Vascular Pharmacology 115 (2019) 64–68

Contents lists available at ScienceDirect

Vascular Pharmacology

journal homepage: www.elsevier.com/locate/vph

Mini-review

GLP-1-based therapies to boost autophagy in cardiometabolic patients: From experimental evidence to clinical trials

Sarah Costantino[a], Francesco Paneni[a,b,*]

[a] Center for Molecular Cardiology, University of Zürich, Switzerland
[b] University Heart Center, Cardiology, University Hospital Zurich, Switzerland

ARTICLE INFO

Keywords:
Autophagy
Obesity
Cardiometabolic
Adipose tissue
Endothelial dysfunction
Clinical trials

ABSTRACT

Obesity has many deleterious effects on the cardiovascular system, mediated by changes in insulin sensitivity, dyslipidaemia, oxidative stress and inflammation. Current therapies mainly focus on caloric intake suppression and bariatric surgery, however the efficacy of these approaches remains elusive as most patients regain their body weight within the next 5 years. A better understanding of the pathophysiology of obesity is of paramount importance for the development of new therapeutic strategies to prevent vascular complications. Autophagy has emerged as key self-degrading process responsible for the maintenance of cellular homeostasis. Defects in autophagy homeostasis are implicated in metabolic disorders, including obesity, insulin resistance, diabetes mellitus and atherosclerosis. Most importantly, autophagy regulates animal lifespan. Albeit ample preclinical evidence supports the therapeutic promise of autophagy modulators for the treatment of obesity and metabolic diseases, the clinical efficacy of pharmacological modulation of autophagy remains to be proven. Recent work has shown that GLP-1-based therapeutic approaches may positively affect autophagy in perivascular adipose tissue, thus improving obesity-related endothelial dysfunction. In the present review we discuss current evidence on the role of autophagy in obesity, with a specific focus on DPP-4 inhibitors (DPP-4i) and GLP-1 receptor agonists (GLP-1 RA) as modulators of this process. Experimental evidence on GLP-1-based approaches is critically discussed in light of recent clinical trials with DPP-4i and GLP-1 RA.

1. Obesity, PVAT and endothelial dysfunction

Worldwide, almost 3 million people die each year due to complications of being overweight or obese. The International Diabetes Federation has recently estimated that by the year 2040 almost 600 million people will be overweight or obese [1]. Excess body weight has many deleterious effects on the cardiovascular system, mediated by changes in insulin sensitivity, dyslipidaemia, oxidative stress and inflammation [2,3]. Current therapies to fight obesity mainly focus on caloric intake suppression and bariatric surgery, however the efficacy of these approaches remains to be proven as most of patients regain their weight within 5 years [4]. A better understanding of the pathophysiology of obesity is of paramount importance for the development of new therapeutic strategies to prevent vascular complications and mortality in these patients. Emerging evidence indicates that obesity alters both the endocrine and paracrine actions of adipocyte-derived factors, with subsequent disruption of vascular homeostasis, eventually leading to endothelial dysfunction and arterial hypertension. Perivascular adipose tissue (PVAT) has recently shown to be heavily implicated in the pathophysiology of obesity-related endothelial dysfunction [5]. Under physiological conditions, PVAT attenuates agonist-induced vasoconstriction by releasing vasoactive molecules including hydrogen peroxide, angiotensin 1–7, adiponectin, methyl palmitate, hydrogen sulfide, NO and leptin [5]. By contrast, in the setting of obesity, PVAT undergoes molecular alterations favouring a pro-inflammatory phenotype, with enhanced secretion inflammatory adipocytokines, leading to an impairment of PVAT-vasorelaxing effects [6,7]. The vasodilator response to acetylcholine is reduced only in PVAT-containing, but not in PVAT-free thoracic aorta isolated from diet-induced obese mice, indicating a unique role for PVAT in obesity-induced vascular dysfunction [8]. Furthermore, PVAT dysfunction has also been observed in small arteries isolated from visceral fat arteries of obese individuals [9]. Altogether, current evidence suggests that PVAT represents an attractive therapeutic target to rescue endothelial dysfunction in obesity. Although previous work has provided key insights in this field, therapeutic strategies aimed at rescuing obesity-related

* Corresponding author at: Division of Cardiovascular Epigenetics, Center for Molecular Cardiology, University of Zürich, Wagistrasse 12, Schlieren CH-8952, Zurich, Switzerland.
E-mail address: francesco.paneni@uzh.ch (F. Paneni).

https://doi.org/10.1016/j.vph.2019.03.003
Received 26 December 2018; Received in revised form 5 March 2019; Accepted 22 March 2019
Available online 26 March 2019

PVAT dysfunction have yet to be developed.

