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REVIEW

GLP-1: benefits beyond pancreas

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Abstract
Introduction Glucagon-like peptide 1 (GLP-1) is an intestinal hormone secreted after the ingestion of various nutrients. The main role of GLP-1 is to stimulate insulin secretion in a glucose-dependent manner. However, the expression of GLP-1 receptor was found to be expressed in a variety of tissues beyond pancreas such as lung, stomach, intestine, kidney, heart and brain. Beyond pancreas, a beneficial effect of GLP-1 on body weight reduction has been shown, suggesting its role for the treatment of obesity. In addition, GLP-1 has been demonstrated to reduce cardiovascular risk factors and to have a direct cardioprotective effect, fostering heart recovery after ischemic injury. Further, data from both experimental animal models and human studies have shown beneficial effect of GLP-1 on bone metabolism, either directly or indirectly on bone cells.
Materials and methods We review here the recent findings of the extra-pancreatic effects of GLP-1 focusing on both basic and clinical studies, thus opening future perspectives to the use of GLP-1 analogs for the treatment of disease beyond type 2 diabetes.
Conclusion Finally, the GLP-1 has been demonstrated to have a beneficial effect on both vascular, degenerative diseases of central nervous system and psoriasis.

Keywords GLP-1 · Pancreas · Body weight · Cardiovascular system · Bone · Central nervous system

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Introduction

Glucagon-like peptide 1 (GLP-1) is a gut-derived hormone that is secreted in response to oral nutrient intake, displaying a potent insulinotropic activity in several species, including humans [1]. To exert its biological effect, GLP-1 binds its specific GLP-1 receptor that is a G protein-coupled receptor family. Upon binding to its receptor, GLP-1 increases the intracellular cAMP levels stimulating insulin secretion in pancreatic beta cells in a glucose-dependent manner [2]. In addition, GLP-1 has been reported to have a beneficial effect per se on insulin resistance. D'Alessio et al. [3] investigated the effect of GLP-1 infusion in healthy subjects in which GLP-1 improved glucose tolerance both through its insulinotropic action and by increasing glucose effectiveness thus suggesting that GLP-1 has direct effects on tissues involved in glucose disposition. The insulin sensitizer effect of GLP-1 may be due to a direct effect to recruit muscle microvasculature, to increase muscle delivery of insulin and to enhance muscle

use of glucose [4] and may be indirectly mediated by the suppression of glucagon secretion that in turn results in a reduction of the hepatic glucose production [5, 6]. Furthermore, GLP-1 inhibits gastrointestinal secretion and motility, including gastric emptying, induces satiety and reduces food intake, thus promoting weight loss and increasing insulin sensitivity [7, 8]. However, GLP-1 receptors have been found to be expressed in several tissues beyond pancreas, and in particular in lung, in the stomach, intestine, kidney, heart and brain [9]. Thus, several beneficial effects of GLP-1 have been reported beyond the glycemic control. In particular, GLP-1 has been demonstrated to have both a direct cardioprotective effect and indirect beneficial effect on cardiovascular risk biomarkers (blood pressure, cholesterol levels, postprandial triglyceride and glucose levels, coagulability, and inflammation) [10]. The improvement of cardiovascular biomarkers is also due to the effect of GLP-1 on obesity. In fact GLP-1 plays an important role in reducing the appetite and increasing satiety acting on different brain areas such as the hypothalamic nuclei, thalamus, hippocampus, lateral septum, and subfornical organ [11]. In addition, GLP-1 slows nutrient absorption decreasing postprandial production of apolipoprotein B-48 [12], decreasing gastric acid secretion in response to gastrin release and meal intake. GLP-1 also inhibits gastric emptying via vagal afferent-mediated central mechanisms [13]. The involvement of GLP-1 in bone metabolism comes from evidence obtained in knockout mice for GLP-1 receptor that shows a cortical osteopenia, bone fragility and increased bone resorption and osteoclast numbers [14]. These effects seem to be mostly mediated by the effect of calcitonin stimulated by GLP-1 since mice, by contrast to human subjects, express GLP-1 receptor on thyroid C cells [14]. However, clinical evidence in humans is still not enough to allow definitive conclusions. Finally GLP-1 has been shown to have beneficial effects on central nervous system and mostly to exert a neuroprotective effect in rodent models of stroke, Alzheimer's disease and Parkinson's disease [15].

