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Fasting GLP-1 Levels and Albuminuria Are Negatively Associated in Patients with Type 2 Diabetes Mellitus

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Abstract: Glucagon-like peptide-1 (GLP-1) is an incretin hormone that acts on the pancreas to increase insulin and decrease glucagon secretion. Albuminuria is the pivotal marker for diabetic nephropathy, which is the leading microvascular complication of diabetes mellitus. Most of the previous studies mainly focused on the clinical trials of the therapeutic renal protective effect after administration of GLP-1 receptor agonists (GLP-1 RAs), not prior to administration. Therefore, this study aimed to investigate the association between fasting plasma GLP-1 levels and albuminuria before GLP-1 RA administration. A cross-sectional study was designed to evaluate the association between fasting plasma GLP-1 levels and albuminuria in patients with type 2 diabetes mellitus (T2DM). A total of 68 T2DM participants were analyzed from the data at Wonkwang University Hospital in Iksan, Korea. Logistic regression analysis was performed to evaluate the odds ratio (OR) and 95% confidence interval (CI) of the incidence of albuminuria between the GLP-1 low group (Group L) and the high group (Group H). The OR (95% CI) for the incidence of albuminuria comparing the Group L with the Group H of fasting plasma GLP-1 levels was 3.410 (1.160-10.023), p = 0.026 after adjustment for age, gender, fasting plasma glucose, HbA1c, C-peptide, the use of ACE inhibitors or ARBs, SGLT-2 inhibitors, and DPP-4 inhibitors. As a continuous variable, the OR (95% CI) for the incidence of albuminuria associated with the reduction of each 1 pmol/L in fasting plasma GLP-1 levels was 1.673 (1.173-1.870), *p* = 0.018, after full adjustment. This study showed the negative association between fasting plasma GLP-1 levels and the incidence of albuminuria in Korean patients with T2DM, before GLP-1 RA administration. This result suggests that endogenous GLP-1 may play a role in attenuating albuminuria.

Keywords: type 2 diabetes mellitus; glucagon-like peptide-1; albuminuria

1. Introduction

The prevalence of diabetes has continued to increase worldwide over the past decades. Similarly, in Korea, the prevalence of diabetic patients is 16.7% among adults over 30 years of age, with the total number of diabetic patients estimated to be 5.7 million, according to the Diabetes Fact Sheet in Korea published in 2022 (1).

Among the major microvascular complications of diabetes, diabetic nephropathy has emerged as the leading cause of end-stage renal disease. Furthermore, diabetic nephropathy is known to elevate the risk of cardiovascular disease and mortality even before reaching end-stage renal failure (2).

Albuminuria, defined as a urine albumin-to-creatinine ratio (UACR) equal to or greater than 30 mg/g in the urine, is observed in the early stages of renal disease associated with diabetes. The incidence of albuminuria, which contributes to both the diagnosis and prognosis of diabetic

nephropathy, is well correlated with a decrease in glomerular filtration rate (GFR) and increased incidence of cardiovascular diseases (3-5).

The incretin hormone glucagon-like peptide-1 (GLP-1), which is comprised of 30 amino acids, is secreted by enteroendocrine L cells primarily found in the mucosa of both the small intestine and colon (6). It is released in reaction to glucose stimulation in the intestine shortly after a meal. Although GLP-1 primarily stimulates pancreatic β-cells to enhance insulin secretion, it also induces the reduction of glucagon secretion. Additionally, GLP-1 increases glucose uptake and glycogen synthesis in peripheral tissues, delays gastric emptying, and promotes satiety, thus suppressing appetite (7).

GLP-1 levels are decreased in patients with type 2 diabetes mellitus (T2DM) (8). Since the approval of exenatide, the initial commercial GLP-1 receptor agonist (GLP-1 RA), by the US Food and Drug Administration in April 2005 for treating T2DM, GLP-1 RAs have become a crucial option in diabetic therapeutics. Apart from their glucose-lowering effects, this class of medication has been noted for not only providing cardiovascular protection, but also demonstrating renal protective effects in previous cardiovascular clinical trials (CVOTs). Specifically, numerous GLP-1 RAs have shown improvements in albuminuria-based renal outcomes (9-11).