2. Role of autophagy in cardiometabolic states

Accumulating evidence indicates that autophagy plays an essential role in a variety of human diseases [10]. The autophagic response is a complex biological process promoting lysosomal degradation of unnecessary or dysfunctional cellular components, namely misfolded or aggregated proteins as well as damaged organelles (i.e. mitochondria, endoplasmic reticulum). Under physiological conditions, a basal autophagic activity allows the turnover of cytosolic components [11]. Systemic or tissue-specific deletion of autophagy-related genes in various organisms, including mice, may lead to serious malformations and even death, supporting the hypothesis that autophagy is an essential process that contributes to health and overall well-being [12]. In response to adverse stimuli (nutrient deprivation, oxidative stress, toxic bioproducts) the activity of the autophagic machinery is significantly amplified with the aim of recycling nutrients and generating energy for maintenance of cell viability under unfavourable conditions. Although basal autophagy is critical to maintain cellular and whole-body homeostasis, both increases and decreases in autophagy to excessive degree can be maladaptive. In cardiac hypertrophy, heart failure, and ischemia/reperfusion, autophagic flux is abnormally elevated, thus contributing to cardiac dysfunction [13]. By contrast, in conditions such as aging, autophagic activity and processing are attenuated, thus perturbing cellular homeostasis and contributing to cardiac disease. Notably, a recent study has shown that genetically-modified mice with constitutive activation of autophagy display increased lifespan and healthspan as compared to their wild-type littermates [14]. Autophagy is also implicated in the pathophysiology of diabetes and atherosclerosis. Genetic disruption of autophagy components (i.e. Atg7) leads to the formation of large inclusion bodies containing polyubiquitinated proteins in pancreatic β cells, with subsequent cellular hypertrophy, impaired insulin production and hyperglycemia [15]. Interestingly, reactivation of autophagy in secretory-deficient β-cells preserves insulin secretion and cell viability [16]. In experimental models of atherosclerosis, mild oxidative stress seems to activate autophagy, which in turn facilitates the removal of damaged organelles [17]. Under these conditions, autophagy appears to play a protective role against atherogenesis, in part due to a reduction in the number of macrophages in the atherosclerotic plaque. As a consequence of defective autophagic flux, dysfunctional organelles (i.e. mitochondria) start accumulating in cells exposed to ambient hyperglycemia or in vascular cells from diabetic mice. Since mitochondria are the primary site of the production of reactive oxygen species (ROS), diabetes-related impairment of autophagy may favour the accumulation of ROS in vascular cells, thus affecting NO bioavailability, inflammatory response and insulin signalling [18]. Hence, hyperglycemia-induced defects of the autophagic machinery may significantly alter the molecular phenotype and functionality of several cells constituting the vessel wall. More recently, autophagy has shown to be sensitive to changes in nutrient status, as shown in experimental models of obesity [19]. Risk factors often clustering in obesity and metabolic syndrome, such as dyslipidaemia, high blood pressure and dysglycemia, are actively involved in the impairment of the autophagic flux [20]. In turn, defective autophagy might promote metabolic dysregulation and adipogenesis [21]. The role of autophagy in adipose tissue development, adipogenesis and lipid metabolism has gained increasing attention over the last years. Pharmacological inhibition of autophagy in human adipose tissue explants resulted in elevated secretion of pro-inflammatory cytokines, suggesting an inhibitory role for autophagy in adipose tissue inflammation [22]. Although these studies have contributed to elucidate the key role of autophagy in the regulation of inflammatory and metabolic processes, we are still far from having developed breakthrough therapeutic approaches to restore autophagy in patients with metabolic and cardiovascular disease. Indeed, ample preclinical evidence supports the therapeutic promise of autophagy modulators for the treatment of obesity and metabolic diseases, whereas the clinical efficacy of pharmacological modulation of autophagy remains elusive.

