

A Significant Effect of Oral Semaglutide on Cardiovascular Risk Factors in Patients With Type 2 Diabetes

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Abstract

Background: The once-daily glucagon-like peptide 1 (GLP-1) analogue, liraglutide has been shown to reduce major adverse cardiovascular events (MACE) and progression of chronic kidney disease (CKD). The once-weekly GLP-1 analogue, semaglutide also reduced MACE and renal events. Based on the evidence for GLP-1 analogues on MACE and renal events, the guideline recommended to treat high-risk diabetic individuals with GLP-1 analogues to reduce MACE and CKD progression. Recently, a once-daily oral semaglutide was developed and shown to reduce MACE. However, its effects on renal outcome and cardiovascular metabolic risk factors remain unknown.

Methods: We retrospectively picked up patients who had taken oral semaglutide from March 2021 to June 2022 and compared metabolic parameters at baseline with the data at 3, 6 months after the start of oral semaglutide.

Results: We found 47 patients who had taken oral semaglutide. Body weight significantly decreased at 3 and 6 months after the start of oral semaglutide, and systolic blood pressure significantly decreased after 6 months. Hemoglobin A1c (HbA1c) tended to decrease after 3 months and significantly decreased after 6 months. Serum low-density lipoprotein cholesterol (LDL-C) levels significantly decreased after 6 months and non-high-density lipoprotein-cholesterol (non-HDL-C) levels tended to decrease after 6 months. Urinary albumin to creatinine ratio (UACR) tended to decrease after 3 and 6 months. Such favorable metabolic changes by oral semaglutide were observed more prominently in patients who had not ever used GLP-1 analogues than in patients who switched from subcutaneous GLP-1 analogues.

Conclusions: Our study showed that oral semaglutide improved body weight, blood pressure, HbA1c, LDL-C, non-HDL-C and UACR, in type 2 diabetic obese patients, especially, in patients who had not ever used GLP-1 analogues.

Keywords: Blood pressure; Glucagon-like peptide 1 analogue; Non-high-density lipoprotein-cholesterol; Semaglutide; Urinary albumin

Introduction

Recently, cardiovascular safety is required for the newly-developed drugs for diabetes. The first once-daily glucagon-like peptide 1 (GLP-1) analogue, liraglutide was developed, and the Liraglutide Effect and Action in Diabetes (LEAD) 2 study demonstrated that the once-daily liraglutide induced similar glycemic control, reduced body weight, and lowered the occurrence of hypoglycemia compared with sulfonylurea [1]. The LEAD 6 study showed that the once-daily liraglutide provided significantly greater improvements in glycemic control than did exenatide twice a day and was generally better tolerated [2]. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial demonstrated that the development of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes was significantly lower with liraglutide than with placebo [3]. Furthermore, the LEADER trial also showed the renal outcome occurred such as a new onset of macroalbuminuria, in fewer participants in the liraglutide group than in the placebo group [4].

Semaglutide, a GLP-1 analogue with an extended half-life of approximately 1 week was developed. In the SUTAIN-6, the once-weekly subcutaneous semaglutide on major adverse cardiovascular events (MACE) was investigated in patients with type 2 diabetes at high cardiovascular risk [5]. This once-weekly subcutaneous semaglutide reduced MACE as compared with placebo (hazard ratio (HR): 0.74; 95% confidence interval (CI): 0.58 - 0.95; $P < 0.001$). Semaglutide also reduced the development or worsening of diabetic kidney disease as compared with placebo (HR: 0.64; 95% CI: 0.46 - 0.88; $P = 0.005$). Based on the evidence for GLP-1 analogues on MACE and renal events, the American Diabetes Association and the European Association for the Study of Diabetes recommend to treat high-risk diabetic individuals with GLP-1 analogues to reduce MACE and chronic kidney disease (CKD) progression [6]. Very recently, a once-daily oral semaglutide was developed, and its effects on MACE was investigated in type 2 diabetic patients at high cardiovascular risk in the PIONEER 6 [7]. Oral semaglutide reduced the development of MACE as compared with placebo (HR: 0.79; 95% CI: 0.57 - 1.11; P

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< 0.001).

In the PIONEER 6, hemoglobin A1c (HbA1c) decreased more by oral semaglutide than by placebo (-1.0 vs. -0.3%), as did body weight (-4.2 kg vs. -0.8 kg). Systolic blood pressure decreased more by oral semaglutide than placebo, and serum low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) levels were modestly lower in patients with oral semaglutide. However, the effects of oral semaglutide on renal function was not investigated in the PIONEER 6. Further, there are no real-world data examining the effects of oral semaglutide on metabolic risk factors.

