with led to upregulation of AT2R in addition to cardiac ACE2 [149]. A study composed of 12 young healthy males, infusion of synthetic human GLP-1 for 2hr diminished AngII quantities by 19% ($p=0.05$) along with stimulated natriuresis [149]. Such pre clinical, as well as clinical findings pointed that GLP-1 possesses the capability of hampering ACE in addition to activating ACE2.

Pathological myocardial hypertrophy portrays a foundational event for HF. In hypertensive mice stimulated by Angiotensin II (AngII), GLP-1R activation resulted in normalization of BP, diminished cardiac hypertrophy, vascular fibrosis, endothelial impairment, OS along with vascular inflammation [150]. In case of SHR, a GLP-1R agonist, liraglutide diminished cardiac weight, as well as cardiac muscle cell volume [151]. Cultured H9C2 cardiac cells which got stimulated by Angiotensin II (AngII), GLP-1R there diminished myocardial cell volume, hampered atrial natriuretic peptide (ANP) quantities, β myosin heavy chain (β -MHC) in addition to Rho kinase (ROCK) 2 along with diminished myosin light chain as well as myosin phosphatase target subunit 1 (MYPT) phosphorylation, a biomarker of the ROCK actions. H9C2 therapy of protein kinase A (PKA) hampering agent led to elimination of the GLP-1 actions, hampering actions got escalated by ROCK hampering agent Y27632. Such findings pointed that GLP-1 possesses the capability of reverting myocardial hypertrophy via cAMP/PKA/RhoA/ROCK2 signaling [151], in the manner illustrated in Figure 3A.

Mice getting normal chow diet as well as ROCK hampering agent Y27632, escalated number of enteroendocrine L cells in the intestinal tissue, escalated plasma quantities of GLP-1 in addition to insulin along with diminished blood glucose quantities in contrast to control mice [152]. In case of diabetic mice (lesser streptozocin (STZ) dosages, in addition to, high fat diet (HFD), delivery of GLP-1 analog, exendin-4 significantly reverted escalated myocardial lipid accrual, OS, apoptosis as well as cardiac remodeling in addition to impairment [153]. In case of SHR, liraglutide along with alogliptin were efficacious in diminishing ANP as well as BNP (biomarkers for the cardiac hypertrophy along with) along with BP as well as histopathological alteration [154]. Furthermore, liraglutide as well as alogliptin significantly diminished the quantities of AngII in addition to AT1R, whereas leading to upregulation of



Courtesy reference no-103- **Legend for Figure 3.** Mechanisms of GLP-1 RA on prevention of pathologic cardiac hypertrophy by (A) regulating the expression of the Ang II/AT1R/ACE2 pathway by inhibiting Ang II-induced RhoA/ROCK2 activation (which regulates MYPT1 and MLC phosphorylation) and (B) by activating the AMPK/mTOR/p70S6K pathway (adapted from Refs. [149,151]). Interrupted line = inhibition. Abbreviations: GLP-1 RA = glucagon-like peptide 1 receptor agonism, GLP-1R = glucagon-like peptide 1 receptor, cAMP = cyclic adenosine 3',5'-monophosphate, PKA = protein kinase A, Ang II = angiotensin II, ROCK2 = Rho kinase 2, MYPT1 = Myosin phosphatase target subunit 1, MLC = myosin light chain, RAAS = renin angiotensin aldosterone system, AT1R = angiotensin receptor type 1, AT2R = angiotensin receptor type 2, ACE2 = angiotensin converting enzyme 2, AMPK = Adenosine monophosphate (AMP)-activated protein kinase, mTOR = mammalian target of rapamycin, p70S6K = p70 ribosomal S6 protein kinase, ANP = atrial natriuretic peptide, BNP = brain natriuretic peptide, β -MHC = β myosin heavy chain

AT2R, along with ACE2 quantities. This got reflected in lesser AT1R: AT2R ratio [154]. Both of them significantly escalated expression of GLP-1R as well as AMP-activated protein kinase (AMPK) phosphorylation, whereas diminishing the phosphorylation of mammalian target of rapamycin (mTOR) in addition to, p70 ribosomal S6 protein kinase (S6K) [154]. In the aforementioned study, hampering of protein generation by AMPK got attained by modulating hampering of mTOR, a substantially conserved serine/threonine kinase which facilitates protein generation, cell proliferation, in addition to cell growth. The compound C, which portrays an AMPK hampering agent along with (mTOR activator MHY1485, diminished anti hypertrophic actions of GLP-1. Such observations pointed that GLP-1R is implicated in the expression of Ang II/AT1R/ACE2 as well as activation of AMPK/mTOR/p70S6K pathways, therefore avoidance of cardiac hypertrophy [154], pointed that GLP-1 agonists in the form of therapy which is of utility in pathological myocardial hypertrophy (see Figure 3B).

