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Original Article

Correlation Study of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) on Diabetic Patients with Hypertension

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Abstract

Background: We aimed to investigate the effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on blood pressure, blood glucose and blood lipid in diabetic patients with hypertension.

Methods: A total of 300 diabetic patients and essential hypertension admitted to the Second Affiliated Hospital of Dalian Medical University, Dalian, China from January 2021 to December 2022 were selected. They were divided into an observation group and a control group using a random number table method. The control group was treated with conventional antihypertensive drugs, hypoglycemic drugs, and lipid-lowering drugs. The observation group was supplemented with liraglutide based on the control group. Blood pressure, blood glucose and blood lipid of the two groups were compared at the initial stage of medication and after 4 weeks and half a year, and the influencing factors of patients with persistent hypertension were further analyzed through Logistic regression.

Results: After 4 weeks and 6 months of medication, inter group comparisons showed that systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG) and glycated hemoglobin (HbA1c), as well as total cholesterol (TC), triacylglycerol (TG), and plasma arteriosclerosis index (AIP) in the observation group were significantly lower than those in the control group ($P<0.05$). Multivariate Logistic regression model analysis showed that age, smoking history, drinking history, taking conventional antihypertensive drugs, taking hypoglycemic drugs, taking lipid-lowering drugs, BMI, FBG, HbA1c and LDL-C were independent influencing factors for persistent hypertension ($P<0.05$).

Conclusion: GLP-1RAs could effectively improve the indexes including blood pressure, blood glucose and blood lipid in diabetic patients with hypertension.

Keywords: Glucagon-like peptide-1 receptor agonists; Type 2 diabetes; Essential hypertension

Introduction

Type 2 diabetes (T2DM) is often accompanied by a variety of target organ damages in the occurrence and progression of the disease. With the continuous increase of blood glucose, the risk of related complications also increases greatly, among which cardiovascular disease is the main cause of death in diabetic patients (1). In addition, most diabetic patients are in a high-risk state of multiple cardiovascular risk factors such as overweight or obesity, hypertension and hyperlipidemia. Therefore, the

comprehensive intervention of blood glucose reduction, weight loss, blood pressure reduction and lipid regulation should be emphasized when formulating prevention and treatment strategies (2-4). Myocardial hypertrophy is a compensatory response to various cardiovascular diseases, including hypertension, valvular heart disease, ischemic heart disease and cardiomyopathy. Among them, hypertension is one of the chronic diseases with the largest number of patients in China. At present, there have been more than 270 million patients, which is the most important risk factor for the death of cardiovascular and cerebrovascular diseases (5).

In recent years, glucagon-like peptide 1 receptor agonists (GLP-1RAs) as a new hypoglycemic drug widely used in the treatment of T2DM, to enhance insulin secretion and inhibit glucagon secretion in a glucose concentration dependent manner by activating the glucagon-like peptide-1 (GLP-1) receptor, so as to achieve the effect of blood glucose (6,7). In addition to the involvement in glycemic control, GLP-1RAs also have a protective effect on the cardiovascular system (8).

We aimed to investigate the effects of GLP-1RAs on metabolic indexes such as blood pressure, blood glucose and lipids in diabetic patients with hypertension and to analyze relevant influencing factors in patients with persistent hypertension during follow-up, so as to provide more evidence for clinical application.

Methods

Research Subjects

A total of 300 diabetic patients complicated with essential hypertension admitted to the Second Affiliated Hospital of Dalian Medical University (Dalian, China) from January 2021 to December 2022 were selected. The patients meeting the inclusion and exclusion criteria were randomly divided into two groups: The control group was treated with conventional antihypertensive drugs, hypoglycemic drugs, and lipid-lowering drugs. The observation group was injected with GLP-1RAs subcutaneously based on the control group. The initial dose in the first week was 0.6 mg each time, once a day, and the dose for Week 2-24 was 1.2 mg each time, once a day.

Inclusion and exclusion criteria

Inclusion criteria: 1) Patients who meet the diagnostic criteria for T2DM in *the Chinese Guidelines for the Prevention and Treatment of T2DM (2020 Edition)* and the diagnostic criteria for hypertension in the *Chinese Guidelines for the Prevention and Treatment of Hypertension (2018 Revision)*; 2) Patients over 18 years old; 3) Patients with normal liver and kidney functions; 4) Patients who cooperated in completing the examination, have clear awareness, and voluntarily participate in this study.