Nevertheless, most of the studies have focused on clinical trials examining the therapeutic effects of post-administration of GLP-1 RAs rather than pre-administration in patients with T2DM. Thus, this study aims to explore associations between fasting plasma GLP-1 levels and albuminuria in patients with T2DM.

2. Method

2.1. Study Population and Design

A cross-sectional study was designed to evaluate associations between fasting plasma GLP-1 levels and albuminuria on T2DM. Participants with T2DM were recruited from Wonkwang University Hospital in Iksan, Korea. The data on age, gender, smoking status, exercise frequency, blood pressure, body mass index (BMI), cholesterol level, renal function, diabetes status, insulin resistance, lipid-lowering drug use, antihypertensive use, inflammatory markers, and albuminuria were collected and analyzed.

A total of 120 patients were recruited from August 2017 to May 2018. Among these participants, we excluded participants who were diagnosed with cardiovascular diseases (myocardial infarction, bypass surgery, or stroke, n = 28) or cancer (n = 16). In addition, we excluded those who received GLP-1 RA treatment (n = 15) . Furthermore, those who had missing data were excluded (no data of GLP-1 level, n = 5). Several participants met more than two criteria. After these exclusions, the final study population included 68 participants. The study was conducted in accordance with the principles of the Declaration of Helsinki (12). All study participants provided written informed consent prior to their enrollment in the study. The study protocol was approved by the institutional review board of Wonkwang University Hospital (WKUH 2017-07-025-001).

2.2. Measurement

Systolic and diastolic blood pressures were measured using a mercury manometer. BMI was calculated by dividing the body weight in kilograms (kg) by the square of height in meters (m^2). Venous blood samples were collected after overnight fasting. Plasma glucose, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglyceride levels were measured using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan). Plasma active GLP-1 levels were measured by ELISA (immuno-Biological Laboratories Co., Ltd.; Code No. 27784 GLP-1, Active form Assay Kit-IBL). Glycated hemoglobin (HbA1c) levels were measured using high-performance liquid chromatography. Serum high-sensitivity C-reactive protein (hs-CRP) levels were measured by immunoturbidimetry.

A random urine sample was obtained to measure creatinine and albumin levels. Urinary albumin/creatinine ratios (UACRs) were calculated, and proteinuria was diagnosed as UACR >30

mg/g. Estimated GFRs were calculated using the Modification of Diet in Renal Disease (MDRD) equation (13).

Insulin resistance was defined by the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), calculated as the product of fasting plasma insulin level (µU/mL) and fasting plasma glucose (FPG) level (mg/dL), divided by 405. β-cell insulin secretory function was evaluated by the Homeostatic Model Assessment of β-cell function [HOMA-β (%)], calculated as the product of 360 and fasting plasma insulin level (µU/mL), divided by glucose minus 63 (14).

T2DM was defined as fasting glucose ≥ 126 mg/dL, HbA1c ≥ 6.5%, self-reported physician's diagnosis, and/or intake of antidiabetic medications. Hypertension was defined as an average systolic blood pressure equal or more than 140 mm Hg or diastolic blood pressure equal or more than 90 mm Hg or self-reported physician's diagnosis or intake of antihypertensive agents.

2.3. Statistics Analysis

Continuous variables with normal distributions were presented as mean ± standard deviation, and continuous variables with non-normal distributions were presented as medians (interquartile range). Categorical data are expressed as frequencies and percentages. Student's t-test or Mann–Whitney U test was used for comparisons of the characteristics of study participants at baseline. Pearson's Chi-Square test was performed for categorical variables to compare baseline characteristics. According to fasting plasma GLP-1 levels, participants were divided into Group L (the lower half) and Group H (the higher half).

Logistic regression analysis was performed to evaluate the odds ratio (OR) and 95% confidence interval (CI) of incidence of albuminuria between Group L and Group H of fasting plasma GLP-1 levels and fasting plasma GLP-1 levels in reduction of 1 pmol/L as a continuous variable.

Two-sided probability values < 0.05 were considered to indicate statistical significance. All statistical analyses were performed using SPSS Software (Version 21, SPSS, Inc., Chicago, IL).