3. GLP-1-based interventions and PVAT autophagy

Recent evidence has shown that DPP4 inhibitors (DPP-4i), a class of drugs widely used for the management of hyperglycaemia in patients with type 2 diabetes (T2D), exert a variety of pleiotropic effects on obesity-related disorders, namely inflammation and hepatic steatosis [22,23]. The dipeptidyl peptidase 4 (DPP-4) protease cleaves proline dipeptides from the N-terminus of polypeptides including glucagon-like peptide 1 (GLP-1), a gut-derived hormone that stimulates insulin while inhibiting glucagon secretion [24]. GLP-1-based therapeutic interventions were recently shown to induce autophagy via the AMPK/mTOR pathway, thus attenuating non-alcoholic fatty liver disease in experimental models of obesity [25,26]. In a recent issue of *Vascular Pharmacology*, Zhu and colleagues showed that modulation of autophagy by DPP-4i may contribute to ameliorate obesity-related alterations of PVAT, thus rescuing endothelial dysfunction [27]. In aortic segments from diet-induced obese mice, the presence of PVAT significantly impaired endothelium-dependent vasodilation, while the DPP-4i alogliptin prevented this phenomenon. PVAT dysfunction in obese mice was associated with defective autophagy whereas DPP-4 blockade was capable of restoring the autophagic flux (Fig. 1). Consistently, pharmacological modulation of autophagy – either by the autophagy inhibitor CQ or the autophagy activator rapamycin - reversed PVAT-induced endothelial dysfunction, thus supporting a causal role of autophagy in this setting [27]. Notably, the beneficial effects of DPP-4i on PVAT autophagy were GLP-1 dependent. Indeed, in cultured adipocytes exposed to palmitic acid, alogliptin alone failed to rescue fatty acid-induced impairment of autophagy, while concomitant administration of GLP-1 was able to reactivate autophagy [27]. These results were confirmed by the observation that GLP-1 receptor blockade by exendin 9–39 abolished the effects of alogliptin on autophagy. Restoration of autophagy by alogliptin and GLP-1 was able to restore adiponectin levels while blunting the secretion of tumour necrosis factor-α (TNF-α) in PVAT [27]. Given the pivotal role of adiponectin and TNF-α as modulators of endothelial function in obesity, the findings of Zhu et al. may have potential impact for the prevention of vascular complications in cardiometabolic patients. Although these results provide insights into new therapies modulating autophagy in PVAT, it remains unclear how restoration of autophagy affects the transcriptional profile and secretome of PVAT. Previous work has shown that defective autophagy may foster pro-inflammatory and senescent phenotypes due to endoplasmic reticulum (ER) stress [28]. However, further studies are needed to demonstrate the causal link between ER stress, PVAT dysfunction and vascular disease in obesity. Another important evidence gap in this field is whether autophagy has a causal or circumstantial role in the vascular complications of obesity. Modulation of autophagy might also contribute to explain the recent findings by Osto et al., where a GLP-1-mediated mechanism was found to rescue obesity-induced endothelial dysfunction in obese patients undergoing RYGB [29]. These latter findings suggest that RYGB patients might benefit from GLP-1 based interventions. Although PVAT has shown to be a pivotal target of GLP-1, we cannot exclude that other cell types are involved in the GLP-1-dependent effects on vascular phenotype. A recent study using *glp1r*-Cre mice crossed with fluorescent reporter strains, showed that GLP1-RA is expressed in pancreatic β- and δ-cells, vascular smooth muscle, cardiac atrium, gastric antrum/pylorus, enteric neurones, as well as vagal and dorsal root ganglia [30]. Moreover, GLP1-RA was found to be expressed in several inflammatory cells including macrophages [31]. Hence, one can assume that the effects of GLP-1 on perivascular adipose tissue may be also mitigated by inflammatory cells in the perivascular space. GLP-1-dependent changes of macrophage polarization and macrophage secretome might impact

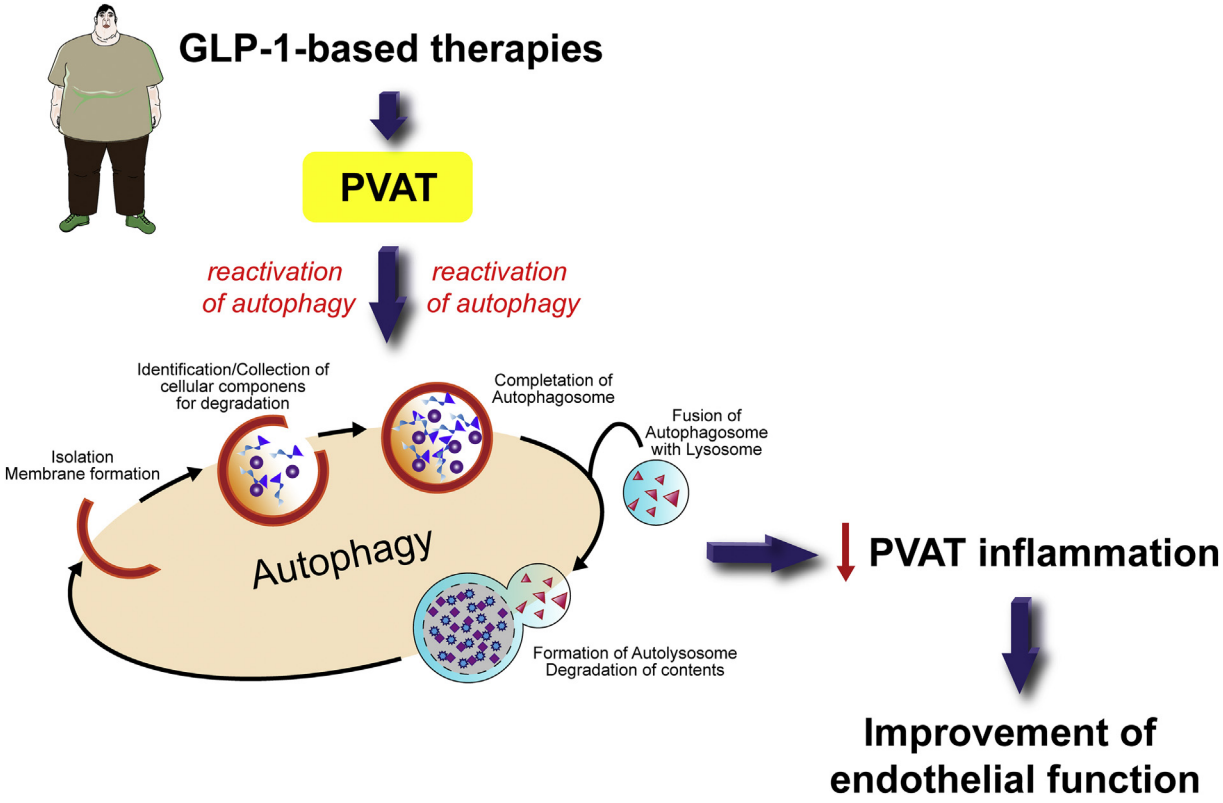

Fig. 1. Schematic showing the effects of GLP-1-based therapies on PVAT autophay and vascular function in obesity. PVAT, perivascular adipose tissue.

on endothelial function and vascular remodelling in obesity. Further studies will help to elucidate the contribution of different inflammatory cells in the GLP-1-related effects on the obese vasculature.