In case of T2DM patients AMPK phosphorylation, that gets determined in peripheral blood mononuclear cells (PBMC) is significantly diminished [155]. In case of cultured human

aortic endothelial cells, liraglutide, which portrays a GLP-1R agonist, stimulating ADAM10-based ectodomain shedding of receptor advanced glycation end-products (RAGE) through AMPK activation [156]. Nevertheless, no clinical studies have evaluated the actions of GLP-1RA on the activation of such AMPK/mTOR pathway which has protection conferring cardiac actions in patients of MetS. Therefore there is plausibility that patients of MetS / T2DM possess diminished AMPK phosphorylation quantities in PBMC in contrast to healthy persons, in addition to, GLP-1RA might be capable of escalating AMPK phosphorylation quantities.

In case of T2DM patients getting glucose diminishing agents, the group of Leguina-Ruzzi et al., Jalliet et al. [103,157], found an escalation of Rho associated protein kinase (ROCK) activation, the manner estimated by 2 direct ROCK targets in the PBMC by 4.2 times along with 5.7 times ($p < 0.001$). Escalated ROCK activation possessed a significant association with serum glucose quantities [134]. Greater quantities of ROCK activation have further been displayed in patients of MetS [157,158]. Significant diminishing of left atrial diameter was found in HFpEF patients subsequent to resynchronization treatment,

that was related to significant diminishing of ROCK activation in circulating leukocytes[159]. Despite GLP-1RA diminished ROCK activation as well as hypertrophy. In case of cultured cardiac myoblast induced Angiotensin II (AngII), there is no accessibility of results of GLP-1RA on ROCK activation in patients of MetS / T2DM in addition to GLP-1RA might diminish ROCK activation in PBMC in addition to body weight, plasma glucose along with insulin quantities, escalate aerobic capability as well as plausibility of diminishing left atrial volume, improvement of left atrial working, plausibly causing avoidance of HF in patients of MetS / T2DM.

In case of mouse model analogous to HFpEF cardiometabolic phenotype, in aged female mice getting HFD in addition to AngII, along with GLP-1RA liraglutide, ameliorated the cardiometabolic impairment, diminished cardiac hypertrophy, myocardial fibrosis, atrial weight, quantities of NP, as well as congestion in lungs[160]. Hiramatsu et al.[161], explored the effectiveness in addition to safety of liraglutide in patients of T2DM on peritoneal dialysis (n=16). The left ventricular (LV) mass index (LVMI) got significantly diminished by 20% subsequent to 12 months of liraglutide[161]. In case of a separate study liraglutide delivery was attempted in 97 patients of T2DM[162], blood glucose quantities, BP, albuminuria along with LVMI got significantly diminished subsequent to 24 hrs of liraglutide therapy ($p < 0.05$) [162].

In the setting of HFpEF exercise works in the form of main therapeutic has been found in a sophisticated pre clinical, model mice GLP-1 implicated in the controlling skeletal muscle remodeling for escalating the exercise endurance plausibility working through GLP-1 modulated ion AMPK phosphorylation[163]. In case of STEP-HFpEF Trial that implicated HFpEF patients with obesity, significant improvement of exercise capability occurred in patients getting semaglutide subsequent to 52 wk duration of semaglutide in contrast to placebo[164]. Particularly in patients getting semaglutide an improvement of 21.5 m in reference to 6 min walking stretch investigation, semaglutide in contrast to placebo, who illustrated only 1.2 m improvement. Furthermore, semaglutide group illustrated 13.3% weight loss in contrast to placebo, who illustrated only 2.6% weight loss[164]. In case of aforementioned study corresponding alteration in exercise capability was found in patients having mildly diminished ejection fraction[165].