3. Results

We analyzed and characterized associations between GLP-1 levels and albuminuria in 68 participants (43 men and 25 women) after exclusion of 52 patients among the 120 participants with T2DM. Table 1 summarizes the baseline clinical and biochemical characteristics of study participants with low and high plasma fasting GLP-1 levels (Group L and Group H). Participants in Group L had more men (n = 26, 76.5 %) compared to those in Group H (n = 17, 50.0 %, p = 0.044). Participants in Group L also had higher creatine (0.9 ± 0.4 mL/min/1.73 m²) compared to those in Group H (0.7 ± 0.3 mL/min/1.73 m², p = 0.040). In addition, those in Group L significantly had higher UACR [55.0 (0.0-470.0)] compared to those in Group H [10.0 (0.0-60.0), p = 0.036]. There were no significant differences in other parameters between the two groups.

Table 1. Baseline characteristics of participants with type 2 diabetes mellitus in the lower half (Group L) and the higher half (Group H) of fasting plasma GLP-1 levels.

Variables	Fasting plasma GLP-1 (pmol/L)		Total n = 68	p-value
	Group L (<1.83) n = 34	Group H (1.83-3.32) n = 34		

Age (years)	59.3 ± 9.8	56.7 ± 10.0	58.8 ± 9.9	
Men, n (%)	26 (76.5)	17 (50.0)	43 (63)	
Systolic BP (mmHg)	131.3 ± 15.9	127.8 ± 11.9	129.5 ± 14.0	
Diastolic BP (mmHg)	74.5 ± 11.2	76.4 ± 10.9	75.4 ± 11.0	0.291
Body mass index (kg/m²)	26.0 ± 3.4	25.2 ± 5.3	25.6 ± 4.4	0.044
Waist circumference (cm)	92.0 ± 8.6	93.0 ± 10.4	92.5 ± 9.4	0.326
Total cholesterol (mg/dL)	156.0 ± 31.3	169.6 ± 34.3	162.8 ± 33.3	0.493
HDL cholesterol (mg/dL)	46.9 ± 8.0	47.9 ± 10.7	47.4 ± 9.4	0.505
LDL cholesterol (mg/dL)	75.6 ± 17.7	82.7 ± 18.4	79.2 ± 18.3	0.754
Triglycerides (mg/dL)	148.5 (110.0-198.0)	160.0 (110.0-217.0)	155.0 (110.0-212.0)	0.093 / 0.656
Duration of diabetes (months)	121.9 ± 91.2	84.4 ± 79.4	102.9 ± 86.8	0.109 / 0.840
HbA1c (%)	8.3 ± 2.1	7.7 ± 1.5	8.0 ± 1.9	0.086
Fasting plasma glucose (mg/dL)	200.1 ± 78.5	177.0 ± 79.5	188.5 ± 79.3	0.132
Fasting insulin (uIU/mL)	12.9 (5.9-22.2)	20.0 (8.1-32.9)	14.5 (7.5-29.8)	0.231 / 0.130
HOMA-IR	5.4 (2.8-13.5)	10.9 (3.3-17.0)	6.7 (3.0-14.3)	0.275 / 0.448
HOMA-β (%)	27.4 (16.6-68.7)	41.9 (17.0-85.1)	32.7 (17.0-84.7)	0.079 / 0.040
Estimated GFR (mL/min/1.73 m²)	90.9 ± 27.9	103.6 ± 27.2	97.3 ± 28.1	0.067
Creatinine (mg/dL)	0.9 ± 0.4	0.7 ± 0.3	0.8 ± 0.3	<0.001
hs-CRP (mg/dL)	0.4 (0.2-1.1)	0.9 (0.3-1.7)	0.5 (0.2-1.4)	0.036
GLP-1 (pmol/L)	1.4 ± 0.3	2.5 ± 0.5	2.0 ± 0.6	
Urine albumin creatinine ratio (mg/g)	55.0 (0.0-470.0)	10.0 (0.0-60.0)	10.0 (0.0-195.0)	

* Continuous variables with normal distributions are expressed as mean ± standard deviation, whereas continuous variables with non-normal distributions are expressed as median (interquartile range). Categorical variables are expressed as percentages (%). ** Abbreviations: GLP-1, Glucagon-like peptide-1; BP, Blood pressure; HDL, High density lipoprotein; LDL, Low density lipoprotein; HOMA-IR, Homeostatic model assessment for insulin resistance; HOMA-β, Homeostasis model assessment of β-cell function; GFR, Glomerular filtration rate; CRP, C-reactive protein.