Given this growing body of evidence that shows pleiotropic effects of GLP-1 in extra-pancreatic tissues, this article will review the preclinical and clinical evidence, focusing on the latest data, showing the effects of GLP-1 on the cardiovascular system, body weight, bone and central nervous system. This may allow a potential and future use of GLP-1 analogs' therapy as a multifactorial treatment for disease beyond type 2 diabetes (Fig. 1; Table 1).

Distribution of GLP-1 and GLP-1 receptors

Active GLP-1 is a peptide of 30 amino acids expressed and secreted by endocrine L cells of intestinal mucosa at the ileum and colon level. GLP-1 derives from the same precursor of glucagon through the cleavage action of proconvertase 1/3. The proglucagon gene is localized on human chromosome 2q36–q37 and comprises 6 exons. In the gut, proteolytic processing of proglucagon generates GLP-1 and GLP-2, whereas glucagon is produced in the pancreas [1, 16]. In the intestine, GLP-1 is produced as an inactive 37-amino acid peptide. The active form is produced by post-translational cleavage of six amino acids from the N-terminal end of GLP-1 (1-37). The truncated peptides of GLP-1 (GLP-1 7-36 amide or GLP-1 7-37) are the active equipotent insulinotropic forms; however, in current literature, the unqualified designation GLP-1 covers only the truncated peptide [1]. In addition, almost all secreted GLP-1 is amidated at the glycine end of the C-terminal with an improved stability. Only 10–15 % of secreted GLP-1 reaches systemic circulation in the intact form. This rapid initial whole body clearance is due to the liver metabolism and also to the activity of dipeptidyl peptidase-4 (DPP4) which is expressed in both enterocytes and endothelial cells of the lamina propria capillaries [1].

Three hormonal products, GLP-1, GLP-2 and oxyntomodulin, arise from its processing in neurons. GLP-1 secreting neurons are mainly located in the hindbrain nucleus of the solitary tract suggesting that GLP-1 plays a role in the control of food intake [1, 17]. GLP-1 cells in the nucleus of the solitary tract stick out throughout the brain to other nuclei involved in energy homeostasis (e.g., the paraventricular, the dorsomedial and the arcuate nucleus of the hypothalamus), and also to nuclei associated with reward and motivation such as the ventral tegmental area and the nucleus accumbens [18, 19].

GLP-1 receptor (GLP-1R) belongs to the Gsprotein-coupled receptor (GPCR) family which activates downstream pathways including cAMP/protein kinase A (PKA), cAMP/guanine-nucleotide exchange factor (Epac) or phosphatidylinositol-3 kinase/PKC pathways. Classically, GLP-1Rs are ubiquitous being found with the highest expression in β- and δ-cells of the pancreas and lungs, and the less expression in parietal cells of the stomach, pylorus, adipose tissue, heart, kidney, pituitary and the brain [1, 20]. However, using a new monoclonal antibody for immunohistochemistry and by confirmation with binding studies, in humans and monkeys it has been recently shown that in the pancreas, GLP-1R protein was predominantly localized in β-cells and, weakly in acinar cells without expression in pancreatic ductal epithelial cells. In the kidney and lung, GLP-1R protein was exclusively expressed in smooth muscle cells of arteries and arterioles within a consistent expression in renin-secreting cells of the juxtaglomerular apparatus. In the gut, the highest GLP-1R protein expression was detected in the Brunner's gland in the duodenum, with lower level expression in parietal cells and in