Present Corroboration of GLP-1RA Utility For Avoidance Of Cardiovascular Damage Along With Latest Clinical Novelty

A meta-analysis of randomized controlled trials **inclusive**

of 800 patients with acute myocardial infarction (MI) who were going through angioplasty, GLP-1RA vis a vis placebo therapy escalated LVEF by 2.5% as well as, diminished infarct size by 5.3 g (95% CI: -10.4 to 0.2)[166]. GLP-1RA diminished cardiovascular processes risk in patients with T2DM by variable mechanistic modes. Apart from diminishing glycemic quantities, GLP-1RA led to significant weight reduction, activation of cyclic adenosine mono phosphate (cAMP) / PKA pathway, in addition to caused hampering of RSA activation, evoking anti hypertensive, anti inflammatory, anti atherosclerotic, along with nephroprotective actions. GLP-1RA diminished risk of MI, cardiovascular demise as well as stroke[2,167]. Despite GLP-1RA caused avoidance of atherosclerotic CVD events[168], continues to be uncharted, it possesses the capability of avoidance of HF[168]. A meta-analysis constituted of over 56,000 patients with T2DM, GLP-1RA illustrated statistically significant, diminishing of major adverse cardiovascular events (MACE-by 12%), all cause mortality (in 12%), in addition to wide renal composite results (in 17%), as well as diminished risk of hospitalization for HF (in 9%)[169].

In case of recent STEP-HFpEF, performed in patients with obesity semaglutide therapy for a year caused higher diminishing of symptoms in addition to physical restrictions, higher enhancement of exercise working, along with higher weight reduction in contrast to placebo[13]. Additionally, semaglutide diminished inflammation as well as body weight in a comparable magnitude, in full LVEF categories[165]. Avogaro et al. [170], in meta-analysis performed by them explored the actions of semaglutide on N-terminal pro-brain natriuretic peptide quantities (NT-proBNP which were inclusive of full randomized controlled trials which contrasted GLP-1RA with placebo (9 trials, 543 patients in GLP-1RA n=536 in placebo), a higher diminishing of NT-proBNP quantities were found in GLP-1RA group in contrast to placebo (-0.14 SD, $p = 0.03$), autonomous of baseline age, body weight, in addition to metabolic regulation [170]. Therefore earlier GLP-1RA initiation might be capable of ameliorating / postponement of risk of later generation of HF in patients with T2DM [170]. In a meta-regression, assessment in patients with T2DM (inclusive of n=60,079 pts, 30,693 on GLP-1RA) diminishing of HbA1c got correlated with the three point MACE-cardiovascular demise, MI/ stroke[170]. A three point MACE (LogRR-0.290, $p = 0.012$) was found with determined RR diminishing of 25% for every 1% absolute diminishing of HbA1c quantities [171]. Diminishing of body weight got correlated with the three point MACE (LogRR-0.068, $p = 0.047$) with determined RR, diminishing of

7% for every 1kg diminishing of body weight, diminishing of SBP along with LDL-C did not correlate with the three point MACE[175]. Therefore again proving earlier GLP-1RA initiation might be capable of ameliorating / postponement of risk of later generation of HF in patients with T2DM [171].

In reference to SELECT trial a multicenter, double blind, randomized, placebo-controlled trial with semaglutide got performed in patients with ≥ 45 yrs of age with prior CVD initiation in addition to BMI ≥ 27 kg/m², however without diabetes (8803 got randomized to semaglutide, along with 8801 got randomized to placebo) with average time period follow up 39.8 $\pm$ 9.4 mths[172]. A primary cardiovascular end point process took place in 6.5% of semaglutide group along with 8% of placebo group (HR, 0.80, 95%CI: 0.72 to 0.90, $p < 0.001$), whereas inimical sequelae causing persistence of stoppage of trial agent took place in 16.6% of semaglutide group and 8.2% of placebo group ($p < 0.001$). Here weekly semaglutide delivery corroborated superiority over placebo in diminishing of incidence of demise, resulting from cardiovascular etiological factor, nonfatal MI / nonfatal stroke[172].