Materials and Methods

To understand the effects of oral semaglutide on cardiovascular metabolic risk factors, we retrospectively picked up patients who had taken oral semaglutide from March 2021 to June 2022 and compared metabolic parameters at baseline with the data at 3, 6 months after the start of oral semaglutide. The study protocol was approved by the Ethics Committee of the National Center for Global Health and Medicine (NCGM-S-004524-00), and the study was performed in accordance with the Declaration of Helsinki. The information about medical history, medication, demographic and laboratory data were obtained via an electronic medical record.

Statistical analyses were performed by using SPSS version 23. The paired *t*-test was used to statistically analyze comparison in metabolic parameters between before and after the start of oral semaglutide. P value of < 0.05 was considered to be statistically significant. P value of < 0.1 was considered to have tendency.

Results

We found 47 patients who had taken oral semaglutide. Thirty-one patients were treated by daily dose of 7 mg of oral semaglutide, and seven and nine patients were treated by daily dose of 14 mg and 3 mg of oral semaglutide, respectively. Baseline characteristics for patients who had taken oral semaglutide are shown in Table 1. Mean body mass index (BMI) was over 30 kg/m², indicating the inclusion of many obese patients in this study. More than 80% and 70% of patients had been taking sodium-glucose cotransporter 2 (SGLT2) inhibitors and metformin, respectively. Eleven patients had used once-weekly GLP-1 analogues (subcutaneous semaglutide, n = 8; dulaglutide, n = 3). In short, 11 patients had undergone the switching from once-weekly subcutaneous GLP-1 analogues to oral semaglutide. More than 90% of patients had dyslipidemia and 66% of patients had been taking statins. More than 60% of patients had hypertension and approximately 60% of patients had been taking angiotensin receptor blockers.

Changes in metabolic parameters after the start of oral semaglutide in all patients are shown in Table 2. Body weight significantly decreased at 3 and 6 months after the start of oral semaglutide, and systolic blood pressure significantly decreased after 6 months. HbA1c tended to decrease after 3

months and significantly decreased after 6 months. Serum LDL-C levels significantly decreased after 6 months and non-high-density lipoprotein-cholesterol (non-HDL-C) levels tended to decrease after 6 months. Urinary albumin to creatinine ratio (UACR) tended to decrease after 3 and 6 months.

Changes in metabolic parameters after the start of oral semaglutide in patients who had not ever used GLP-1 analogues are shown in Table 3. Body weight significantly decreased at 3 and 6 months after the start of oral semaglutide, and systolic blood pressure significantly decreased after 6 months. HbA1c significantly decreased after 3 and 6 months. Serum TG levels tended to decrease after 3 months and significantly decreased after 6 months. Serum levels of both LDL-C and non-HDL-C significantly decreased after 3 and 6 months. UACR tended to decrease after 6 months.

Changes in metabolic parameters after the start of oral semaglutide in patients who switched from GLP-1 analogues are shown in Table 4. Body weight significantly decreased at 6 months after the start of oral semaglutide, and serum uric acid (UA) levels showed a significant decrease after 3 months. However, diastolic blood pressure tended to increase after 3 months. Further, serum LDL-C levels tended to increase after 3 months, and non-HDL-C levels significantly increased after 3 months. We could not find any differences in HbA1c, TG and UACR at 3 and 6 months after the start of oral semaglutide.

Discussion

The once-daily subcutaneous liraglutide induced a significant reduction of body weight of 2.3 kg after 36 months of the start of liraglutide [3]. In the SUTAIN-6, at week 104, patients receiving 0.5 mg and 1.0 mg lost weight by 3.6 kg and 4.9 kg, respectively [5]. Reduction of body weight by GLP-1 analogues is considered to be associated with the reduction of MACE and CKD progression. The PIONEER 6 showed that body weight decreased more by oral semaglutide than by placebo (-4.2 kg vs. -0.8 kg) [7]. Our study also showed a significant decrease in body weight by -1.2 kg and -2.4 kg after 3 and 6 months, respectively.

In the LEADER trial, systolic blood pressure was 1.2 mm Hg (95% CI: 1.9 - 0.5) lower in the liraglutide group than the placebo group [3]. In the SUTAIN-6, the mean systolic blood pressure in the semaglutide group, as compared with the placebo group, was 1.3 mm Hg lower in the group receiving 0.5 mg (P = 0.10) and 2.6 mm Hg lower in the group receiving 1.0 mg (P < 0.001) [5]. The PIONEER 6 showed that oral once-daily semaglutide significantly reduced systolic blood pressure by 2.6 mm Hg as compared with placebo. Our study also showed a significant decrease of systolic blood pressure by 6.2 mm Hg after 6 months. Reduction of systolic blood pressure by GLP-1 analogues may contribute to suppression of cardiovascular and renal events.