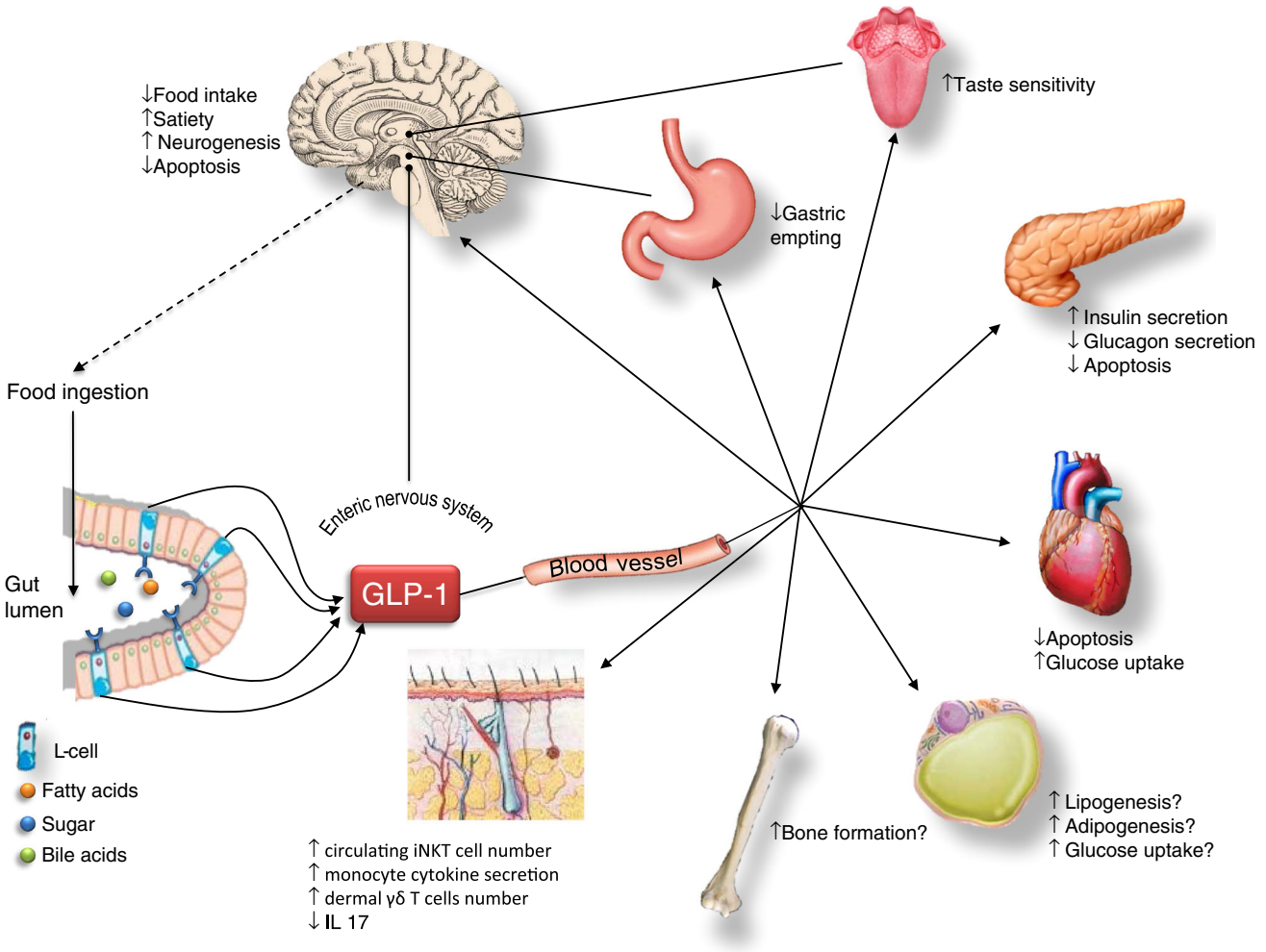

Fig. 1 Physiology of Glucagon-like peptide-1 (GLP-1) secretion and action on extra-pancreatic organs and tissues. Various organs affected by GLP-1 actions are depicted in the figure. GLP-1 is released postprandially by intestinal L cells. In the stomach, GLP-1 slows motility resulting in delayed gastric emptying. In the central nervous system (CNS), GLP-1 is an important neurotransmitter for regulating appetite, taste sensitivity and eating behavior. GLP-1 promotes satiety and leads to reduced food intake and body weight. Additional long-term effects of GLP-1 on the CNS comprise an improvement of learning and memory, as well as a stimulation of neurogenesis. In the heart, GLP-1 has preventive effects on cardiac cell apoptosis and ischemic damage. GLP-1 appears to promote bone formation and to inhibit bone resorption, also resulting in an improvement of bone strength. Moreover, GLP-1 release potentially exerts anabolic effects on adipose tissue. Finally GLP-1 seems to increase circulating iNKT cell number, to modulate monocyte cytokine secretion, to decrease of dermal γδ T cells number and IL-17 expression