In recent years production of double GLP-1R as well as GIPR has been attained. Tirzepatide was the starting agent [173]. In case of 8 RCT's, which implicated 7491 patients with T2DM [174], contrasted GLP-1RA, insulin along with placebo group, diminishing of body weight, in addition to BP got attained in the tirzepatide therapy group (overweight / obese patients with T2DM) in a dose based fashion. Such double GLP-1R / GIPR agonists resulted in greater weight reduction in contrast to lone GLP-1R [174]. Additionally, an innovative triple receptor agonist (retatrutide) that targets glucagon receptor (GCGR), glucose dependent insulin tropic peptide receptor (GIPR) as well as GLP-1R has got formed for the therapy of metabolic aberrations correlated with obesity along with diseases generated secondary to that by unique mechanistic modes[175]. In case of individuals with T2DM, in a phase 2 study (n=281) using placebo, GLP-1RA, dulaglutide, as well as retatrutide illustrated clinically significant enhancement of glycemic regulation in addition to, diminishing of body weight, in a dose based fashion at 36 wks by 3.2%, 10.4%, 16.8% along with 16.9% (using dosages of 0.5, 4, 8 as well as 12mg once weekly respectively) in contrast to 3%, using placebo as well as 2% having safety profile commensurate with GLP-1RA, GLP-1R as well as GIPR agonists[176].

CONCLUSIONS ALONG WITH DIRECTIONS

In case of such trial 24.2 % diminishing of body weight

was found subsequent to 48 weeks with 12 mg retatrutide [177]. This phase II trial yielded an informed dose selection for a phase 3 program.

With the present pathophysiological outcomes, clinical validation, along with recent innovations in reference to the germane part of GLP-1 RA in avoidance of HFpEF as well as its actions on reverse remodeling in addition to clinical data, significant mechanistic queries continue in patients with obesity, MetS, or in obese T2DM patients. In the aforementioned clinical situations, such queries might get widely categorized into two main groups.

i) Firstly, does GLP-1RA significantly activate germane cardioprotective/reverse remodeling mechanistic modes, for instance the endogenous counter-controlling RAS (ACE2 along with angiotensins 1-7 and 1-9) as well as the AMPK/mTOR pathway? ii) Secondly, do GLP-1 RA possess the capability of getting believed to be a significant avoidance gadget for crucial inimical cardiac remodeling mechanistic modes, for instance the PKA/RhoA/ROCK pathway, aldosterone actions, in addition to, systemic microinflammation inimical sequelae?

Delivery of GLP-1 RA to patients with MetS or T2DM might be an avoidance action for HFpEF. It is capable of stimulating weight reduction, result in improvement of glucose in addition to, insulin quantities, escalate aerobic capability, along with an improvement of left atrial volume as well as working, LV structure in addition to working.

There might be capacity of attaining by escalating cardioprotective quantities of Ang 1-9, 1-7, ACE 2, NEP, along with the AMPK/mTOR pathway, whereas diminishing quantities of Ang II, aldosterone, as well as Rho kinase activation (Figure 4), in addition to, might possess ramifications in reference to getting novel greater efficacious therapies in reference to such situations. Nevertheless, noticeably it is significant that further clinical along with preclinical research get performed to corroborate as well as escalate the clinical influence of such mechanistic modes.

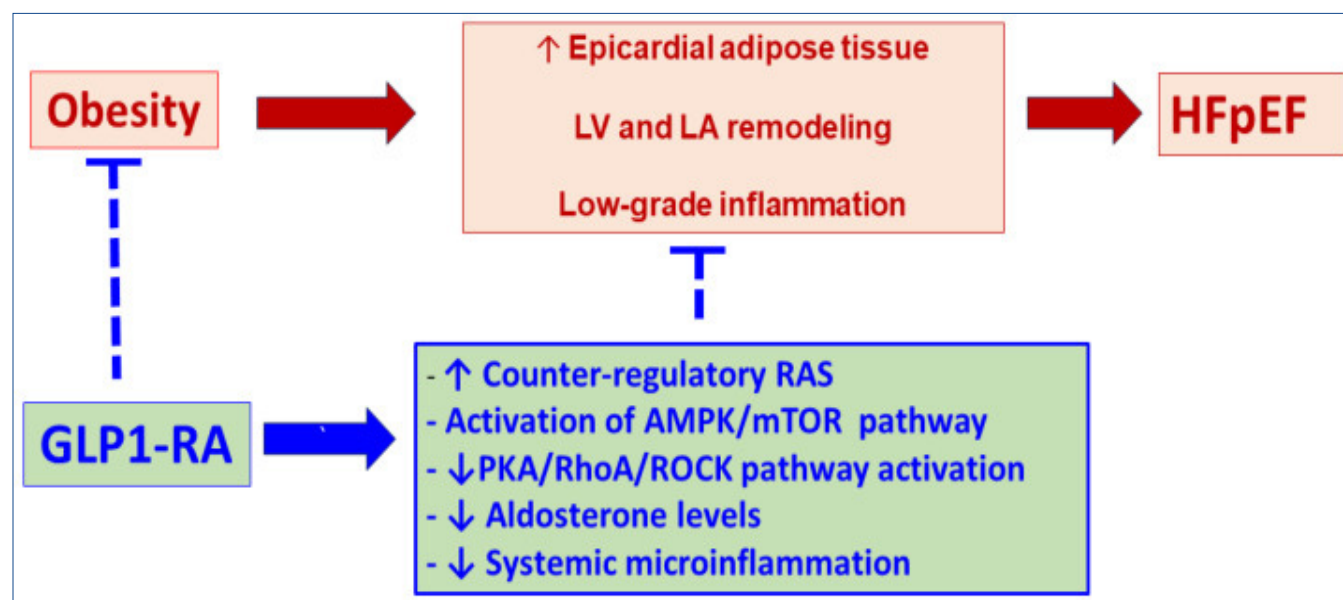
Additionally, Hullon et al. [178], in an exhaustive review in his study with the objective of evaluating association amongst endothelial impairment in HFpEF in addition to the mechanistic modes of GLP-1R agonists, illustrated that HFpEF is linked to diverse comorbidities, for instance obesity, DM, in addition to hypertension, that aid in endothelial impairment. GLP-1R agonists, semaglutide as well as liraglutide, have shown significant cardioprotective actions, improvement of vascular endothelial working, diminishing inflammation, resulting in avoidance of atherosclerosis. Clinical trials,