There are only three studies including the PIONEER 6 which investigated the effects of oral semaglutide on serum lipids. Dahl et al studied the effects of oral semaglutide on glucose and lipid metabolism in 15 type 2 diabetic patients [8]. In their study, oral semaglutide reduced fasting and postpran-

Table 1. Baseline Characteristics for Patients Who Had Taken Oral Semaglutide (N = 47)

Clinical characteristics	
Age (years old)	58.2 ± 13.5
Gender (male/female)	25/22
Body weight (mean ± SD, kg)	78.9 ± 17.7
Body mass index (mean ± SD, kg/m ²)	30.5 ± 6.0
Systolic blood pressure (mean ± SD, mm Hg)	133.1 ± 14.1
Diastolic blood pressure (mean ± SD, mm Hg)	77.9 ± 10.6
Comorbidities	
Dyslipidemia (n, %)	43, 91.5%
Hypertension (n, %)	30, 63.8%
Hyperuricemia (n, %)	12, 25.5%
Treatments for type 2 diabetes	
Dipeptidyl peptidase-4 inhibitors (n, %)	30, 63.8%
Metformin (n, %)	35, 74.5%
Sodium-glucose cotransporter 2 inhibitors (n, %)	39, 83.0%
Sulfonylurea (n, %)	8, 17.0%
α-glucosidase inhibitors (n, %)	7, 15.0%
Pioglitazone (n, %)	17, 36.2%
Insulin (n, %)	3, 6.4%
Glucagon-like peptide 1 analogues (n, %)	11, 23.4%
Treatments for hypertension	
Angiotensin receptor blockers (n, %)	28, 59.6%
Calcium antagonists (n, %)	15, 31.9%
Diuretics (n, %)	2, 4.3%
α, β-blockers (n, %)	4, 8.5%
Treatments for dyslipidemia	
Statins (n, %)	31, 66.0%
Ezetimibe (n)	6, 12.8%
Eicosapentaenoic acid (n, %)	6, 12.8%
Pemafibrate (n, %)	5, 10.6%
Fenofibrate (n, %)	1, 2.1%
Treatments for hyperuricemia	
Febuxostat (n, %)	3, 8.9%
Topiroxostat (n, %)	1, 3.3%
Allopurinol (n, %)	2, 4.9%
Dotinurad (n, %)	1, 3.3%

SD: standard deviation.

dial plasma glucose levels and fasting TG, very low-density lipoprotein (VLDL) and apolipoprotein B48 (apoB48) as compared with placebo. Since apoB48 reflects postprandial hyperlipidemia, a decrease of apoB48 indicates an improvement of postprandial hyperlipidemia. Furthermore, since an elevation of VLDL is commonly observed in an insulin resistant-state [9, 10], a decrease of VLDL suggests an improvement of diabetic

dyslipidemia due to insulin resistance. Arai et al studied the efficacy and safety of oral semaglutide in 16 type 2 diabetic patients with non-alcoholic fatty liver disease [11]. In their study, body weight, liver function and HbA1c were significantly improved after 12 weeks. An improvement of insulin resistance and TG was also observed after 24 weeks. Our study showed that oral semaglutide improved diabetic dyslipidemia

Table 2. Changes in Metabolic Parameters After the Start of Oral Semaglutide in All Patients (N = 47)