Table 2 displays correlations between fasting plasma GLP-1 levels and metabolic, anthropometric, and biochemical parameters. In Pearson's correlation analysis, the fasting plasma GLP-1 levels were positively correlated with estimated GFR, but negatively correlated with UACR. In multiple regression analyses, the fasting plasma GLP-1 levels were negatively correlated with fasting plasma glucose and UACR.

Table 3 shows the ORs and 95% CIs for the incidence of albuminuria between Group L and Group H of fasting plasma GLP-1 levels and fasting plasma GLP-1 levels in reduction of 1 pmol/L as a continuous variable. In the unadjusted model (Model 1), the OR (95% CI) for the incidence of albuminuria comparing Group L with Group H of fasting plasma GLP-1 levels was 2.987 (1.108-8.049), *p* = 0.031. This association was maintained in Model 2, which is further adjusted for age, gender, fasting plasma glucose, HbA1c, and C-peptide levels [OR (95% CI) = 3.121 (1.133-8.603), *p* = 0.028]. In Model 3, after further adjustment for the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors, the OR (95% CI) for the incidence of albuminuria comparing Group L with Group H of fasting plasma GLP-1 levels was 3.410 (1.160-10.023), *p* = 0.026.

Table 2. Correlations between fasting plasma GLP-1 levels and metabolic, anthropometric, and biochemical parameters (Univariate and Multivariate Models).

Univariate Model	Fasting plasma GLP-1 (pmol/L)	
	r	*p*-value
Age (years)	-0.161	0.190
Men [no. (%)]	0.154	0.210
Body mass index (kg/m²)	-0.039	0.749
Waist circumference (cm)	-0.051	0.740
Systolic BP (mmHg)	-0.173	0.172
Estimated GFR (ml/min/1.73 m²)	0.275	0.034
hs-CRP (mg/L)	-0.089	0.472
Total cholesterol (mg/dL)	0.126	0.307
Triglyceride (mg/dL)	0.099	0.422
LDL cholesterol (mg/dL)	0.075	0.543
HDL cholesterol (mg/dL)	-0.090	0.465
Fasting plasma glucose (mg/dL)	-0.060	0.626
Fasting plasma insulin (μU/mL)	0.162	0.197
HOMA-IR	0.109	0.388
HOMA-β (%)	-0.015	0.920
HbA1c (%)	-0.089	0.472
Urine albumin creatinine ratio (mg/g)	-0.252	0.038

Multivariate Model	Fasting plasma GLP-1 (pmol/L)		
	β	95% CI	*p*-value
Fasting plasma glucose (mg/dL)	-0.002 ± 0.001	-0.004 - 0.000	0.047
Urine albumin creatinine ratio (mg/g)	-0.305 ± 0.133	-0.571 - -0.038	0.026

* Abbreviations: GLP-1, Glucagon-like peptide-1; BP, Blood pressure; GFR, Glomerular filtration rate; hs-CRP, high-sensitive-C-reactive protein; LDL, Low density lipoprotein; HDL, High density lipoprotein; HOMA-IR, Homeostatic model assessment for insulin resistance; HOMA-β, Homeostasis model assessment of β-cell function; CI, confidence interval.

Table 3. Odd ratios and 95% confidence intervals for the incidence of albuminuria between the lower half (Group L) and the higher half (Group H) of fasting plasma GLP-1 levels and in fasting plasma GLP-1 levels for the decline of each 1 pmol/L as a continuous variable.

	Fasting plasma GLP-1 (pmol/L)				
	Group L (<1.83) n = 34	Group H* (1.83-3.32) n = 34	*p*-value	The decline of 1 pmol/L as a continuous variable	*p*-value
Model 1	2.987 (1.108-8.049)	1	0.031	1.556 (1.003-1.802)	0.049
Model 2	3.121 (1.133-8.603)	1	0.028	1.622 (1.091-1.843)	0.030
Model 3	3.410 (1.160-10.023)	1	0.026	1.673 (1.173-1.870)	0.018

Data are expressed as OR (95% CI). *1 as a reference value. Model 1: unadjusted. Model 2: adjusted for age, gender, fasting plasma glucose, HbA1c, and C-peptide levels. Model 3: adjusted for Model 2 plus the use of ACE inhibitors or ARBs, SGLT-2 inhibitors, and DPP-4 inhibitors. * Abbreviations: GLP-1, Glucagon-like peptide-1; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; SGLT-2, sodium-glucose cotransporter-2; DPP-4, dipeptidyl peptidase-4; CI, confidence interval.