for instance the STEP-HFpEF trial, as has been above-mentioned have demonstrated positive outcomes in diminishing symptoms along with physical restrictions in HFpEF patients. They have demonstrated that GLP-1R agonists present a promising therapeutic option for HFpEF by targeting endothelial impairment in addition to the other pathophysiological mechanistic modes (Figure 5). Nonetheless greater work is required to work out the precise mechanistic modes via which GLP-1R agonists evoke their benefits as well as to generate their long-term safety in addition to the efficaciousness in variable HFpEF populations [178].

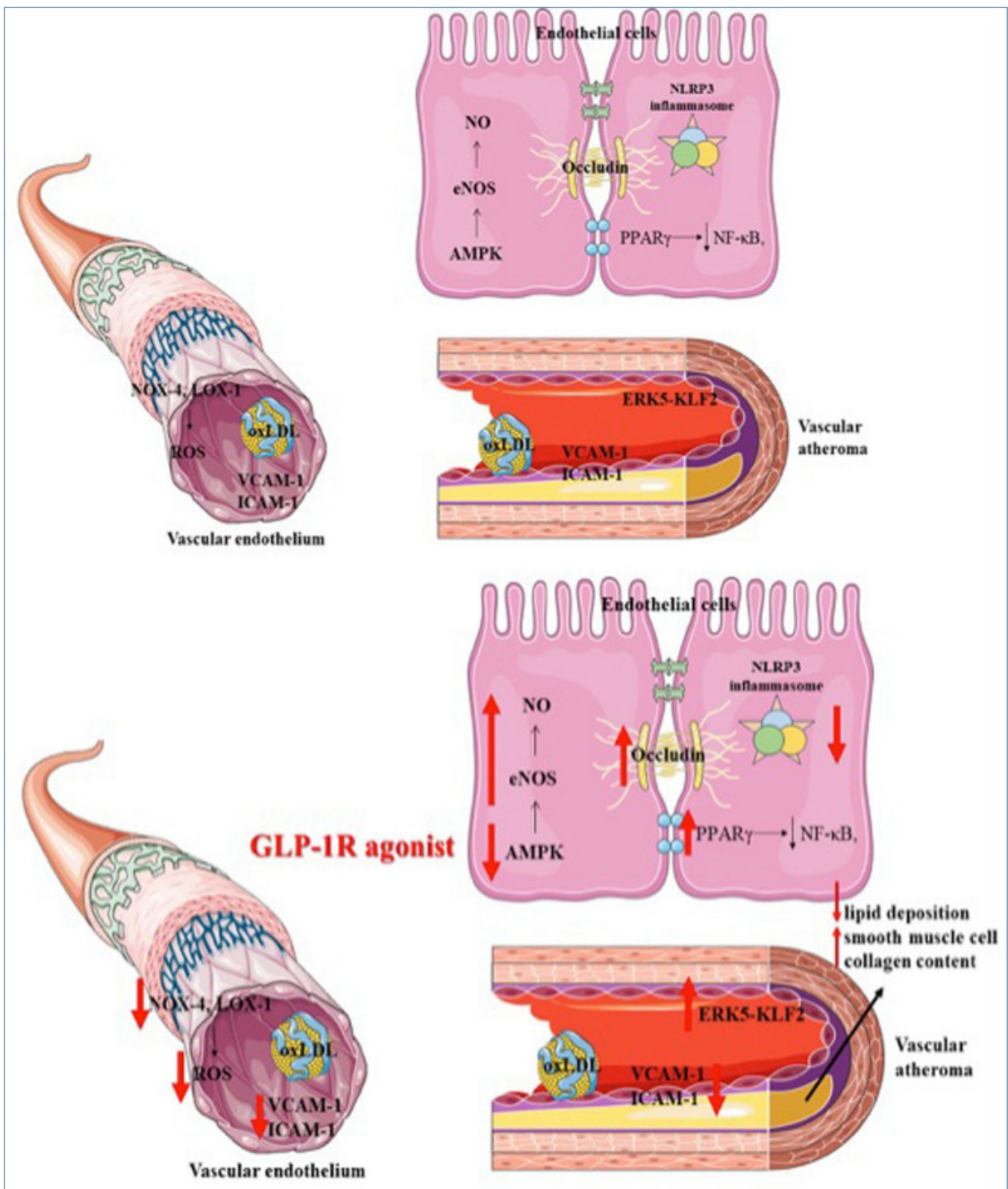
Kim SE, Yo NBS [179], further updated part of obesity in HFpEF as well as aiding via plethora of pathophysiological pathways, inclusive of systemic inflammation, neurohormonal activation, in addition to, mechanical hampering. Additionally, apart from SGLT2 hampering agents, GLP-1 RAs in the treatment of obesity have illustrated significant plausibility for improvement of HFpEF outcomes. Furthermore they showed the manner recent studies have assessed agents that are capable of targeting inflammatory pathways in patients with HFpEF