myenteric plexus neurons. In the heart, GLP-1R protein was localized in myocytes of the sinoatrial node [9]. It has been also demonstrated both as mRNA and protein in macrophages and monocytes [9, 21]. It has to be noted that GLP-1R expression presents differences among the species, first of all no staining has been demonstrated in primates in thyroid, and in the liver, whereas its expression is much lower in humans than in rodents in C cells [9]. More recently, in rodents and mammals, the expression of GLP-1 protein has been identified in taste cells and that of GLP-1R in adjacent taste nerve fibers [22], suggesting that the system may act with an alternative and intriguing way on food intake.

Although their primary sequence is identical and until now no GLP-1R subtypes have been identified, all the GLP-1Rs in different tissues have similar but not identical ligand-binding capacity to GLP-1 maybe due to post-translational modifications as glycosylation [23]. Furthermore, their sequence seems to be homologous to these sequences of the family of G protein receptors for several other endocrine peptides such as glucagon, secretin, calcitonin, GHRH, PTH and vasoactive intestinal peptide [1]. Some evidence, in particular in myocardium, osteoblasts and lymphocytes models, also suggests that extra-pancreatic effects of GLP-1 could be mediated by receptors other than the "classical" GLP-1 receptor [24–26]. Furthermore,

Table 1 Effects of Glucagon-like peptide-1 (GLP-1) on extra-pancreatic organs and tissues

GLP-1 target	Effect	
	↓	↑
Brain	Food intake	Satiety
	Apoptosis	Neurogenesis
Tongue		Taste sensitivity
Heart	Apoptosis	Glucose uptake
Stomach	Gastric emptying	
Adipocyte		Lipogenesis?
		Adipogenesis?
		Glucose uptake?
Bone		Bone formation?
Skin	Cytokine secretion	Circulating iNKT cell number
	Dermal γδ T cells number	
	IL-17 expression	

the GLP-1 (9-36), which is classically considered as an insulinotropic-inactive metabolite, shares some of the cardiac effects of the "active" GLP-1 (7-36), at least in rodents [25].

It appears clear as the widely distribution of GLP-1, and even more of GLP-1R justifies the pleiotropic actions discussed below (Fig. 1; Table 1).

GLP-1 and central nervous system

GLP-1 receptors are present in several regions of the brain, especially in the ones controlling appetite and satiety [27] as already described. In this regard, one of the effects of GLP-1 receptor agonists' administration is the body weight reduction [28]. This effect seems to be mediated by reducing appetite and promoting satiety and, at the same time, by acting on energy expenditure and thermogenesis [29]. Such actions on the central nervous system may occur both by direct and indirect pathways. Indirect circuits have a greater effect and they involve hepatic and gastrointestinal vagal fibers in which GLP-1 receptors have been identified [30]; in fact, several experiments conducted in vagotomised animals showed no reduction in food intake or lack of neuronal activation in several brain areas related to eating control after GLP-1 administration [31–33]. Gut-derived GLP-1 is able to cross the blood–brain barrier in mice, thus exerting its central activity [34]. In addition, GLP-1 receptor agonists may play a protective role against Alzheimer's disease (AD). In mouse models of AD, GLP-1 receptor activating drugs exerts favorable effects on synaptogenesis, neurogenesis, cell repair, and inflammation reduction [35]. Liraglutide, an agonist of GLP-1, in AD mouse model, was found to prevent synapse loss and deterioration of synaptic plasticity in the hippocampus [36]. Similarly, overall β-amyloid plaque count in the cortex and dense-core plaque numbers were reduced, together with soluble amyloid oligomers. Such beneficial effect was evident even on cognitive function; in fact, liraglutide-treated AD animals' recognition memory was restored, while saline-treated AD mice failed to discriminate between novel and familiar objects. Also, liraglutide-treated AD mice learned the Morris water maze task faster with significantly reduced escape latencies compared with saline-treated controls and liraglutide-treated mice remembered the exact location of the platform after the reversal task, while the saline-treated AD group did not [36]. Moreover, liraglutide and other GLP-1 analogs' administration enhanced synaptic plasticity in area CA1 of the hippocampus in rats, therefore suggesting that GLP-1 therapy could potentially ameliorate the impaired neuronal communication in AD [37]. Recent findings also point out that liraglutide decreases the hyperphosphorylation of tau and neurofilament proteins in the brain and improves the learning and memory ability in mice models of AD [38, 39].

