GLP-1 Receptor Agonists in DKD

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Diabetic kidney disease (DKD) is one of the most common complications in type 2 diabetes mellitus (T2D) and a major cause of morbidity and mortality in diabetes. Previous studies have demonstrated that GLP-1 receptor agonists (GLP-1 RA) have improved macrovascular and microvascular outcomes independent of glycemic differences, including DKD. GLP-1Ras' improvement on kidney physiology is mediated by natriuresis, reduction in hyperfiltration and renin-angiotensin-aldosterone system (RAAS) activity and anti-inflammatory properties. These findings translate into improved clinical outcomes such as an enhanced urine albumin-to-creatinine ratio (UACR) and a reduction in renal impairment and the need for renal replacement therapies (RRT).

Keywords: GLP-1 receptor agonists ; diabetic kidney disease

1. The Association of GLP-1 and Gut-Renal Axis

As mentioned above, GLP-1 and GIP are two incretin hormones responsible for the reduction in blood glucose levels in response to nutrient ingestion. In fact, humans submitted to an oral glucose load showed a much greater increase in plasma insulin levels than those infused with intravenous glucose administration [1]. This phenomenon is known as the incretin effect, and it is estimated to account for approximately 50–70% of the overall insulin secretory response after nutrient ingestion [2].

Nevertheless, not only a gut-pancreas connection has been demonstrated but also a contribution to the physiological control of water and electrolyte balance upon meal ingestion. The regulation of the gut-renal axis is mediated by multiple pleiotropic actions in different locations such as the central nervous system, adjusting thirst, intestinal co-transporters to control fluid and electrolyte absorption and secretion and also on the kidney, by the stimulation of renal tubular excretion and/or reabsorption of fluid and electrolytes [3][4]. As the effect previously exposed with oral glucose administration, GLP1 release by oral sodium load can stimulate more rapidly the tubular excretion by the kidney than given intravenously, independent of changes in the levels of aldosterone and atrial natriuretic peptide on plasma [5][6]. The same changes have been observed on potassium and phosphate metabolism [7].

The role of GLP1 is not only limited on tubular effects but also on changes on hemodynamics. For example, a postprandial hyperfiltration induced after ingestion of a high protein meal by an increase in renal blood flow was identified. This mechanism contributes in part of sodium and solutes homeostasis after ingestion by increasing the pressure and vasodilation of the afferent arteriole through nitric oxide [8]. From a pathophysiological point of view, an impaired gut-renal axis implies a reduction in urinary secretion and, therefore, a salt-sensitive hypertension. The glomerular hyperfiltration classically has been related to T2D and the CKD progression. Nevertheless, the postprandial hyperfiltration induced by GLP1 is minimal and has no clinical impact [9].

2. Renoprotective Mechanisms of GLP1-RAs in T2D

There are several experimental studies that evaluate the effects of GLP1 and GLP1-RAs on the renal metabolism and shed light on the main mechanisms responsible for changes in eGFR, a reduction in albuminuria and other renal outcomes seen in clinical studies. In this section, we will explain in detail the main mechanisms underlying the attenuation of DKD by GLP1-RAs.

2.1. Glucose Lowering

The main renoprotective effect of incretin-based therapies such GLP1-RAs is mediated by regulation of the glucose metabolism. Indeed, the most known effect of the GLP1 gut derived hormone is the reduction in hyperglycemia in T2D which is severely impaired or lost on those patients [10][11]. Its mechanism is based on increasing the insulin secretion and synthesis in pancreatic islet cells and a decrease in glucagon secretion and β-cell apoptosis [12][13]. In fact, it has been

published that GLP-1RAs reduce HbA1c levels by ~1.0% compared with a placebo [14]. Other actions that contribute to glucose homeostasis include the diminution of gastric emptying and small intestine peristalsis and suppression of endogenous glucose production [15][16]. Another fact that supports this proposition is that the reduction in new-onset albuminuria in clinical studies with GLP-1RA is accompanied by effective glucose lowering [17].

2.2. Oxidative Stress and Inflammation

Various reports have shown that T2D is associated with chronic low-grade inflammation, which is linked with oxidative stress, proliferation and fibrosis that affect kidney function and morphology [18]. Experimental studies have reported that GLP1-RAs inhibit inflammatory signaling pathways of DKD, such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase by activating protein kinase A (PKA) and the production of cyclic adenosine monophosphate (cAMP), which is paralleled by reductions in albuminuria and improved histological features of DKD [19]. For example, exendin-4 was shown to inhibit proliferation and fibrosis in human mesangial cells by stimulation of cAMP and PKA [20].

Another main molecular target implicated in oxidative stress and progression to DKD is the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB). The activation of this pro-inflammatory protein complex is induced by hyperglycemia and attenuates the therapeutic effects of the GLP-1R agonist by its downregulation [21]. The beneficial effects of GLP1-R signaling might also be mediated by increasing eNOS endothelial levels and inhibiting the expression of TNF-alfa in podocytes, both mediated by NF-kB downregulation [10][22]. Similarly, liraglutide has been shown to reduce the structural damage of podocytes in a model of glomerulopathy related to obesity [10]. Additionally, in rodent models treated with liraglutide, this GLP-1RA also modulates other pathways involved DKD, such as JAK/STAT and MAPK pathways present in kidney endothelial cells in rat CKD models [14][11].