	N	Baseline	After 3 months	N	Baseline	After 6 months
Body weight (kg)	40	78.9 ± 17.7	77.5 ± 17.9**	25	79.7 ± 19.3	77.3 ± 19.5**
Systolic blood pressure (mm Hg)	41	133.1 ± 14.1	130.1 ± 15.8	25	134.0 ± 14.7	127.8 ± 14.3**
Diastolic blood pressure (mm Hg)	41	77.9 ± 10.6	76.7 ± 11.7	25	77.9 ± 10.6	77.0 ± 12.6
Plasma glucose (mg/dL)	40	179.2 ± 96.1	170.6 ± 57.8	26	183.5 ± 116.2	162.3 ± 63.1
HbA1c (%)	41	8.1 ± 1.5	7.9 ± 1.5*	26	8.4 ± 1.5	7.8 ± 1.5**
AST (IU/L)	41	30.3 ± 17.3	29.0 ± 14.3	28	32.1 ± 19.3	31.0 ± 20.0
ALT (IU/L)	41	43.2 ± 32.5	40.4 ± 27.6	28	45.0 ± 35.0	41.0 ± 35.0
GGT (IU/L)	36	49.5 ± 43.8	45.5 ± 37.1	24	56.3 ± 51.2	53.0 ± 51.0
TG (mg/dL)	39	205.5 ± 129.2	199.0 ± 168.9	26	210.9 ± 137.5	190.2 ± 123.9
HDL-C (mg/dL)	39	52.2 ± 13.5	51.0 ± 11.5	26	50.8 ± 14.1	49.2 ± 13.1
LDL-C (mg/dL)	37	96.8 ± 28.5	92.5 ± 25.6	26	101.0 ± 31.0	91.3 ± 25.5**
Non-HDL-C (mg/dL)	36	128.3 ± 36.6	125.0 ± 36.1	24	132.0 ± 39.6	122.2 ± 31.7*
UA (mg/dL)	39	5.1 ± 1.2	4.9 ± 1.3	27	5.1 ± 1.5	5.1 ± 1.2
eGFR (mL/min/1.73 m ²)	41	80.5 ± 25.3	82.5 ± 25.3	28	80.6 ± 26.8	78.7 ± 26.8
UACR	25	107.9 ± 224.9	62.5 ± 117.4*	14	123.1 ± 255.8	93.9 ± 211.8*

Values were shown as mean ± SD. *P < 0.1, **P < 0.05 vs. baseline. HbA1c: hemoglobin A1c; ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; GGT: gamma-glutamyl transferase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; TG: triglyceride; UA: uric acid; UACR: urinary albumin to creatinine ratio.

such as LDL-C and non-HDL-C in addition to an improvement of HbA1c, which agreed with the result of the PIONEER 6 and the study by Dahl et al. Reduction of body weight, improve-

ments in postprandial glucose/lipid metabolism and insulin resistance by oral semaglutide might have induced decrease in HbA1c, LDL-C and non-HDL-C in our study. The switch-

Table 3. Changes in Metabolic Parameters After the Start of Oral Semaglutide in Patients Who Had not Used GLP-1 Analogues (N = 36)

	N	Baseline	After 3 months	N	Baseline	After 6 months
Body weight (kg)	29	77.2 ± 17.5	75.8 ± 17.8**	19	77.1 ± 17.6	75.0 ± 18.0**
Systolic blood pressure (mm Hg)	30	133.7 ± 15.7	130.3 ± 18.2	19	135.0 ± 16.0	129.3 ± 16.0**
Diastolic blood pressure (mm Hg)	30	78.9 ± 11.4	76.0 ± 11.7	19	79.5 ± 11.3	78.6 ± 13.3
Plasma glucose (mg/dL)	29	188.3 ± 109.6	171.1 ± 59.6	20	189.6 ± 130.3	166.4 ± 71.1
HbA1c (%)	30	8.3 ± 1.3	8.0 ± 1.5**	20	8.6 ± 1.5	7.9 ± 1.6**
AST (IU/L)	30	30.9 ± 19.7	29.0 ± 16.1	22	32.4 ± 21.6	30.2 ± 22.1
ALT (IU/L)	30	43.6 ± 36.6	40.1 ± 30.8	22	43.6 ± 38.3	38.5 ± 38.1
GGT (IU/L)	26	54.0 ± 49.8	49.2 ± 41.6	19	58.9 ± 56.7	53.9 ± 56.2
TG (mg/dL)	28	212.4 ± 137.9	179.3 ± 115.8*	20	218.1 ± 145.0	176.3 ± 100.6**
HDL-C (mg/dL)	28	54.0 ± 14.1	52.2 ± 11.6*	20	53.7 ± 14.4	52.1 ± 12.9
LDL-C (mg/dL)	26	100.6 ± 31.5	90.5 ± 27.6**	20	102.8 ± 33.5	90.3 ± 26.3**
Non-HDL-C (mg/dL)	26	132.8 ± 39.6	121.8 ± 35.5**	18	135.7 ± 42.9	120.1 ± 32.9**
UA (mg/dL)	28	5.0 ± 1.2	5.0 ± 1.2	21	4.9 ± 1.3	4.9 ± 1.2
eGFR (mL/min/1.73 m ²)	30	81.3 ± 24.5	83.1 ± 23.7	22	79.3 ± 25.1	77.4 ± 23.1
UACR	19	101.4 ± 220.9	70.4 ± 132.6	11	148.2 ± 285.8	111.2 ± 238.1*

Values were shown as mean ± SD. *P < 0.1, **P < 0.05 vs. baseline. HbA1c: hemoglobin A1c; ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; GGT: gamma-glutamyl transferase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; TG: triglyceride; UA: uric acid; UACR: urinary albumin to creatinine ratio.