Some works have also shown protective effects of GLP-1 agonists against Parkinson's disease (PD). In animal models of PD, treatment with exendin-4, a GLP-1 receptor agonist, promoted adult neurogenesis both in vitro and in vivo, normalized dopamine imbalance, and increased the number of cells positive for markers of dopaminergic neurons in the substantia nigra [40]. Similarly, Li and colleagues found that exendin-4 administration protected dopaminergic neurons against degeneration, preserved dopamine levels, and improved motor function [41]. In addition, Harkavyi et al. [42] suggested that exendin-4 may pharmacologically arrest and possibly reverse lesions of the nigrostriatal system. In human subjects, a proof-of-concept study evaluated the progress of 45 patients affected by PD, who were randomly assigned to receive exenatide, that is a GLP-1 agonist, or to act as controls. Single-blinded rating of the exenatide group suggested improvements in PD across motor and cognitive measures compared to controls [43].

Furthermore, GLP-1 analogs might be useful in the treatment of amyotrophic lateral sclerosis (ALS). Li et al. assessed the therapeutic potential of exendin-4 in both cell culture and in vivo models of ALS and they found that exendin-4 proved to be neurotrophic in NSC-19 cells, by elevating choline acetyltransferase activity, as well as neuroprotective, by protecting cells from hydrogen peroxide-induced oxidative stress and staurosporine-induced apoptosis. In addition, exendin-4 attenuated neuronal cell death and immunohistochemical analysis demonstrated the

rescue of neuronal markers associated with motoneurons [44]. Also, another study assessed the effects of intracerebroventricular injection of GLP-1 releasing mesenchymal stromal cells (MSC) in a mouse model of ALS, finding that treatment prolonged survival, delayed symptom onset and weight loss and led to improvements in motor performance tests compared to vehicle-treated controls [45]. Furthermore, in an ALS in vitro model, some authors examined the neuroprotective effects of the administration of *N*-acetyl-GLP-1(7-34) amide (*N*-ac-GLP-1), an analog of GLP-1, finding that this compound attenuates intracellular calcium transients, thus counteracting, by preventing exocytosis, glutamate-induced apoptosis and ALS-related metabolic disturbances [46].

Finally, GLP-1 analogs may even be useful in stroke therapy, as evidence collected in rodent models of cerebral ischemia indicates that exendin-4 treatment reduces the damaged brain area and cellular apoptosis, improves the functional motor outcome and neuronal survival rate as well as suppresses oxidative stress, inflammatory response and cell death after reperfusion [41, 47–49] (Fig. 1; Table 1).

GLP-1 and body weight

GLP-1 is involved in a wide variety of physiological functions, including the regulation of food intake, taste sensitivity, satiation and gastric emptying as well. Thus, GLP-1 system constitutes an interesting candidate as potential target for new anti-obesity drugs. Indeed, more than 160 clinical trials, in which impact of GLP-1 derivatives and analogs on obesity is directly or indirectly investigated, have been registered, so far, on Clinicaltrials.gov.

Clinical experience provides convincing evidence that treatment with GLP-1R agonists results in clinically relevant beneficial effects on body weight [28, 50, 51]. This has consistently been shown during treatment with short-acting and long-acting GLP-1RA in both T2DM and obese individuals [29]. Nine trials meta-analyzed by Monami et al. showed that treatment with GLP-1 receptor agonists for 6 months led to a significant reduction of BMI, in comparison with placebo [−0.96 (−1.32, −0.59) kg/m^2, $P < 0.001$] [51]. Moreover, the observed GLP-1RA-related weight loss was associated with reduction in total body fat, particularly trunk or visceral fat [52–56].