Exclusion criteria: 1) Patients with secondary hypertension caused by other causes; 2) Patients with severe dysfunction of organs such as heart, liver, brain, and kidneys; 3) Patients complicated with serious diseases such as hematopoietic system, endocrine system, respiratory system and digestive system; 4) Females during pregnancy and lactation; 5) Patients with severe hearing, visual, and language impairments who are unable to cooperate with this study; 6) Patients with malignant tumor, AIDS, systemic infection and other serious diseases, or taking part in other relevant studies at the same time with serious diseases such as malignant tumor, AIDS, systemic infection, or other relevant researchers.

Observation indexes

All patients enrolled were collected for general information on their gender, age, height, weight, smoking and drinking, antihypertensive drugs, hypoglycemic drugs, and lipid-lowering drugs commonly used, and followed up at the initial stage of medication, 4 weeks of medication, and 6 months of medication: 1) The levels of SBP and DBP were measured with an electronic sphygmomanometer or a standard mercury sphygmomanometer. To ensure the validity of the results, 3 quiet measurements were taken and the average value was recorded at the same time; 2) The level of FBG was measured by blood glucose meter, and the level of HbA1c was determined with the automatic biochemical analyzer; 3) In these patients, 3 ml of

fasting venous blood was collected and the levels of TC, TG, HDL-C and LDL-C were measured by the automatic biochemical analyzer. AIP was calculated with the formula as AIP=log (TG/HDL-C). Patients with persistent hypertension were defined as those with blood pressure levels of 140/90 mmHg or above at follow-up at 4 weeks and 6 months of medication.

Ethics

Informed consent was obtained from all individual participants included in the study.

Statistical Analysis

Data were analyzed and processed by SPSS 26.0 software (IBM Corp., Armonk, NY, USA). Measurement data were expressed by $\bar{x} \pm s$ and compared between two groups by independent sample *t*-test. Counting data were expressed by frequency and rate (%), and compared between groups with χ^2. A binary logistic regression model was adopted to analyze the relevant influencing factors based on whether the patients had persistent hypertension as the dependent variable. A dichotomized Logistics regression model was used as the dependent variable. $P<0.05$ was considered as a statistically significant difference.

Results

Comparison of general data before medication

A total of 300 diabetic patients combined with essential hypertension were enrolled in this study. Among these patients, 127 were male, 173 were female. The mean age of the patients in the observation group was 58.95±9.24 years, and the mean age of the patients in the control group was 60.48±9.13 years. The comparison between the observation and the control groups showed that there was no statistically significant difference in gender, age, smoking history, drinking history, BMI and other general data of patients before medication, as well as the use of conventional antihypertensive drugs such as ARB, CCB, β-blocker and nohinol, conventional hypoglycemic drugs such as metformin, acarbose, SGLT2i, flavuron and insulin, and conventional lipid-lowering drugs such as Statins, Xuezhikang and Evolocumab, which were comparable (Table 1).

Table 1: Comparison of general data between the two groups

Observational indexes	*Observation group (n =150)*	*Control group (n =150)*	*Statistics*	*P*
Male/Female (Case)	61/89	66/84	0.341	0.559
Age (Years old)	58.95±9.24	60.48±9.13	-1.446	0.149
Smoking history (Yes, %)	27 (18.00)	21 (14.00)	0.893	0.345
Drinking history (Yes, %)	18 (12.00)	14 (9.33)	0.560	0.454
BMI (kg/m²)	25.07±3.29	25.66±3.48	-1.516	0.131
Antihypertensive drugs				
ARBs (Yes, %)	63 (42.00)	62 (41.33)	0.014	0.907
CCBs (Yes, %)	98 (65.33)	109 (72.67)	1.128	0.288
β-beta-blockers (Yes, %)	93 (62.00)	101 (67.33)	0.934	0.334
Noxinto (Yes, %)	91 (60.67)	102 (68.00)	1.758	0.185
Hypoglycemic drugs				
Metformin (Yes, %)	67 (44.67)	59 (39.33)	0.876	0.349
Acarbose (Yes, %)	43 (28.67)	49 (32.67)	0.564	0.453
SGLT2i (Yes, %)	47 (31.33)	41 (27.33)	0.579	0.447
Sulfonylureas (Yes, %)	8 (5).33	14 (9).33	1.766	0.184
Insulin (Yes, %)	40 (26.67)	50 (33.33)	1.587	0.208
Lipid-lowering drugs				
Statins (Yes, %)	121 (80.67)	132 (88.00)	3.053	0.081
Xuezhikang (Yes, %)	35 (23.33)	27 (18.00)	1.301	0.254
Evolocumab (Yes, %)	17 (11.33)	25 (16.67)	1.772	0.183

Effect of GLP-1RAs on Metabolic Indexes

All patients were followed up at the initial stage of medication, 4 weeks of medication and 6 months of medication, respectively, to observe the effects of GLP-1RAs on blood pressure, blood glucose, blood lipid and other metabolic indexes in diabetic patients with hypertension.