4. Insights from clinical trials

The effects of GLP-1 in modulating autophagy and PVAT functionality may partially contribute to explain the recent success of GLP1-based therapies in patients with T2D. However, randomized controlled trials (RCTs) with GLP1-RA and DPP-4i led to conflicting results in patients with T2D, thus highlighting the need to better understand the mechanism of action of these drug classes [32]. Out of 7 FDA-approved GLP-1RA RCTs, to date only liraglutide and albiglutide have shown a significant reduction of CV events in LEADER and HARMONY OUTCOMES trials, respectively [33,34]. Similar benefits were observed with semaglutide in the SUSTAIN-6 trial, however the sample size was relatively small, and the trial was designed and powered as a non-inferiority trial [35]. Along the same line, the EXSCEL trial showed overall positive results, although the cardiovascular endpoint did not reach statistical significance [36]. In patients with acute coronary syndrome, treatment with lixisenatide failed to reduce cardiovascular events in the ELIXA trial [37]. In the HARMONY OUTCOMES trial, treatment with albiglutide was associated with a significant reduction of the primary composite outcome as compared to placebo (HR 0.78, 95% CI 0·68–0·90), with $p < 0{\cdot}0001$ for non-inferiority and $p = 0{\cdot}0006$ for superiority [34]. The very recent PIONEER 6 trial – a randomized non-inferiority trial testing an oral formulation of semaglutide against placebo in patients with T2D – showed a statistically significant 51% relative reduction in the risk of CV death, as well as a 49% relative reduction in all-cause mortality, whereas no differences were observed for nonfatal MI or stroke between the two treatment arms [38]. Although most of trials with GLP-1RA showed a reduction of CV and total mortality, only few studies showed a reduction of "atherosclerotic" endpoints such as non-fatal MI and stroke. The HARMONY OUTCOMES trial was indeed the only trial where treatment with GLP-1RA was clearly associated with a reduction in the rate of non-fatal MI [34].

On the other hand, clinical trials with DDP-4i were rather disappointing from a cardiovascular perspective [39,40]. Several meta-analyses of retrospective studies have shown that DPP-4i (individually and as a class) were associated with reductions in CV events [41,42]. However, the studies examined were not specifically designed to appraise the effect of DPP-4i on CVD. Three randomized trials - SAVOR–TIMI, EXAMINE and TECOS - were conducted over the last few years to systematically investigate the CV safety and efficacy of DPP-4i in patients with T2DM. Although treatment with DPP-4i was safe, none of these studies demonstrated a reduction of CV events. The SAVOR-TIMI 53 and EXAMINE trial even showed an increase in the risk of heart failure in patients receiving saxagliptin and alogliptin, respectively [43]. In the recent CARMELINA trial, the DPP-4i linagliptin added to usual care failed to impact on cardiac and renal endpoints in T2D patients over a median flow-up of 2.2 years [44]. Although both GLP-1 RA and DPP-4i increase GLP-1 levels, these 2 drug classes present substantial differences in their ability to warrant consistent and selective restoration of GLP-1 levels [45]. While GLP1-RA lead to a "supraphysiological" elevation of endogenous GLP-1 levels, DPP-4i may only secure the restoration of physiological concentrations of the hormone. Hence, circulating levels of GLP-1 are sensibly higher after treatment with GLP1-RA as compared with DPP-4i [46]. Moreover, DPP-4i are less specific, as they do not only potentiate the actions of GLP-1, but also increase the levels of SDF-1 (stromal cell-derived factor 1), NPY (neuropeptide Y), and substance P, eventually leading to activation of sympathetic nervous system, stimulation of β-adrenergic receptors and subsequent cardiomyocyte apoptosis, presumably through a CaMKII ($Ca++$/calmodulin-dependent protein kinase II) pathway [47]. The increase in sympathetic activation may explain the increased risk of heart failure observed with DPP-4i in SAVOR–TIMI and EXAMINE trials. Indeed, β-blockers seemed to have attenuated the risk of heart failure with DPP-4 inhibition in a large-scale trial [48].

In the experimental study by Zhu and colleagues [27], administration of the DPP-4i alogliptin in mice was able to rescue obesity-induced endothelial dysfunction and PVAT autophagy in a GLP-1-dependent manner. Although the beneficial effects of DDP-4i on intermediate cardiovascular endpoints are supported by several experimental studies conducted in obese and diabetic mice, most of these findings are somehow "lost in translation", given the recent failure of this class of drugs in reducing cardio-renal endpoints in patients with cardiometabolic disturbances [47]. The modest elevation of GLP-1 levels following treatment with DPP4i may require RCTs with longer follow-up to better appreciate putative cardiovascular benefits of this class of drugs. However, the concomitant elevation of other peptides, namely SDF-1, NPY and substance P may exert detrimental effects on the cardiovascular system and may therefore vanish any GLP-1-related benefit [47].