As a continuous variable, fasting plasma GLP-1 levels were also negatively associated with the incidence of albuminuria. In Model 1, the OR (95% CI) for the incidence of albuminuria associated with a reduction of 1 pmol/L in fasting plasma GLP-1 levels was 1.556 (1.003-1.802) (*p* = 0.049). This negative association was apparent even after further adjusting for confounders in Model 2 [OR (95%

CI) =1.622 (1.091-1.843), *p* = 0.030]. Finally, this inverse association was still significant after full adjustment for all confounding variables, as above [Model 3; OR (95% CI) = 1.673 (1.173-1.870), *p* = 0.018].

4. Discussion

In this study, we explored associations between fasting GLP-1 levels and albuminuria in patients with T2DM in Korea. We found that there is a negative association between plasma fasting GLP-1 levels and the incidence of albuminuria among patients with T2DM who did not receive GLP-1 RA medications. This negative association remained to be statistically significant after further adjustments for multiple associated confounders.

In addition to showing cardiovascular protecting effects, previous randomized controlled studies demonstrated that GLP-1 RAs improve renal outcomes in patients with T2DM (9-11). A systematic review and meta-analysis of cardiovascular outcome trials including ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN-6 (semaglutide), EXSCEL (exenatide), HARMONY Outcomes (albiglutide), REWIND (dulaglutide), and PIONEER 6 (oral semaglutide) have demonstrated that the use of GLP-1 RA treatment resulted in a significant 17% reduction in a comprehensive kidney outcome (10, 11, 15-22). This improved outcome encompassed the development of new-onset macroalbuminuria, decline in estimated GFR, progression to end-stage kidney disease, or death attributable to kidney causes. As the benefit of a decline in estimated GFR was non-significant and less pronounced than the effect seen with SGLT-2 inhibitors (23, 24), this effect could mostly be attributed to a reduction of albuminuria.

While the exact mechanism remains an area of uncertainty, there are several hypotheses concerning the renal protective effect attributed to the reduction of albuminuria, thought to be attributed to a class effect of GLP-1 RAs. These hypotheses encompass the suppression of oxidative stress and local inflammation (25), the mitigation of oxidative stress-induced autophagy and endothelial dysfunction (26), and the induction of natriuresis and diuresis (27, 28).

Importantly, the aforementioned studies have primarily focused on the therapeutic effects observed after the administration of GLP-1 RAs in T2DM patients, rather than assessing the conditions before administration in the patients. Thus, it is not yet clear how the role of endogenous GLP-1 in normal physiological conditions differs from those resulting from pharmacological GLP-1 RA treatment.

A previous study showed that postprandial GLP-1 levels were independently associated with microalbuminuria in newly diagnosed T2DM patients in China (29). Patients with microalbuminuria demonstrated lower GLP-1 levels at 30 minutes and 120 minutes during a standard meal test compared to patients with normal albuminuria. In contrast, fasting plasma GLP-1 levels were not found to be associated with microalbuminuria (UACR: 30-299 mg/g). We included macroalbuminuria (UACR: > 300 mg/g) in addition to microalbuminuria in T2DM patients and found that GLP-1 levels are indeed negatively associated with the full spectrum of albuminuria.

In addition to postprandial GLP-1 levels, fasting GLP-1 levels also bear significant clinical implications. Elevated fasting plasma GLP-1 concentrations have been correlated with decreased carbohydrate intake and reduced consumption of simple sugars, indicating a potential role of GLP-1 in the reward pathway regulating simple sugar intake (30). Our study also suggests that elevated fasting plasma GLP-1 levels in patients with T2DM may be beneficial in reducing the incidence of albuminuria.