Comparison of blood pressure levels before and after medication between the two groups

The comparison of SBP and DBP at the initial stage of medication between the two groups of patients showed no statistically significant difference. After 4 weeks of medication and 6 months of medication, all patients were followed up. The comparison of blood pressure levels showed that the levels of SBP and DBP in the observation group were significantly lower than those in the control group (P<0.05), as shown in Table 2.

Table 2: Comparison of blood pressure levels before and after medication between the two groups

Grouping	***SBP (mmHg)***			***DBP (mmHg)***		
	Initial Stage of medication	4 weeks of medication	6 months of medication	Initial Stage of medication	4 weeks of medication	6 months of medication
Observation group (n =150)	149.3±7.7	124.5±8.3	121.8±6.5	89.4±10.6	79.5±7.0	77.6±8.2
Control group (n =150)	147.1±14.8	132.2±13.7	129.7±11.4	87.3±11.2	81.5±6.8	80.3±5.9
t	1.615	-5.887	-7.373	1.668	-2.492	-3.273
P	0.108	<0.001	<0.001	0.096	0.013	0.001

Comparison of the levels of blood glucose and HbA1c before and after treatment between the two groups

The comparison of FBG and HbA1c between the two groups of patients at the initial stage of medication showed no statistically significant difference. The results of 4 weeks of medication and 6 months of medication showed that FBG and HbA1c in the observation group were also significantly lower than those in the control group (P<0.05), as shown in Table 3.

Table 3: Comparison of the levels of blood glucose and HbA1c before and after medication between the two groups

Grouping	***FBG (mmol/L)***			***HbA1c (%)***		
	Initial Stage of medication	4 weeks of medication	6 months of medication	Initial Stage of medication	4 weeks of medication	6 months of medication
Observation group (n =150)	8.53±2.19	6.43±1.07	6.28±1.26	8.05±1.23	6.85±0.70	6.29±1.16
Control group (n =150)	8.68±1.86	7.26±2.14	7.01±1.21	8.33±1.42	8.05±1.23	7.18±1.15
t	-0.639	-4.249	-5.171	-1.825	-10.385	-6.659
P	0.523	<0.001	<0.001	0.069	<0.001	<0.001

Comparison of the levels of blood lipid and AIP before and after treatment between the two groups

The comparison of blood lipid levels such as TG, TC, HDL-C, LDL-C, and AIP between the two groups of patients at the initial stage of medication showed no statistically significant difference. After 4 weeks of medication, TG, TC, and AIP of the observation group were significantly lower than those of the control group (P<0.05). There was no statistically significant difference in the levels of HDL-C and LDL-C between the two groups. After six months of medication, the levels of TG, TC, LDL-C, and AIP in the observation group were significantly lower than those in the control group (P<0.05), HDL-C level in the observation group was significantly higher than that in the control group (P<0.05), as shown in Table 4.

Table 4: Comparison of the levels of blood lipid and AIP before and after medication between the two groups

Follow-up time point	*Grouping*	*n*	*TC (mmol/L)*	*TG (mmol/L)*	*HDL-C (mmol/L)*	*LDL-C (mmol/L)*	*AIP*
Initial stage of medication	Observation group	150	4.78±0.90	1.58±0.89	1.05±0.28	2.90±0.83	0.21±0.26
	Control group	150	4.90±1.39	1.62±0.98	1.11±0.31	2.78±1.04	0.24±0.29
	t		-0.888	-0.370	-1.759	1.105	-0.943
	P		0.376	0.712	0.080	0.270	0.346
4 weeks of medication	Observation group	150	4.15±0.93	1.24±0.62	1.15±0.28	2.48±0.86	0.07±0.18
	Control group	150	4.63±1.08	1.50±0.71	1.09±0.28	2.55±0.94	0.14±0.23
	t		-3.265	-3.378	1.856	-0.638	-2.935
	P		0.001	0.001	0.064	0.524	0.004
6 months of medication	Observation group	150	4.09±0.95	1.19±0.55	1.21±0.38	2.26±0.76	0.28±0.21
	Control group	150	4.58±0.88	1.47±0.77	1.08±0.32	2.49±0.84	0.15±0.29
	t		-4.693	-3.642	3.196	-2.458	4.447
	P		<0.001	<0.001	0.002	0.015	<0.001