5. Future perspectives

The work by Zhu et al. [27] should be interpreted as a proof-of-concept study supporting the notion that therapies aimed at boosting GLP-1 levels may rescue endothelial dysfunction by reactivation of autophagic flux in PVAT. Autophagy has recently emerged as key self-degrading process responsible for the maintenance of cellular homeostasis. Defects in autophagy homeostasis are implicated in metabolic disorders, including obesity, insulin resistance, diabetes mellitus and atherosclerosis [21]. Most importantly, recent genetic evidence indicates that autophagy has a crucial role in the regulation of animal lifespan [14]. Basal level of autophagic activity is elevated in many longevity paradigms and the activity is required for lifespan extension. Hence, therapeutic modulation of autophagy represents an attractive approach to prevent premature vascular aging, improve healthspan and promote longevity [49]. The effects of autophagy on lifespan deserve particular attention if we consider that obese patients display telomere shortening and premature aging features [50]. Autophagy is also heavily implicated in the onset and development of obesity-related metabolic cardiomyopathy [51]. In the heart, autophagy helps to meet metabolic requirements during pressure overload, hypertension and ischaemic heart disease. High fat diet in mice leads to elevated levels of LC3II and p62 in the heart, suggesting the adequate initiation of autophagy with inhibition of autophagosome degradation in obesity [52]. Hence, GLP-1-based therapies might contribute to reactivate autophagy not only in PVAT but also in the heart, thus leading to a global cardioprotective effect. In this regard, RCTs with longer follow-up are required to appreciate putative beneficial effects of GLP-1RA on heart failure-related outcomes and atherosclerotic outcomes. Although many drugs that produce beneficial metabolic effects are capable of modulating autophagic flux, autophagy might not be their only and main mechanism of action. For example, metformin has shown to modulate autophagy, however its beneficial effects are mainly driven by activation of AMPK and subsequent induction of GLUT4 translocation and glucose uptake [53]. The same could apply to GLP-1-based therapies, hence further studies are needed to appraise whether autophagy is the main mechanism whereby DPP-4i and GLP-1RA reduce vascular risk in patients. The latter possibility is currently hampered by technical difficulties in measuring autophagy activity or flux in humans [54]. Moreover, obesity is a complex disorder involving multiple metabolic derangements which exhibit tissue specificity. Hence, the global inhibition or activation of autophagy, or the local modulation at an incorrect time point might be counterproductive. Last but not least, most drugs "targeting" autophagy do not directly or specifically modulate autophagy but rather influence upstream pathways, eventually leading to alterations in autophagy. In conclusion, targeting autophagy as a therapeutic strategy for the management of obesity and obesity-related complications has shown promise in preclinical studies. Further studies should focus on the better understanding the role of DPP-4i and GLP-1 as specific modulators of autophagy in patients with cardiometabolic disturbances.

Acknowledgments

F.P. is the recipient of a H.H. Sheikh Khalifa bin Hamad Al Thani Foundation Assistant Professorship at the Faculty of Medicine, University of Zurich. The present work is supported by the Zürich Heart House, the Swiss Heart Foundation, Swiss Life Foundation, Kurt und Senta-Hermann Stiftung, the EMDO Stiftung and the Schweizerische Diabetes-Stiftung to F.P; the Holcim Foundation and the Swiss Heart Foundation (to S.C).

