



## Rapid Reduction of HbA<sub>1c</sub> and Weight in Elderly Patient with Type 2 Diabetes (T2D) And Depression by Oral Semaglutide (Rybelsus)

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### Abstract

**Background:** Oral semaglutide (Rybelsus) has been in focus for type 2 diabetes (T2D).

**Case Presentation:** The patient is a 73-year-old male with T2D treated with metformin, Ipragliflozin, and rosuvastatin. He was diagnosed with depression by the Geriatric depression scale (GDS) with a stable condition by mirtazapine. His diabetic control was exacerbated to HbA<sub>1c</sub> 8.8% and weight 63.5kg in Feb 2022.

**Results:** He started to take Rybelsus, and then clinical improvement was found as HbA<sub>1c</sub> 6.9% and weight 57.5kg for 4 months.

**Discussion:** Remarkable effect of HbA<sub>1c</sub> and weight may be from longer fasting time after post-med, and regular lifestyle from the stable psychosomatic situation.

### Keywords

Oral Semaglutide, Rybelsus, Sodium N-(8-[2-Hydroxybenzoyl] Amino) Caprylate, Geriatric Depression Scale, Mirtazapine, Noradrenergic and Specific Serotonergic Antidepressant, Multiple Meta-Analyses of New Generation Antidepressants Study

### Abbreviations

SNAC: Sodium N-(8-[2-Hydroxybenzoyl] Amino) Caprylate; GDS: Geriatric Depression Scale; NASSA: Noradrenergic and Specific Serotonergic Antidepressant; MANGA: Multiple Meta-Analyses of New Generation Antidepressants Study

### Introduction

For decades, diabetes has been rapidly increasing across the world. Especially, elder diabetic patients have multimorbidity leading to poor quality of life (QOL) [1]. At present, approximately half of all T2D patients are elderly people who are 65 < years old [2].

Diabetes has several complications such as macroangiopathy, microangiopathy, frailty, sarcopenia, and so on [3]. Concerning various aspects of T2D, adequate management for diagnosis and treatment has been presented as a guideline by American Diabetes Association (ADA) in Jan 2022 [4].

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Compared with previous medical circumstances, several types of novel oral hypoglycemic agents (OHAs) have been developed in recent years, which may lead to closer to ideal conditions of glucose variability [5].

Furthermore, older diabetic patients often have depression as a psychosomatic problem. As the increasing number of T2D, the applicable management for diabetes and psychosomatic problems has attracted more attention [6]. Depression has been a prevalent mental disorder for the elderly, but its prevalence varies largely for each investigation for the regional district, culture, and screening tool. Global prevalence was studied for systematic review including 48 studies during 2000-2021 [7]. As a result, globally depression prevalence was 28.4% for the elderly, associated with various heterogeneity. Related factors included screening tool, study quality, sample size, geographic region, and representativeness [8]. From detailed reviews of depression batteries, Geriatric Depression Scale (GDS) shows a valid and reliable screening method for measuring depression degree in elderly people [9]. Further, GDS seems to be sensitive for evaluating elderly people with mild to moderate degrees of physical impairment and dementia. GDS has a short form which is useful for time and various situations.

For pharmacological therapy for T2D, several types of agents have been observed [10]. They include sodium-glucose cotransporter 2 inhibitor (SGLT2i) [10,11], and glucagon-like-peptide 1 receptor agonist (GLP1-RA) [12,13]. As one of the recent medical topics, oral semaglutide (Rybelsus) has been introduced to clinical practice [14]. Authors and our diabetic team have presented various reports concerning T2D so far [15-17]. We experienced a T2D case, which showed an impressive background and clinical progress. The situation and some discussion would be described in this article.

### Case Presentation

#### *History and Physicals:*

The patient is a 73-year-old male with T2D. In the past, he worked in an office in the construction industry. After his retirement at 65 years, he was

pointed out to have hyperglycemia. He has developed depressive symptoms since autumn 2017 and was hospitalized for the treatment of depression in May-August 2018. He had been rather stable with the prescription of mirtazapine (Reflex<sup>®</sup>) for about a year. He tended to remain almost still in his home, and rarely go outside for walks, shopping, or other purposes.