2.3. Natriuresis—Tubular Effect

GLP-1 has been previously demonstrated to induce renal sodium excretion and increase urine flow in experimental and clinical studies in healthy and T2D individuals [23][24][25]. This effect is carried out by GLP1-RA inhibition of sodium-hydrogen exchanger 3 (NHE3), a channel localized in the apical membrane of the epithelial cells of the proximal tubule on the nephron. This process is mediated by PKA activation through cAMP generation and, finally, NHE3 phosphorylation [26] [27]. Additionally, GLP-1RA has an indirect effect also, by influencing the RAAS by reducing renin and angiotensin II circulating levels and action. [28][29]. Furthermore, GLP1-RAs were described to play a role in natriuresis and diuresis, by modulating the tubular ionic exchange of potassium, chloride and calcium [28][30][31].

2.4. Endothelial Function—Glomerular Effect

It is well known that the mechanism of hyperfiltration is a prime disruptor in DKD, especially when it is accompanied by albuminuria and renal function decline, which is observed in advance stages of the disease [32]. The GLP1-RAs' effect on glomerular hemodynamics is still controversial and remains to be elucidated.

In rodent models, GLP1-RA mediated the increase in endothelial nitric oxide synthase (eNOS) activity and expression, and nitric oxide (NO) production was described. This NO increase produces a direct vasodilation effect mainly on preglomerular arterioles that increases the glomerular filtration rate (GFR) [33][34]. Additionally, the increase in GFR and effective renal plasma flow (ERPF) induced by NO-dependent glomerular afferent arteriole vasodilation has been reported in numerous preclinical studies during short-term interventions with GLP-1 and GLP-1RAs [29][35][36]. It should be mentioned that all these models have been performed in rodents without diabetes, and the dose administration of GLP-1 and GLP1-RAs exceeds human therapeutic concentrations. In humans, it has been reported in one clinical study that exenatide infusion in ten healthy overweight men increased inulin-measured GFR and ERPF [37].

On the other hand, other clinical and animal studies suggest that GLP1-RAs' therapies reduce glomerular hyperfiltration and provide renoprotection in DKD. In experimental studies in diabetic rodents, 4–8 weeks of administration of liraglutide and linagliptin significantly reduced glomerular hyperfiltration [38]. In clinical studies, it has been observed that single dose GLP-1 infusion reduced GFR measurements in 16 subjects with obesity that presented hyperfiltration [16]. Additionally, liraglutide produced a decrease in GFR and albuminuria in patients with T2D and normal filtration [38].

These discrepancies on GLP1-RAs' effects on renal hemodynamics may be explained by differences in the characteristics of the studied population, the dose administrated and the posology or differences in study designs.

2.5. Blood Pressure

GLP1RAs treatment points to a clinically relevant lowering effect on blood pressure. These results can be partially explained by indirect effects on weight loss, an increase in natriuresis and the regulation of RAAS [39][40][41]. Moreover,

independent effects on NO dependent vasorelaxation as well as changes in endothelial cell function could be involved. A single-blind randomized crossover study on 12 patients with T2D with stable coronary artery disease that underwent intravenous infusion of human recombinant GLP-1 described a significant increase in the brachial artery diameter. This effect was proven to be mediated by the GLP-1 via expression of the GLP1-receptor in endothelial cells (western blotting of cell lysates) [42]. Similar effects have been observed in the femoral artery after exendin infusion in rats [43]. In a meta-analysis of 60 randomized control trials, blood pressure was only significantly reduced with liraglutide and albiglutide compared with a placebo; a non-statistical effect was observed with exenatide and dulaglutide [40]. Evidence to link blood pressure reduction to GLP-1R signaling and mechanisms is scarce and only partially understood.

2.6. Dyslipidemia

GLP1-RAs have a main glucose lowering effect by stimulating β-cell pancreatic secretion and inhibiting glucagon production. Strict control of dyslipidemia was shown to have a beneficial effect on DKD [41]. This metabolic response implicates changes in the lipid profile resulting in lower levels of triglyceride and low-density lipoproteins, as has been broadly described in literature [44]. Nonetheless, in clinical practice, these changes were marginal in GLP-1 therapies compared to a placebo [45], and the role in DKD remains to be elucidated.

2.7. Body Weight

Abdominal obesity is related with T2D and the associated chronic complications such as DKD [46]. Several studies have shown that being overweight is an independent risk factor for CKD and an increase in visceral fat plays the main role in its pathogenesis. In fact, it is well known that the mechanism of renal damage in obesity is very similar to T2DM, with initial augmentation in eGFR and intraglomerular pression and microalbuminuria that culminate in proteinuria, nodular glomerulosclerosis and tubulointerstitial injury [47][48][49].

Other conventional glucose-lowering treatments such as insulin or sulphonylureas increases body weight [50]; however, it is well known that GLP1-RAs' treatment in monotherapy or adding to another conventional treatment can lead to a statistically significant weight loss and reduction in the abdominal perimeter [51]. These findings were reported by some randomized clinical trials [52][53][54] and meta-analyses [55][56]. It is important to note that the predominant effect of these incretin-based therapies is in the reduction of trunk and visceral fat, rather than in lean tissue mass [51][57].

In fact, semaglutide shines as a weight-loss therapy, reaching a decline of 12.4% compared with a placebo in 68 weeks (95% CI, −13.4 to −11.5; $p < 0.001$). This means that, in absolute terms, semaglutide obtained a reduction in 15.3 kg with respect to the baseline (estimated treatment difference, −12.7 kg; 95% CI, −13.7 to −11.7) [58]. Other GLP1RAs' treatment such as liraglutide or exenatide showed a modest decrease in body weight of −2.51 kg (95% CI, −3.33 to −1.69; $p < 0.001$) and −1.69 kg (95% CI, −2.09 to −1.29; $p < 0.001$), respectively [59][60].

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