References

[1] K. Ogurtsova, J.D. da Rocha Fernandes, Y. Huang, U. Linnenkamp, L. Guariguata, N.H. Cho, D. Cavan, J.E. Shaw, L.E. Makaroff, IDF diabetes atlas: global estimates for the prevalence of diabetes for 2015 and 2040, Diabetes Res. Clin. Pract. 128 (2017) 40–50.
[2] N. Stefan, A. Fritsche, F. Schick, H.U. Haring, Phenotypes of prediabetes and stratification of cardiometabolic risk, Lancet Diabetes Endocrinol. 4 (2016) 789–798.
[3] S. Costantino, S.A. Mohammed, S. Ambrosini, F. Paneni, Epigenetic processing in cardiometabolic disease, Atherosclerosis. 281 (2019) 150–158.
[4] J.W. Zylke, H. Bauchner, The unrelenting challenge of obesity, JAMA 315 (2016) 2277–2278.
[5] N. Xia, H. Li, The role of perivascular adipose tissue in obesity-induced vascular dysfunction, Br. J. Pharmacol. 174 (2017) 3425–3442.
[6] R. Aghamohammadzadeh, R.D. Unwin, A.S. Greenstein, A.M. Heagerty, Effects of obesity on perivascular adipose tissue Vasorelaxant function: nitric oxide, inflammation and elevated systemic blood pressure, J. Vasc. Res. 52 (2015) 299–305.
[7] F. Schinzari, M. Tesauro, A. Veneziani, N. Mores, N. Di Daniele, C. Cardillo, Favorable vascular actions of angiotensin-(1-7) in human obesity, Hypertension 71 (2018) 185–191.
[8] N. Xia, S. Weisenburger, E. Koch, M. Burkart, G. Reifenberg, U. Forstermann, H. Li, Restoration of perivascular adipose tissue function in diet-induced obese mice without changing bodyweight, Br. J. Pharmacol. 174 (2017) 3443–3453.
[9] A. Virdis, E. Duranti, C. Rossi, U. Dell'Agnello, E. Santini, M. Anselmino, M. Chiarugi, S. Taddei, A. Solini, Tumour necrosis factor-alpha participates on the endothelin-1/nitric oxide imbalance in small arteries from obese patients: role of perivascular adipose tissue, Eur. Heart J. 36 (2015) 784–794.
[10] D.C. Rubinsztein, P. Codogno, B. Levine, Autophagy modulation as a potential therapeutic target for diverse diseases, Nat. Rev. Drug Discov. 11 (2012) 709–730.
[11] A.M. Choi, S.W. Ryter, B. Levine, Autophagy in human health and disease, N. Engl. J. Med. 368 (2013) 1845–1846.
[12] B. Levine, G. Kroemer, Autophagy in the pathogenesis of disease, Cell. 132 (2008) 27–42.
[13] S. Sciarretta, Y. Maejima, D. Zablocki, J. Sadoshima, The role of autophagy in the heart, Annu. Rev. Physiol. 80 (2018) 1–26.
[14] A.F. Fernandez, S. Sebti, Y. Wei, Z. Zou, M. Shi, K.L. McMillan, C. He, T. Ting, Y. Liu, W.C. Chiang, D.K. Marciano, G.G. Schiattarella, G. Bhagat, O.W. Moe, M.C. Hu, B. Levine, Disruption of the beclin 1-BCL2 autophagy regulatory complex promotes longevity in mice, Nature 558 (2018) 136–140.
[15] C.D. Gonzalez, M.S. Lee, P. Marchetti, M. Pietropaolo, R. Towns, M.I. Vaccaro, H. Watada, J.W. Wiley, The emerging role of autophagy in the pathophysiology of diabetes mellitus, Autophagy 7 (2011) 2–11.
[16] H.S. Jung, K.W. Chung, J. Won Kim, J. Kim, M. Komatsu, K. Tanaka, Y.H. Nguyen, T.M. Kang, K.H. Yoon, J.W. Kim, Y.T. Jeong, M.S. Han, M.K. Lee, K.W. Kim, J. Shin, M.S. Lee, Loss of autophagy diminishes pancreatic beta cell mass and function with resultant hyperglycemia, Cell Metab. 8 (2008) 318–324.
[17] S.C. Nussenzweig, S. Verma, T. Finkel, The role of autophagy in vascular biology, Circ. Res. 116 (2015) 480–488.
[18] S. Lavandero, M. Chiong, B.A. Rothermel, J.A. Hill, Autophagy in cardiovascular biology, J. Clin. Invest. 125 (2015) 55–64.
[19] L. Galluzzi, F. Pietrocola, B. Levine, G. Kroemer, Metabolic control of autophagy, Cell. 159 (2014) 1263–1276.
[20] J.G. Juarez-Rojas, G. Reyes-Soffer, D. Conlon, H.N. Ginsberg, Autophagy and cardiometabolic risk factors, Rev. Endocr. Metab. Disord. 15 (2014) 307–315.
[21] Y. Zhang, J.R. Sowers, J. Ren, Targeting autophagy in obesity: from pathophysiology to management, Nat. Rev. Endocrinol. 14 (2018) 356–376.
[22] H.J. Jansen, P. van Essen, T. Koenen, L.A. Joosten, M.G. Netea, C.J. Tack, R. Stienstra, Autophagy activity is up-regulated in adipose tissue of obese individuals and modulates proinflammatory cytokine expression, Endocrinology 153 (2012) 5866–5874.
[23] G. Waldrop, J. Zhong, M. Peters, S. Rajagopalan, Incretin-based therapy for diabetes: What a cardiologist needs to know, J. Am. Coll. Cardiol. 67 (2016) 1488–1496.
[24] A.C. Sposito, O. Berwanger, L.S.F. de Carvalho, J.F.K. Saraiva, GLP-1RAs in type 2 diabetes: mechanisms that underlie cardiovascular effects and overview of cardiovascular outcome data, Cardiovasc. Diabetol. 17 (2018) 157.
[25] Y. Zhang, Y. Ling, L. Yang, Y. Cheng, P. Yang, X. Song, H. Tang, Y. Zhong, L. Tang, S. He, S. Yang, A. Chen, X. Wang, Liraglutide relieves myocardial damage by promoting autophagy via AMPK-mTOR signaling pathway in zucker diabetic fatty rat, Mol. Cell. Endocrinol. 448 (2017) 98–107.
[26] Q. He, S. Sha, L. Sun, J. Zhang, M. Dong, GLP-1 analogue improves hepatic lipid accumulation by inducing autophagy via AMPK/mTOR pathway, Biochem.