Next, we need to consider that other medications could affect the results of the study. Plasma GLP-1 levels could be increased by DPP-4 inhibitors, as they inhibit DPP-4 activity, which degrades GLP-1 in the peripheral circulation (31). On the other hand, albuminuria could be reduced by ACE inhibitors and ARBs, which have been shown to delay progression to end-stage kidney disease and reduce cardiovascular risk (32). ACE inhibitors and ARBs decrease intraglomerular pressure by inhibiting angiotensin II-mediated efferent arteriolar vasoconstriction (33). SGLT-2 inhibitors are anti-diabetic medications, which also reduce albuminuria (34). SGLT-2 inhibitors decrease sodium reabsorption in the proximal convoluted tubules and increase sodium delivery to the macula densa

cells, thereby reactivating tubuloglomerular feedback (35). Consequently, SGLT-2 inhibitors inhibit the vasodilation of afferent arteriole, decrease intraglomerular pressure, and reduce albuminuria (36). We incorporated the use of medications that may influence the results as confounding factors.

Considering this is the era of personalized medicine, we need to raise a question of which candidates are suitable to benefit from exogenous GLP-1 RAs for not only glycemic control, but also renal protection in T2DM patients. To the best of our knowledge, there has not been a large-scale randomized controlled trial (RCT) that has examined whether differences in basal GLP-1 levels resulted in different renal protection effects to GLP-1 RAs in T2DM patients. For future research endeavors, it becomes imperative to conduct meticulously designed longitudinal and large-scale studies to gain deeper insights into the impact of GLP-1 on albuminuria.

It is important to acknowledge several limitations of this study. Firstly, this being a cross-sectional study, we should exercise caution in establishing causality between fasting plasma GLP-1 levels and the incidence of albuminuria. Secondly, the participants may not be representative of the entire Korean T2DM population, as they were self-selected, and the study was conducted using a sample from a single center. This introduces the possibility of selection bias, and the results may have limitations in terms of generalizability. Thirdly, the sample size in this study is comparatively limited. Conducting a larger randomized controlled study will serve to validate these results.

Despite these limitations, the study intentionally aimed to validate a direct negative association between plasma fasting GLP-1 levels and albuminuria. Its clinical implication lies in the direct quantification of plasma GLP-1 concentrations, bypassing the conventional post hoc validation of therapeutic effects following GLP-1 RA administration. Other strengths include measuring plasma GLP-1 as active GLP-1, not total GLP-1. Furthermore, we tried to adjust the use of medications that could affect plasma GLP-1 levels and albuminuria. These distinctive characteristics could contribute to the reliability and utility of this study.

5. Conclusions

In this study, we investigated the association between fasting GLP-1 levels and albuminuria in patients with T2DM in Korea. We observed a negative association between plasma fasting GLP-1 levels and the incidence of albuminuria among T2DM patients who were not administered GLP-1 RAs. This association persisted even after adjusting for confounding factors that might influence the results. These findings imply that endogenous GLP-1 may have a role in attenuating albuminuria.

References

1. Association. KD. Diabetes fact sheets in Korea 2022. Korean Diabetes Association. 2022.
2. Fox CS. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis (vol 380, pg 1662, 2012). Lancet. 2013;381(9864):374-.
3. Parving HH. Diabetic nephropathy: prevention and treatment. Kidney Int. 2001;60(5):2041-55.
4. Wada T, Shimizu M, Toyama T, Hara A, Kaneko S, Furuichi K. Clinical impact of albuminuria in diabetic nephropathy. Clin Exp Nephrol. 2012;16(1):96-101.

5. Benzing T, Salant D. Insights into Glomerular Filtration and Albuminuria. N Engl J Med. 2021;384(15):1437-46.

6. Holst JJ. The physiology of glucagon-like peptide 1. Physiol Rev. 2007;87(4):1409-39.

7. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006;368(9548):1696-705.

8. Calanna S, Christensen M, Holst JJ, Laferrere B, Gluud LL, Vilsboll T, et al. Secretion of glucagon-like peptide-1 in patients with type 2 diabetes mellitus: systematic review and meta-analyses of clinical studies. Diabetologia. 2013;56(5):965-72.