It is reasonable that the treatment-related body weight loss can rather be attributed to a decrease in energy intake. In fact, even if in mice model, GLP-1 seems to affect energy expenditure by increased brown adipose tissue thermogenesis [57, 58], the reported effects of GLP-1 on energy expenditure in humans are more inconsistent and conflicting [59–61].

GLP-1 receptors are found in various regions of the brain [62] and, when activated, are believed to promote feeling of satiety, which in combination with GLP-1-induced inhibition of gastrointestinal motility reduces food intake and body weight [63, 64]. In fact, several studies have demonstrated that GLP-1 promotes satiety and suppresses energy intake both in animals [17, 65–68] and human subjects [63, 69–72]. In a meta-analysis of studies in humans evaluating acute effects of GLP-1 infusion on food intake, a mean decrease of 11.7 % in the amount of ad libitum energy intake compared with saline [71] was reported. GLP-1 receptors are expressed in vagal afferent neurons and total subdiaphragmatic or specific afferent vagotomy has been demonstrated to significantly attenuate the satiety effects of intraperitoneally administered GLP-1 [73]. It is likely that GLP-1 acts on vagal afferent terminals in close approximation to the entero-endocrine L cells, suggesting that vagal–brainstem–hypothalamic pathway may play a critical role in the effects of GLP-1 on food intake [31].

GLP-1 is known to delay gastric emptying, inhibit antral contractility, decrease fasting tone of the proximal stomach and enhance gastric accommodation [74–76]. Acute administration of GLP-1 fully inhibited gastric emptying [77, 78] as well as exenatide, liraglutide and lixisenatide are also known to slow down the rate of gastric emptying [79–81]. However, although gastric motility has been reported to be a key mediator of hunger, satiation and satiety [82], GLP-1R agonism-induced deceleration of gastric emptying and occasional nausea could contribute to the weight reducing effects, but seem to play a minor and often temporary role [29].

Noteworthy, GLP-1 signaling plays an important role in the modulation of taste sensitivity. Data in GLP-1R knockout mice model indicate that GLP-1 signaling normally acts to enhance or maintain sweet taste sensitivity, while GLP-1R$^{-/-}$ mice were much more sensitive to the umami stimulus (savory taste) by monosodium glutamate [22] and sour taste [83]. These data suggest a relationship between the modulation of peripheral sensory function and the metabolic response to food intake which could have an impact on eating behavior and hence on weight balance. Interestingly, liraglutide significantly decreased the scores for external eating behavior and food preference [55].

In addition, the relative abundance of GLP-1 receptors in human adipose tissue may suggest a direct action of this peptide in the metabolism of adipose tissue, and hence on weight regulation [84, 85]. Studies performed in isolated rat and human adipocytes have demonstrated that GLP-1 may exert a dose-dependent dual action, with predominant lipogenic activity when used at picomolar concentrations or lipolytic activity when used at nanomolar doses [86–90]. However, the effects of GLP-1 in adipose tissue have been

poorly studied and the effective role of this interaction on weight regulation remains to be explored.

It is worth noting that, currently, GLP-1RA have not been officially approved for the treatment of obesity even though peripheral administration of GLP-1 derivatives and analogs to man have shown relevant effects on food intake and body weight suggesting that such therapies could be employed also in the treatment of obesity (Fig. 1; Table 1).

GLP-1 and cardiovascular system

GLP-1 has been extensively studied in last years in the setting of diabetes mellitus for the improvement of glycemic control. Up to now, growing interest rises on interaction between GLP-1 and cardiovascular system. In fact, experimental studies and clinical data have suggested possible cardiometabolic positive effects of GLP-1, by demonstrating the improvement of cardiac function in patients with heart failure [91]. Thus, it seems that GLP-1 protects heart against acute myocardial ischemic injury [92].

The GLP-1 receptors are widely distributed in several tissues both in animals and humans. Recently, their presence is demonstrated also in myocardium tissue [93, 94]. GLP-1 and GLP-1 agonist bind these receptors, but both in vivo and in vitro studies provide confounding results. These may be explained by the type of GLP-1 agonists and by their different duration of action. Up to now, a complete understanding of the mechanism of GLP-1 actions on myocardial glucose uptake remains far to be comprised.