In Sept 2019, he visited our hospital for a check-up for general health and medical problems. The biochemical exam showed HbA1c of 9.9%, and then SulfonylUrea (glimepiride) was administered. As a result, HbA1c was decreased in the short term, and glucose control was stable during 2020. However, HbA1c and body weight gradually increased from the summer of 2021. In Jan-Feb 2022, his condition increased to 8.8% and 63.5kg.

#### *Several Examinations:*

His blood tests on Jan 2022 were as follows: AST 24 U/L, ALT 15 U/L, ALP 51 U/L (100-340), GGT 20 U/L, TP 7.3 g/dL, LDL 118 mg/dL, HDL 54 mg/dL, TG 116 mg/dL, CRP 0.44 mg/dL, Hb 16.4 g/dL. Detail blood test has been performed twice per year.

Other tests were conducted from Oct 2021 to Feb 2022. Chest X-ray revealed negative results, and Electrocardiogram (ECG) was within normal limits with no ST-T changes. He checked the tests for peripheral artery disease (PAD) twice in Oct 2020 and Oct 2021. The results showed the following: ankle-brachial index (ABI) was 1.17/1.13 and 1.24/1.21, and brachial-ankle pulse wave velocity (baPWV) was 1677/1763/1703 and 1759/1783 (normal range <1600) for right/left, respectively.

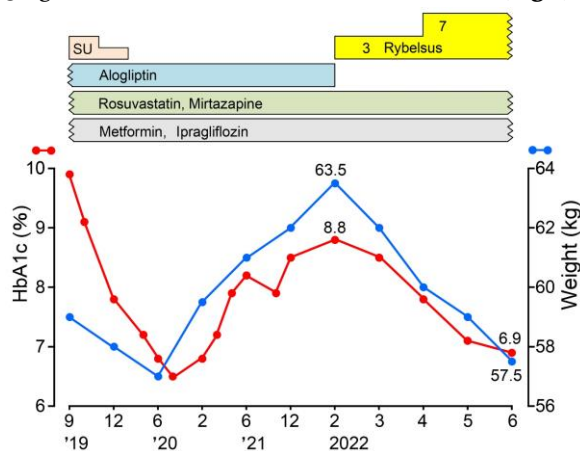
As to the examination of depression, the Geriatric depression scale short version (GDS-15) has been well-known. The case showed more than 11 points in 2017-2018 before admission to the hospital, 6-8 points after discharge, and 3-4 points at present. The evaluation of GDS-15 reveals normal 0-4, light depression 5-10, and heavy depression 11-15 points, respectively.

#### *Clinical Progress:*

Since HbA1c was proved to be of higher value, he

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started to be provided oral semaglutide (Rybelsus) 3mg from Feb 2022 as GLP-1RA (Fig-1).



**Fig-1: Clinical progress of the case with HbA<sub>1c</sub>, weight and treatments**

Simultaneously, alogliptin was discontinued as a dipeptidyl peptidase-4 inhibitor (DPP-4i). After 8 weeks, the dose was increased to 7mg/day. The values of HbA<sub>1c</sub> and body weight were reduced enough to 6.9% and 57.5kg in June 2022. The effects of the decrease of HbA<sub>1c</sub> and weight showed 1.9% and 6 kg during 4 months. As regards to laboratory examinations, liver, renal, lipid, and complete blood count (CBC) results revealed no remarkable changes in the recent two years (Table-1).

### Ethical Considerations:

The present report is fundamentally conducted with the principles of ethics for the Declaration of Helsinki. Furthermore, several comments were accompanied by

the Ethical Guideline in Human Research. These guidelines are also consistent with Good Clinical Practice (GCP). Authors et al. established the ethical committee for this study. This committee is present in Hayashi hospital with several professionals. Their members include the hospital president, physicians, pharmacists, and legal specialists. As to the meeting of the committee, a satisfactory discussion was performed. As a result, full agreements were given according to this protocol. The informed consent was taken from the patient as a document.