(NCT05636176). Ziltivekimab, an IL-6 hampering agent, possesses the plausibility of diminishing the systemic inflammation that aids in myocardial stiffness, diastolic impairment, as well as abnormal remodeling found in HFpEF. Thereby, it is an attractive therapeutic candidate for patients with obesity in addition to HFpEF. Further work is required to corroborate its efficaciousness along with safety for such population, opening the path for its plausible part in the form of an anti-obesity candidate agent for the complicated therapy of HFpEF (see Figure 6),...

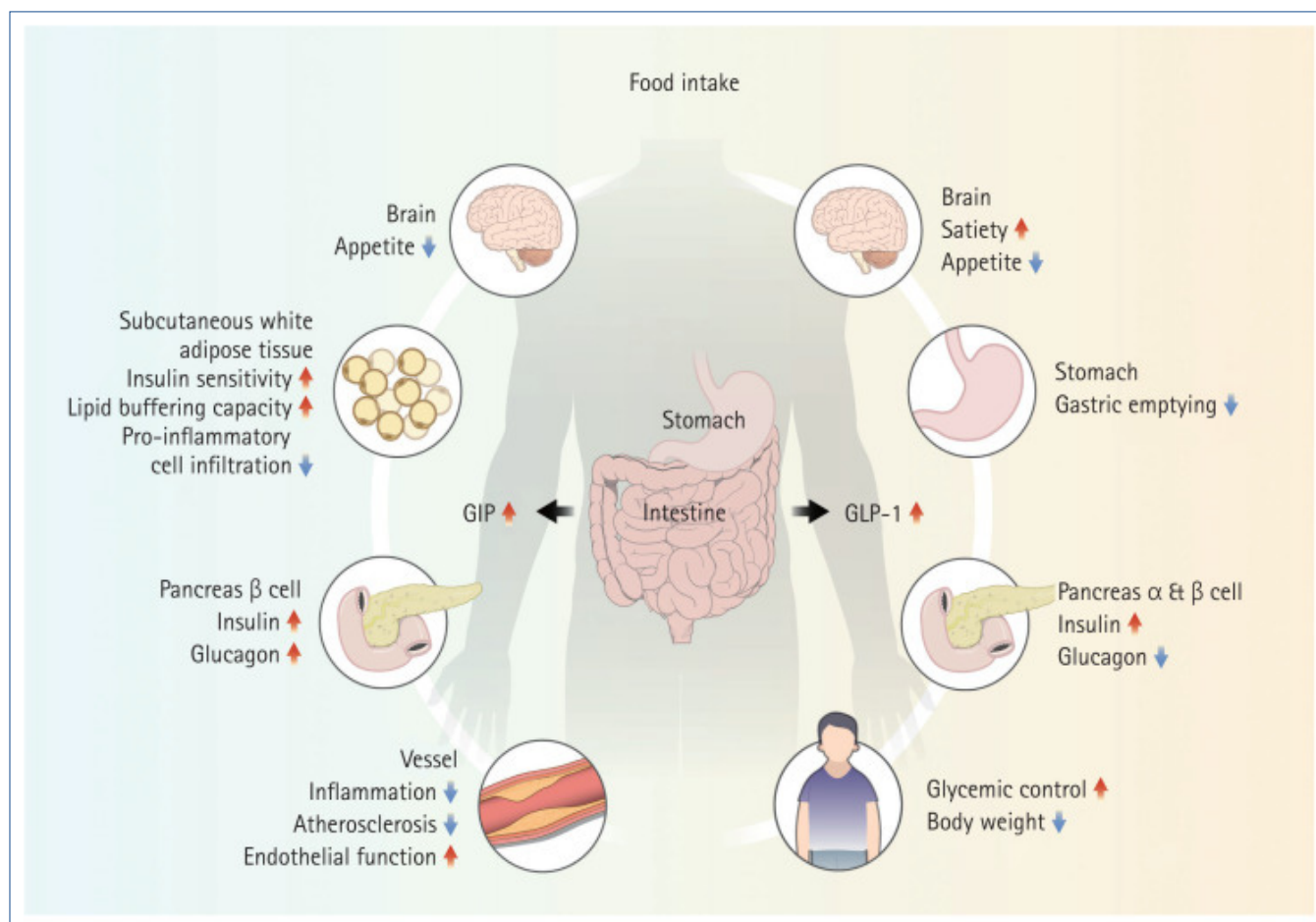
Legend for Figure 6 Courtesy reference no-178- Pathophysiology of obesity and HFpEF. Obesity contributes to HFpEF via several mechanisms. HFpEF, heart failure with preserved ejection fraction; CRP, C-reactive protein; TGF, transforming growth factor; IL, interleukin; SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; SVR, systemic vascular resistance; SV, stroke volume; NP, neprilysin; LV, left ventricle.



Legend for **Figure 4**. Courtesy reference no-103- Mechanisms to prevent HFpEF using a glucagon-like peptide-1 receptor agonist (GLP-1RA) in obesity (as well as in metabolic syndrome and in obese type 2 diabetes). The protective effects of GLP-1 on HFpEF may be attributed to the effects on obesity and its consequences on its ability to inhibit Ang II-induced RhoA/ROCK2 activation, which, in turn, regulates MYPT1 and MLCphosphorylation, thus preventing pathologic