Biophys. Res. Commun. 476 (2016) 196–203.
[27] B. Zhu, Y. Li, W. Mei, M. He, Y. Ding, B. Meng, H. Zhao, G. Xiang, Alogliptin improves endothelial function by promoting autophagy in perivascular adipose tissue of obese mice through a GLP-1-dependent mechanism, Vasc. Pharmacol. (2018), https://doi.org/10.1016/j.vph.2018.11.003.
[28] C. Zhang, T.W. Syed, R. Liu, J. Yu, Role of endoplasmic reticulum stress, autophagy, and inflammation in cardiovascular disease, Front. Cardiovasc. Med. 4 (2017) 29.
[29] E. Osto, P. Doytcheva, C. Corteville, M. Bueter, C. Dorig, S. Stivala, H. Buhmann, S. Colin, L. Rohrer, R. Hasballa, A. Tailleux, C. Wolfrum, F. Tona, J. Manz, D. Vetter, K. Spliethoff, P.M. Vanhoutte, U. Landmesser, F. Pattou, B. Staels, C.M. Matter, T.A. Lutz, T.F. Luscher, 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 (2015) 871–881.
[30] P. Richards, H.E. Parker, A.E. Adriaenssens, J.M. Hodgson, S.C. Cork, S. Trapp, F.M. Gribble, F. Reimann, Identification and characterization of GLP-1 receptor-expressing cells using a new transgenic mouse model, Diabetes. 63 (2014) 1224–1233.
[31] D.J. Drucker, The cardiovascular biology of glucagon-like peptide-1, Cell Metab. 24 (2016) 15–30.
[32] S.R. Das, B.M. Everett, K.K. Birtcher, J.M. Brown, W.T. Cefalu, J.L. Januzzi Jr., R. Rastogi Kalyani, M. Kosiborod, M.L. Magwire, P.B. Morris, L.S. Sperling, 2018 ACC expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways, J. Am. Coll. Cardiol. 72 (2018) 3200–3223.
[33] S.P. Marso, G.H. Daniels, K. Brown-Frandsen, P. Kristensen, J.F. Mann, M.A. Nauck, S.E. Nissen, S. Pocock, N.R. Poulter, L.S. Ravn, W.M. Steinberg, M. Stockner, B. Zinman, R.M. Bergenstal, J.B. Buse, Committee LS and Investigators LT. Liraglutide and cardiovascular outcomes in type 2 diabetes, N. Engl. J. Med. 375 (2016) 311–322.
[34] A.F. Hernandez, J.B. Green, S. Janmohamed, R.B. D'Agostino Sr., C.B. Granger, N.P. Jones, L.A. Leiter, A.E. Rosenberg, K.N. Sigmon, M.C. Somerville, K.M. Thorpe, J.J.V. McMurray, S. Del Prato, Harmony outcomes c and investigators. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony outcomes): a double-blind, randomised placebo-controlled trial, Lancet 392 (2018) 1519–1529.
[35] S.P. Marso, S.C. Bain, A. Consoli, F.G. Eliaschewitz, E. Jodar, L.A. Leiter, I. Lingvay, J. Rosenstock, J. Seufert, M.L. Warren, V. Woo, O. Hansen, A.G. Holst, J. Pettersson, T. Vilsboll, Investigators S, Semaglutide and cardiovascular outcomes in patients with type 2 diabetes, N. Engl. J. Med. 375 (2016) 1834–1844.
[36] R.R. Holman, M.A. Bethel, R.J. Mentz, V.P. Thompson, Y. Lokhnygina, J.B. Buse, J.C. Chan, J. Choi, S.M. Gustavson, N. Iqbal, A.P. Maggioni, S.P. Marso, P. Ohman, N.J. Pagidipati, N. Poulter, A. Ramachandran, B. Zinman, A.F. Hernandez, Group ES, Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes, N. Engl. J. Med. 377 (2017) 1228–1239.
[37] M.A. Pfeffer, B. Claggett, R. Diaz, K. Dickstein, H.C. Gerstein, L.V. Kober, F.C. Lawson, L. Ping, X. Wei, E.F. Lewis, A.P. Maggioni, J.J. McMurray, J.L. Probstfield, M.C. Riddle, S.D. Solomon, J.C. Tardif, E. Investigators, Lixisenatide in patients with type 2 diabetes and acute coronary syndrome, N. Engl. J. Med. 373 (2015) 2247–2257.
[38] S.C. Bain, O. Mosenzon, R. Arechavaleta, P. Bogdanski, A. Comlekci, A. Consoli, C. Deerochanawong, K. Dungan, M.C. Faingold, M.E. Farkouh, D.R. Franco, J. Gram, C. Guja, P. Joshi, R. Malek, J.F. Merino-Torres, M.A. Nauck, S.D. Pedersen, W.H. Sheu, R.J. Silver, C.J. Tack, N. Tandon, O.K. Jeppesen, M. Strange, M. Thomsen, M. Husain, Cardiovascular safety of oral semaglutide in patients with type 2 diabetes: rationale, design and patient baseline characteristics for the PIONEER 6 trial, Diabetes Obes. Metab. 21 (2019) 499–508.