Analysis on Factors Associated with Persistent Hypertension in Patients

Univariate analysis

After the end of follow-ups, patients with blood pressure levels of 140/90mmHg or above after 4 weeks of medication and 6 months of medication were defined as patients with persistent hypertension. Whether they were patients with persistent hyperemia was the dependent variable. Whether to add liraglutide (GLP-1RAs: observation group = 1, control group = 0), gender (male = 1, female = 2), age, smoking history (with = 1, without = 0), drinking history (with = 1, without = 0), whether to take conventional antihypertensive drugs such as ARB, CCB, β-blockers and nohinol (yes = 1, no = 0), whether to take conventional hypoglycemic drugs such as metformin, acarbose, SGLT2i, flavuron, insulin (yes =1, no =0), whether to take conventional lipid-lowering drugs such as Statins, Xuezhikong and Evolocumab (yes = 1, no = 0) and the measured values of BMI, FBG, HbA1c, TC, TG, HDL-C and LDL-C after following up

for six months were taken as independent variables, and univariate Logistic regression analysis was performed (P<0.05), as shown in Table 5.

Table 5: Univariate analysis on influencing factors in patients with persistent hypertension

Covariates	*Patients with persistent hypertension*		*OR*	χ^2/t	*P*
	Yes (n =82)	No (n =218)			
GLP-1RAs (observation/control group)	31/51	119/99	0.506	6.713	0.010
Gender (male/female)	46/36	81/137	0.463	8.757	0.003
Age (years old)	65.18±10.12	57.66±7.93	1.101	6.773	<0.001
Smoking history (Yes, %)	23 (28.05)	25 (11.47)	3.009	12.189	<0.001
Drinking history (Yes, %)	16 (19.51)	16 (7.34)	3.061	9.266	0.002
Conventional antihypertensive drugs (Yes, %)	51 (62.20)	196 (89.91)	0.185	31.462	<0.001
Conventional hypoglycemic drugs (Yes, %)	39 (47.56)	183 (83.94)	0.173	40.998	<0.001
Conventional lipid-lowering drugs (Yes, %)	58 (70.73)	195 (89.45)	0.285	15.801	<0.001
BMI (kg/m²)	26.55±3.54	24.92±3.23	1.152	3.786	<0.001
FBG (mmol/L)	7.18±1.40	6.43±1.19	1.595	4.620	<0.001
HbA1c (%)	7.26±1.29	6.54±1.16	1.605	4.658	<0.001
TC (mmol/L)	4.57±0.94	4.25±0.94	1.442	2.623	0.009
TG (mmol/L)	1.54±0.90	1.25±0.56	1.818	3.354	0.001
HDL-C (mmol/L)	1.08±0.30	1.16±0.37	0.514	1.692	0.092
LDL-C (mmol/L)	2.64±0.83	2.28±0.78	1.741	3.498	0.001

Multivariate analysis

In order to make the results more robust, the indexes with P<0.1 in the univariate analysis were enrolled in the multivariate Logistic regression model. The results showed that age, smoking history, drinking history, BMI, FBG, HbA1c and LDL-C were independent risk factors for persistent hypertension in diabetic patients with hypertension, and taking conventional antihypertensive drugs, hypoglycemic drugs or lipid-lowering drugs were protective factors (Table 6).