Notwithstanding the wide evidence of GLP-1 action in diabetic patients, limited is the knowledge on its effects on cardiovascular system. Both GLP-1 and GLP-1 receptor agonist increase blood pressure and cardiac frequency in a rat model [95, 96]. GLP-1 infusion showed a marked improvement in cardiac performance in dogs with dilated cardiomyopathy [97]. The activation of GLP-1 receptor in isolated rat hearts mitigated myocardial injury and improved end-diastolic pressure as well as rate pressure, through a direct effect on cardiovascular cells and pathway [98]. This myocardial improvement was related to a significant reduction in myocardial necrosis, with a consequent reduction of infarct size [98]. In addition GLP-1 has been shown to improve heart recovery and function after ischemia and to promote cell survival preventing oxidative stress-mediated apoptosis in human progenitor cardiac cells [99]. These effects seem to be explained by the increased myocardial glucose uptake induced by GLP-1, with a consequent overcoming insulin resistance under ischemic condition. Furthermore, GLP-1 infusion in rat models seems to attenuate the development of hypertension [100, 101], and to reduce oxidative stress and inflammatory state on endothelial cells [102, 103]. Finally, GLP-1 could prevent the development of atherosclerotic lesions by suppressing macrophage foam cell formation [104].

These promising results in animal models suggest that therapy with GLP-1 receptor agonist in humans may preserve cardiomyocyte viability, increase metabolic efficiency and inhibit remodeling occurring in the ischemic heart. Phase 2 trials of GLP-1 in human with cardiovascular diseases seem to confirm these protective effects of incretins [97, 105, 106]. A GLP-1 infusion for 72 h in patients with myocardial infarction improves left ventricular function, reducing hospital stay and mortality, independently from myocardial infarction location or diabetes history [106]. Furthermore, a GLP-1 long-term infusion improves functional heart capacity and diastolic dysfunction, both in diabetic and non-diabetic patients [15, 105, 107, 108]. Gejl et al. [109] have demonstrated that GLP-1 did not induce the overall myocardial glucose uptake, but promote changes in the myocardial glucose uptake dependent on the rate of baseline glucose uptake. Fonseca et al. [110] have demonstrated that 26 weeks of treatment with incretins in diabetic patients, significantly reduced lipid asset and cardiovascular risk biomarkers, such as brain natriuretic protein (BNP), plasminogen activator inhibitor (PAI)-1 and high-sensitivity C-reactive protein (CRP). Lønborg et al. [111] have demonstrated that intravenous administration of low-dose of GLP-1 receptor agonist at the time of reperfusion in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention, increased myocardial salvage and smaller infarct size. Recently, Monami et al. [92] analyzed all these results in a comprehensive meta-analysis in which all GLP-1 receptor agonist classes showed a significant lower incidence of major cardiovascular events, myocardial infarction and cardiovascular mortality than placebo. Furthermore, ongoing clinical trials have been designed to evaluate cardiovascular endpoints during use of GLP-1 receptor agonists. Finally, GLP-1 receptor agonists are able to reduce endothelial dysfunction in clinical trials involving diabetic patients, considering intima–media thickness that is a recognized marker of subclinical atherosclerosis [112].

However, confusing results are present in the literature on the chronic use of dipeptidyl peptidase-4 inhibitors (DDP4i) that increase GLP-1 serum levels. A recent meta-analysis showed that the chronic use of DDP4i was associated to an increased risk of heart failure, without any clear difference among drugs of this class [113]. This result could be due to differences in patients enrolled in trials evaluating cardiovascular outcome [113]. In fact, these trials enrolled older patients, with a longer duration of diabetes, poorer renal function than other trials [113]. On the other hand, another meta-analysis showed that DDP4i

use was not related to cardiovascular harm than placebo [114]. Given these challenging results, new trials are needed to completely understand the effect of DDP4i on cardiovascular outcomes.

In conclusion, preclinical and proof-of-concept trials demonstrate that the activation of GLP-1 receptors on cardiomyocytes increases glucose uptake, protecting myocardial cells against apoptosis throughout a series of downstream pathways. However, the mechanism by which GLP-1 receptor activation leads to a myocardial protection remains unclear. At the same time, the potential, beneficial hemodynamic effects of GLP-1 remain to be elucidated and large prospective trials on cardiovascular outcomes are needed to demonstrate the efficacy of GLP-1 in diabetic and pre-diabetic patients (Fig. 1; Table 1).