myocardial remodeling and HFpEF. Interrupted line = inhibition. Abbreviations: LV = left ventricle, LA = left atrium, RAS = renin angiotensin system, AMPK = AMP-activated protein kinase, mTOR = mammalian target of rapamycin, PKA = protein kinase A, ROCK = Rho-associated coiled-coil containing kinase.



Legend for Figure5 Courtesy reference no-178-: Effects of GLP-1 agonists on vascular endothelium*. NOX-4 (NADPH oxidase 4), LOX-1 (lectin-like ox-LDL receptor-1), ROS (reactive oxygen species), oxLDL (oxidized LDL), VCAM-1 (vascular cell adhesion molecule-1), ICAM-1 (intercellular adhesion molecule-1), NO (nitric oxide), eNOS (endothelial nitric oxide synthase), AMPK (AMP-activated protein kinase), NLRP3 (NOD-like receptor family, pyrin domain-containing 3), PPAR γ (peroxisome proliferator-activated receptor γ). The GLP-1 agonists effects demonstrated in this figure are mediated through GLP-1 receptors in the vascular endothelium. *This illustration was created using Servier Medical Art for medical illustrations



Legend for Figure 6- Courtesy reference no-179- Pathophysiology of obesity and HFpEF. Obesity contributes to HFpEF via several mechanisms. HFpEF, heart failure with preserved ejection fraction; CRP, C-reactive protein; TGF, transforming growth factor; IL, interleukin; SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; SVR, systemic vascular resistance; SV, stroke volume; NP, neprilysin; LV, left ventricle.

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