Table 6: Multivariate analysis on influencing factors in patients with persistent hypertension

Covariates	*β*	*SE*	*Wald* χ^2	*P*	*OR (95%CI)*
Age	0.133	0.025	27.224	<0.001	1.142 (1.086，1.200)
Smoking History	1.917	0.534	12.882	<0.001	6.799 (2.387，19.364)
Drinking History	1.635	0.641	6.516	0.011	5.130 (1.462，18.002)
Conventional antihypertensive drugs	-1.913	0.512	13.993	<0.001	0.148 (0.054，0.402)
Conventional hypoglycemic drugs	-2.169	0.442	24.096	<0.001	0.114 (0.048，0.272)
Conventional lipid-lowering drugs	-1.196	0.562	4.527	0.033	0.302 (0.100，0.910)
BMI	0.223	0.062	12.800	<0.001	1.250 (1.106，1.412)
FBG	0.469	0.172	7.395	0.007	1.598 (1.140，2.240)
HbA1c	0.627	0.177	12.556	<0.001	1.872 (1.323，2.648)
LDL-C	0.920	0.254	13.147	<0.001	2.509 (1.526，4.126)
Constant term	-21.292	3.587	35.243	<0.001	-

Discussion

The previous research have shown that angiotension II (AngII) produced by the activation of the renin-angiotensin-aldosterone system (RAAS) is an important pathological basis for the development of hypertension, myocardial fibrosis and heart failure (9). The reduction of Ang II generation by angiotensin converting enzyme inhibitors (ACEI) and the blockade of Ang II by using angiotensin receptor blockers (ARB) have become a conventional drug use in the clinical treatment of all kinds of cardiovascular diseases (10). However, in practice, this kind of drugs also have certain side effects (11). Therefore, it is of great clinical translational medicine significance to seek other methods to reduce Ang II injury, expand the status quo that the prevention and treatment of Ang II-related cardiovascular diseases is limited to RAAS, and clarify its protective mechanism.

Glucagon-like peptide 1 (GLP-1) is a peptide hormone secreted by intestinal L cells, which is widely known for its hypoglycemic effect. A large number of studies have shown that GLP-1RAs can improve myocardial glucose uptake, improve endothelial function, dilate blood vessels, anti-inflammatory, anti-atherosclerosis, regulate blood lipid, control blood pressure and heart rate (12). At the same time, it can regulate a variety of coronary heart disease risk factors in diabetic patients, but also inhibit the development of arteriosclerosis plaque through special mechanisms, and reduce the occurrence of terminal cardiac events including cardiovascular death (13). In this paper, the effects of GLP-1RAs on blood pressure, blood glucose and lipid levels in diabetic patients with hypertension were analyzed, and the influencing factors of persistent hypertension in enrolled patients were further analyzed, in order to provide more evidence for the clinical application of GLP-1RAs. We showed that in these 300 diabetic patients with essential hypertension, SBP and DBP, FBG, HbA1c, TG, TC and AIP were significantly lower than that of the control group, and LDL-C of the observation group was also significantly lower than that of the control group. Compared with conventional treatment, adding GLP-1RAs showed significant efficacy in antihypertensive drugs, hypoglycemic drugs and lipid-lowering drugs in diabetic patients with hypertension, and this result is similar to studies at home and abroad. A meta-analysis of 8 trials involving 468 subjects (14) demonstrated that GLP-1RAs significantly reduced body weight, BMI, waist circumference, FBG, HbA1c, TC, TG and effectively improved metabolic markers in diabetic patients with non-alcoholic fatty liver disease. A review of current GLP-1RAs (15) suggests that GLP-1RAs have weight-lowering effects while reducing HbA1c and do not have an inherent risk of hypoglycemic episodes yet.

Multivariate Logistic regression analysis found that smoking history and drinking history were independent risk factors for persistent hypertension (OR>1 and $P<0.05$) in diabetic patients with hypertension, the risk of persistent hypertension increased with age, BMI, FBG, HbA1c and LDL-C (OR>1 and $P<0.05$), and taking antihypertensive drugs, hypoglycemic drugs and lipid-lowering drugs were independent protective factors for persistent (OR <1 and $P<0.05$) in diabetic patients with hypertension. The results of this study confirmed that smoking, drinking, increased age, increased BMI, hyperglycemia and high levels of LDL-C are independent risk factors for hypertension, which has a good reference for blood pressure control in diabetic patients with hypertension (16). In addition, it was found in this study that taking conventional antihypertensive drugs, hypoglycemic drugs and lipid-lowering drugs were protective factors for persistent hypertension in patients, without correlation between the addition of liraglutide (GLP-1RAs) and persistent hypertension in the research subjects. This result may be due to the inclusion of too many influencing factors, small sample size and potential selection bias, and the subsequent expanded population can be further verified by observational studies.

Conclusion

GLP-1RAs can effectively improve blood pressure, blood glucose and lipid indexes in diabetic patients with hypertension, which was compatible with the comprehensive intervention strategies of glucose reduction, weight loss, antihypertensive and lipid regulation recommended in the current prevention and treatment guidelines for T2DM.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

The authors declare that there is no conflict of interest.