9. Mosenzon O, Schechter M, Leibowitz G. Kidney Outcomes With Glucagon-Like Peptide-1 Receptor Agonists in Patients With Type 2 Diabetes. Adv Chronic Kidney Dis. 2021;28(4):347-60.

10. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. Lancet. 2019;394(10193):131-8.

11. Mann JFE, Orsted DD, Brown-Frandsen K, Marso SP, Poulter NR, Rasmussen S, et al. Liraglutide and Renal Outcomes in Type 2 Diabetes. N Engl J Med. 2017;377(9):839-48.

12. World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-4.

13. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130(6):461-70.

14. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9.

15. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med. 2015;373(23):2247-57.

16. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016;375(4):311-22.

17. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016;375(19):1834-44.

18. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2017;377(13):1228-39.

19. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Sr., Granger CB, Jones NP, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet. 2018;392(10157):1519-29.

20. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394(10193):121-30.

21. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2019;381(9):841-51.

22. Kristensen SL, Rorth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol. 2019;7(10):776-85.

23. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Furtado RHM, et al. Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus. Circulation. 2019;139(17):2022-31.

24. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019;380(24):2295-306.

25. Tanaka T, Higashijima Y, Wada T, Nangaku M. The potential for renoprotection with incretin-based drugs. Kidney Int. 2014;86(4):701-11.

26. Cai X, She M, Xu M, Chen H, Li J, Chen X, et al. GLP-1 treatment protects endothelial cells from oxidative stress-induced autophagy and endothelial dysfunction. Int J Biol Sci. 2018;14(12):1696-708.

27. Crajoinas RO, Oricchio FT, Pessoa TD, Pacheco BP, Lessa LM, Malnic G, et al. Mechanisms mediating the diuretic and natriuretic actions of the incretin hormone glucagon-like peptide-1. Am J Physiol Renal Physiol. 2011;301(2):F355-63.

28. Asmar A, Cramon PK, Simonsen L, Asmar M, Sorensen CM, Madsbad S, et al. Extracellular Fluid Volume Expansion Uncovers a Natriuretic Action of GLP-1: A Functional GLP-1-Renal Axis in Man. J Clin Endocrinol Metab. 2019;104(7):2509-19.

29. Song LL, Wang N, Zhang JP, Yu LP, Chen XP, Zhang B, et al. Postprandial glucagon-like peptide 1 secretion is associated with urinary albumin excretion in newly diagnosed type 2 diabetes patients. World J Diabetes. 2023;14(3):279-89.

30. Basolo A, Heinitz S, Stinson EJ, Begaye B, Hohenadel M, Piaggi P, et al. Fasting glucagon-like peptide 1 concentration is associated with lower carbohydrate intake and increases with overeating. J Endocrinol Invest. 2019;42(5):557-66.
31. McIntosh CH, Demuth HU, Pospisilik JA, Pederson R. Dipeptidyl peptidase IV inhibitors: how do they work as new antidiabetic agents? Regul Pept. 2005;128(2):159-65.
32. Chu CD, Powe NR, McCulloch CE, Banerjee T, Crews DC, Saran R, et al. Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use Among Hypertensive US Adults With Albuminuria. Hypertension. 2021;77(1):94-102.
33. Robles NR, Romero B, de Vinuesa EG, Sanchez-Casado E, Cubero JJ. Treatment of proteinuria with lercanidipine associated with renin-angiotensin axis-blocking drugs. Ren Fail. 2010;32(2):192-7.
34. Loutradis C, Papadopoulou E, Angeloudi E, Karagiannis A, Sarafidis P. The Beneficial Hemodynamic Actions of SGLT-2 Inhibitors beyond the Management of Hyperglycemia. Curr Med Chem. 2020;27(39):6682-702.
35. Skrtic M, Cherney DZ. Sodium-glucose cotransporter-2 inhibition and the potential for renal protection in diabetic nephropathy. Curr Opin Nephrol Hypertens. 2015;24(1):96-103.
36. Gerard AO, Laurain A, Favre G, Drici MD, Esnault VLM. Activation of the Tubulo-Glomerular Feedback by SGLT2 Inhibitors in Patients With Type 2 Diabetes and Advanced Chronic Kidney Disease: Toward the End of a Myth? Diabetes Care. 2022;45(10):e148-e9.