[39] S.L. Zheng, A.J. Roddick, R. Aghar-Jaffar, M.J. Shun-Shin, D. Francis, N. Oliver, K. Meeran, Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis, JAMA. 319 (2018) 1580–1591.
[40] A.J. Scheen, Cardiovascular effects of new Oral glucose-lowering agents: DPP-4 and SGLT-2 inhibitors, Circ. Res. 122 (2018) 1439–1459.
[41] F. Paneni, T.F. Luscher, Cardiovascular protection in the treatment of type 2 diabetes: a review of clinical trial results across drug classes, Am. J. Cardiol. 120 (2017) S17–S27.
[42] H.M. Ahmed, H. Khraishah, L. Cho, Cardioprotective anti-hyperglycaemic medications: a review of clinical trials, Eur. Heart J. 39 (2018) 2368–2375.
[43] F. Paneni, DPP-4 inhibitors, heart failure and type 2 diabetes: all eyes on safety, Cardiovasc Diagn Ther. 5 (2015) 471–478.
[44] J. Rosenstock, V. Perkovic, O.E. Johansen, M.E. Cooper, S.E. Kahn, N. Marx, J.H. Alexander, M. Pencina, R.D. Toto, C. Wanner, B. Zinman, H.J. Woerle, D. Baanstra, E. Pfarr, S. Schnaidt, T. Meinicke, J.T. George, M. von Eynatten, D.K. McGuire, Investigators C, Effect of Linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial, JAMA (2018), https://doi.org/10.1001/jama.2018.18269.
[45] E. Ferrannini, R.A. DeFronzo, Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes, Eur. Heart J. 36 (2015) 2288–2296.
[46] D.X. Brown, M. Evans, Choosing between GLP-1 receptor agonists and DPP-4 inhibitors: a pharmacological perspective, J. Nutr. Metab. 2012 (2012) 381713.
[47] M. Packer, Have dipeptidyl peptidase-4 inhibitors ameliorated the vascular complications of type 2 diabetes in large-scale trials? The potential confounding effect of stem-cell chemokines, Cardiovasc. Diabetol. 17 (9) (2018).
[48] M. Packer, Do DPP-4 inhibitors cause heart failure events by promoting Adrenergically mediated cardiotoxicity? Clues from laboratory models and clinical trials, Circ. Res. 122 (2018) 928–932.
[49] A.M. Leidal, B. Levine, J. Debnath, Autophagy and the cell biology of age-related disease, Nat. Cell Biol. 20 (2018) 1338–1348.
[50] M. Gielen, G.J. Hageman, E.E. Antoniou, K. Nordfjall, M. Mangino, M. Balasubramanyam, T. de Meyer, A.E. Hendricks, E.J. Giltay, S.C. Hunt, J.A. Nettleton, K.D. Salpea, V.A. Diaz, R. Farzaneh-Far, G. Atzmon, S.E. Harris, L. Hou, D. Gilley, I. Hovatta, J.D. Kark, H. Nassar, D.J. Kurz, K.A. Mather, P. Willeit, Y.L. Zheng, S. Pavanello, E.W. Demerath, L. Rode, D. Bunout, A. Steptoe, L. Boardman, A. Marti, B. Needham, W. Zheng, R. Ramsey-Goldman, A.J. Pellatt, J. Kaprio, J.N. Hofmann, C. Gieger, G. Paolisso, J.B.H. Hjelmborg, L. Mirabello, T. Seeman, J. Wong, P. van der Harst, L. Broer, F. Kronenberg, B. Kollerits, T. Strandberg, D.T.A. Eisenberg, C. Duggan, J.E. Verhoeven, R. Schaakxs, R. Zannolli, R.M.R. Dos Reis, F.J. Charchar, M. Tomaszewski, U. Mons, I. Demuth, A.E.I. Molli, G. Cheng, D. Krasnienkov, B. D'Antono, M. Kasielski, B.J. McDonnell, R.P. Ebstein, K. Sundquist, G. Pare, M. Chong, M.P. Zeegers, Group T, Body mass index is negatively associated with telomere length: a collaborative cross-sectional meta-analysis of 87 observational studies, Am. J. Clin. Nutr. 108 (2018) 453–475.
[51] C. Ruperez, C. Lerin, G. Ferrer-Curriu, M. Cairo, A. Mas-Stachurska, M. Sitges, J. Villarroya, M. Giralt, F. Villarroya, A. Planavila, Autophagic control of cardiac steatosis through FGF21 in obesity-associated cardiomyopathy, Int. J. Cardiol. 260 (2018) 163–170.
[52] X. Xu, Y. Hua, S. Nair, Y. Zhang, J. Ren, Akt2 knockout preserves cardiac function in high-fat diet-induced obesity by rescuing cardiac autophagosome maturation, J. Mol. Cell Biol. 5 (2013) 61–63.
[53] S.A. Hawley, A.E. Gadalla, G.S. Olsen, D.G. Hardie, The antidiabetic drug metformin activates the AMP-activated protein kinase cascade via an adenine nucleotide-independent mechanism, Diabetes. 51 (2002) 2420–2425.
[54] S.R. Yoshii, N. Mizushima, Monitoring and measuring autophagy, Int. J. Mol. Sci. 18 (2017).