References

1. Lee SK, Shin DH, Kim YH, Lee KS (2019). Effect of Diabetes Education through Pattern Management on Self-Care and Self-Efficacy in Patients with Type 2 Diabetes. *Int J Environ Res Public Health*, 16(18): 3323.
2. Shrestha P, Kaiti R, Shyangbo R (2022). Blindness among Patients with Type II Diabetes Mellitus Presenting to the Outpatient Department of Ophthalmology of a Tertiary Care Centre: A Descriptive Cross-sectional Study. *JNMA J Nepal Med Assoc*, 60(254): 877-880.
3. Deerochanawong C, Chan SP, Matawaran BJ, et al (2019). Use of sodium-glucose co-transporter-2 inhibitors in patients with type 2 diabetes mellitus and multiple cardiovascular risk factors: An Asian perspective and expert recommendations. *Diabetes Obes Metab*, 21: 2354-2367.
4. Jia W, Weng J, Zhu D, et al (2019). Standards of medical care for type 2 diabetes in China 2019. *Diabetes Metab Res Rev*, 35(6): e3158.
5. Gilbert MP, Pratley RE (2020). GLP-1 Analogs and DPP-4 Inhibitors in Type 2 Diabetes Therapy: Review of Head-to-Head Clinical Trials. *Front Endocrinol (Lausanne)*, 11:178.
6. Franch-Nadal J, Granado-Casas M, Mata-Cases M, Ortega E, Vlacho B, Mauricio D (2022). Determinants of response to the glucagon-like peptide-1 receptor agonists in a type 2 diabetes population in the real-world. *Prim Care Diabetes*, 16: 810-817.
7. Kelkar A, Kelkar J, Mehta H, Amoaku W (2018). Cataract surgery in diabetes mellitus: A systematic review. *Indian J Ophthalmol*, 66(10): 1401-1410.
8. Howse PM, Chibrikova LN, Twells LK, Barrett BJ, Gamble JM (2016). Safety and Efficacy of Incretin-Based Therapies in Patients with Type 2 Diabetes Mellitus and CKD: A Systematic Review and Meta-analysis. *Am J Kidney Dis*, 68: 733-742.
9. Jensterle M, Rizzo M, Haluzík M, Janež A (2022). Efficacy of GLP-1 RA Approved for Weight Management in Patients With or Without Diabetes: A Narrative Review. *Adv Ther*, 39(6): 2452-2467.
10. Cheng Z, Zhang M, Hu J, et al (2018). Mst1 knockout enhances cardiomyocyte autophagic flux to alleviate angiotensin II-induced cardiac injury independent of angiotensin II receptors. *J Mol Cell Cardiol,* 125: 117-128.
11. Mathey CM, Maj C, Scheer AB, et al (2022). Molecular Genetic Screening in Patients With ACE Inhibitor/Angiotensin Receptor Blocker-Induced Angioedema to Explore the Role of Hereditary Angioedema Genes. *Front Genet*, 13: 914376.
12. Holst JJ, McGill MA. (2012). Potential new approaches to modifying intestinal GLP-1 secretion in patients with type 2 diabetes mellitus: focus on bile acid sequestrants. *Clin Drug Investig*, 32(1): 1-14.
13. Gu Y, Sun L, Zhang W, et al (2023). Comparative efficacy of 5 sodium-glucose cotransporter protein-2 (SGLT-2) inhibitor and 4 glucagon-like peptide-1 (GLP-1) receptor agonist drugs in non-alcoholic fatty liver disease: A GRADE-assessed systematic review and network meta-analysis of randomized controlled trials. *Front Pharmacol*, 14: 1102792.

14. Zhu Y, Xu J, Zhang D, et al (2021). Efficacy and Safety of GLP-1 Receptor Agonists in Patients with Type 2 Diabetes Mellitus and Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. *Front Endocrinol (Lausanne)*, 12: 769069.
15. Nauck MA, Quast DR, Wefers J, Meier JJ (2021). GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. *Mol Metab*, 46: 101102.
16. Zhang X, Yip TC, Tse YK, et al (2023). Trends in risk factor control and treatment among patients with non-alcoholic fatty liver disease and type 2 diabetes between 2000 and 2020: A territory-wide study. *Aliment Pharmacol Ther*, 57: 1103-1116.