Table 4. Changes in Metabolic Parameters After the Start of Oral Semaglutide in Patients Who Switched From Other GLP-1 Analogues (N = 11)

	N	Baseline	after 3 months	N	Baseline	after 6 months
Body weight (kg)	11	83.5 ± 18.0	81.8 ± 18.4	6	87.8 ± 24.0	84.8 ± 23.7**
Systolic blood pressure (mm Hg)	11	131.5 ± 8.9	129.5 ± 6.4	6	131.0 ± 5.5	123.0 ± 9.2
Diastolic blood pressure (mm Hg)	11	75.1 ± 9.3	78.5 ± 12.0*	6	78.7 ± 10.9	71.8 ± 9.2
Plasma glucose (mg/dL)	11	155.4 ± 39.0	169.3 ± 55.5	6	163.5 ± 49.3	148.7 ± 21.4
HbA1c (%)	11	7.6 ± 1.3	7.8 ± 1.3	6	7.8 ± 1.5	7.6 ± 1.2
AST (IU/L)	11	28.5 ± 7.4	28.7 ± 7.8	6	31.2 ± 7.0	34.2 ± 9.9
ALT (IU/L)	11	42.1 ± 18.6	41.4 ± 16.9	6	50.0 ± 20.1	50.3 ± 18.7
GGT (IU/L)	10	37.6 ± 18.6	35.9 ± 20.4	5	46.2 ± 20.7	49.8 ± 27.1
TG (mg/dL)	11	187.7 ± 107.8	249.2 ± 261.5	6	187.2 ± 117.5	236.8 ± 186.8
HDL-C (mg/dL)	11	47.6 ± 11.1	48.0 ± 11.2	6	41.2 ± 7.5	39.5 ± 8.8
LDL-C (mg/dL)	11	89.2 ± 19.0	97.3 ± 20.3*	6	94.8 ± 21.5	95.0 ± 24.6
Non-HDL-C (mg/dL)	10	116.8 ± 25.4	133.5 ± 38.1**	6	121.0 ± 27.6	129.2 ± 29.7
UA (mg/dL)	11	5.1 ± 1.6	4.8 ± 1.6**	6	5.8 ± 1.8	5.6 ± 1.5
eGFR (mL/min/1.73 m ²)	11	78.3 ± 28.5	80.7 ± 30.5	6	85.3 ± 34.7	83.3 ± 40.7
UACR	6	128.5 ± 257.5	37.4 ± 43.9	3	31.4 ± 27.5	30.4 ± 18.6

Values were shown as mean ± SD. *P < 0.1, **P < 0.05 vs. baseline. GLP-1: glucagon-like peptide 1; HbA1c: hemoglobin A1c; ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; GGT: gamma-glutamyl transferase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; TG: triglyceride; UA: uric acid; UACR: urinary albumin to creatinine ratio.

ing from subcutaneous GLP-1 analogues to oral semaglutide induced elevation in diastolic blood pressure, LDL-C and non-HDL-C, suggesting that subcutaneous GLP-1 analogues may be more effective than oral semaglutide in improving metabolic factors.

The LEADER trial demonstrated that the once-daily liraglutide reduced the new onset of persistent macroalbuminuria as compared with placebo (HR: 0.74; 95% CI: 0.60 - 0.91; P = 0.004). Further, the *post-hoc* analysis of the SUSTAIN 1-7 demonstrated that the once-weekly subcutaneous semaglutide was associated with a significant improvement of UACR [12]. To our knowledge, present study is the first to show that oral semaglutide tended to decrease urinary albumin excretion. Improvements in body weight, blood pressure, insulin resistance, glucose and lipid metabolism, may be associated with an improvement of albuminuria. The SUSTAIN 6 showed a contribution of anti-inflammatory properties of semaglutide to renal protection [1].

Limitations of the study need to be addressed. The number of patients studied is small. This is a cross-sectional study, limiting inferences of causality and its direction.

In conclusion, our study showed that oral semaglutide improved body weight, blood pressure, HbA1c, TG, LDL-C, non-HDL-C and UACR, in type 2 diabetic obese patients, especially, in patients who had not ever used GLP-1 analogues.

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Authors have no financial disclosures to report.

Conflict of Interest

The authors declare that they have no conflict of interest concerning this article.

Informed Consent

Not applicable.

Author Contributions

HY designed the research, and MH, HA and HK collected and analyzed data. HY wrote and approved the final paper.

Data Availability

The data supporting the findings of this study are available

from the corresponding author upon reasonable request.

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