GLP-1 and bone metabolism

Food intake may influence the circadian rhythm of bone turnover markers. It has been suggested that bone formation and resorption markers are both lower in the fed state, although the underlying mechanism remains unclear and the clinical impact is small and largely unpredictable [115]. Moreover, the circadian variation in bone resorption, with the peak during the night, could be determined, even only in part, by the nightly fast [116].

These first observations have suggested a potential role on bone turnover of GLP-1 and other hormones released after absorption of nutrients.

In mouse model, genetic disruption of pancreatic GLP-1 receptor led to cortical osteopenia and bone fragility, as well as increased osteoclastic numbers and bone resorption. GLP-1 did not show direct effects on osteoclasts and osteoblasts, however, GLP-1R$^{-/-}$ mice exhibited higher levels of urinary deoxypyridinoline; a marker of bone resorption, and reduced levels of calcitonin mRNA transcripts in the thyroid. Moreover, calcitonin treatment effectively suppressed urinary levels of deoxypyridinoline in GLP-1R$^{-/-}$, mice and the GLP-1 receptor agonist exendin-4 increased calcitonin gene expression in the thyroid of wild-type mice [14]. Therefore, GLP-1 receptor signaling demonstrates to be effective in the control of bone resorption through a calcitonin-dependent pathway. In both insulin-resistant and type 2 diabetic rat models, GLP-1 exerts a normalizing effect on their impaired bone structure. Overall in mouse models GLP-1 appears to have a double effect on bone metabolism, one direct and another indirect, the latter via thyroid C cells [117]. Furthermore it seems to improve bone strength [118]. In human tissues the G protein-coupled GLP-1 receptor is expressed on osteoblastic precursor cells and studies in vitro demonstrate that GLP-1 can functionally interact with human osteoblasts through a receptor different from the GLP-1 receptor described for pancreas [26] (Fig. 1; Table 1).

GLP-1 and skin

The effect of GLP-1 on skin was suggested by a study performed in mice that expressed the GLP-1 receptor in the hair follicles, as well as in cultures of skin-derived cells that also express nestin, a marker of cultured cells that have dedifferentiated by epithelial to mesenchymal transition. In humans, the effect of GLP-1 on skin was suggested by the beneficial effect of GLP-1 agonists in patients with both psoriasis and type 2 diabetes. Psoriasis is a common skin disease characterized by chronic inflammation, different degrees of scaling, erythema, itching, and plaque formation. Psoriasis has been demonstrated to have a tight association with increased rates of cardiovascular disease, obesity and type 2 diabetes, conditions characterized by enhanced local and/or systemic inflammation [119]. The improvement of psoriasis was immediately shown after the initiation of therapy with both liraglutide and exenatide [120, 121]. A prospective cohort study performed in patients with both psoriasis and diabetes reported an improvement of psoriasis after 10 weeks of treatment with liraglutide hypothesizing that it may be due to the ability of GLP-1 to increase circulating iNKT cell number and to modulate monocyte cytokine secretion [122]. A possible explanation of the beneficial effect of GLP-1 agonists on psoriasis may be provided by Faurschou et al. [123] that found an increased presence of GLP-1Rs in psoriasis plaque, likely due to infiltration with immune cells, compared to skin of healthy subjects. Buysschaert et al. [124] demonstrated that this favorable outcome was associated with a decrease of dermal γδ T cells number and IL-17 expression in psoriasis lesions. However, further studies are needed to establish long-term efficacy of GLP-1 agonists in diabetic patients with psoriasis (Fig. 1; Table 1).

Conclusion

Research results obtained to date have shown that GLP-1 action is much broader than supposed. In fact, a beneficial effect of GLP-1 has been demonstrated on body weight, bone regulation, cardiovascular system, skin and nervous central system. Based on these assumptions, extra-pancreatic effects of GLP-1 need to be further investigated to clarify its effects on both diabetes-related complications independently of glycemic control and disease beyond type 2 diabetes. Results of these clinical investigations may allow to extend the future clinical use of GLP-1 analogs beyond glycemic control.

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