### Discussion

Recent research development has brought the clinical introduction of oral semaglutide (Rybelsus) [14]. It was due to the application of absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) that enabled the oral administration of the peptide [18,19]. As a matter of fact, oral semaglutide could reveal clinical efficacy and cardiovascular safety, which equals the subcutaneous route [20]. Consequently, SNAC is expected to develop a further drug delivery system (DDS) in the future [21].

In this case, administration of Rybelsus markedly reduced HbA<sub>1c</sub> and body weight for 4 months, indicating excellent clinical efficacy. Several reasons may be present, which are i) he could take the medicine regularly every morning, ii) he has continued the lifestyle with rare breakfast, iii) he can keep fasting

**Table-1: Changes in the main biochemical data**

Category	Test	2000	2021	2021	2022	Unit
		July	January	July	January	
Liver	GOT	20	22	20	24	(U/L)
	GPT	10	12	12	15	(U/L)
	ALP	93	120	40	51	(U/L)
	GGT	19	27	21	20	(U/L)
	TP	7.0	7.3	7.2	7.3	(g/dL)
Renal	Cre	0.88	1.01	1.03	1.04	(mg/dL)
	eGFR	64.7	56.9	55.0	54.0	(mL/min/1.73m <sup>2</sup> )
Lipids	LDL	185	117	123	118	(mg/dL)
	HDL	58	61	50	54	(mg/dL)
	TG	104	97	109	116	(mg/dL)
Others	Hb	14.3	15.5	15.7	16.4	(g/dL)
	CRP	0.02	0.28	0.11	0.44	(mg/dL)

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90-120 min post-med. When the fasting period becomes more, the blood concentration is increased from several experimental data of Rybelsus [22]. When comparing the blood concentration of semaglutide, 0.80 for 30 min fasting and 1.39 for 120 min fasting [23].

The current case was also diagnosed as depression for years. Several reports have been found about diabetes and depression. Comorbidity of diabetes and depression has been well-known. A systematic review was performed for 5 years [24]. As a result, the prevalence rate for depression showed >3 times more in T1D (12% vs 3.2%), and about twice higher in T2D (19.1% vs 10.7%). Regarding sex differences, females (with and without diabetes) showed a higher prevalence of depression than males. Further, regarding the relationships between diabetes, depression, and dementia, a systematic review was conducted over 6 years [25]. The protocol included Embase, PubMed, and PsycINFO, and 10 articles from 19 papers were analyzed. Cases with both diabetes and depression showed larger declines for behaviors that were expressed by the standardized mean difference (SMD). They were executive function -0.39, language -0.80, memory -0.63, overall cognition -0.77, and greater dementia risk (HR 1.82) than patients with only diabetes.

He has been treated for depression, and his symptom was stable for intake of Mirtazapine 15mg per day. Mirtazapine (Reflex<sup>®</sup>) has been developed as a Noradrenergic and Specific Serotonergic Antidepressant (NaSSA). As to mirtazapine, a systematic review and meta-analysis were found by the Multiple Meta-Analyses of New Generation Antidepressants (MANGA) Study Group [26]. Relative risk (RR) of response was analyzed. Compared to the tricyclics for a short-term response, no significant differences were found. In contrast, mirtazapine showed superiority over SSRIs in terms of both the response (RR 1.36) and remission (RR 1.68).

As mentioned above, mirtazapine has been widely used in the world. Its characteristic aspects include the following: i) reduction of depression and anxiety in the light of serotonin axis, ii) improvement of motivation and energy in the light of the noradrenaline axis, and

iii) promotion of appetite and sleep from anti-histamine effect [27]. For acute phase therapy of depression, antidepressive agents were compared by search of Cochrane data [28]. From 4974 cases in 29 RCT reports, clinical response for a short period between mirtazapine and tricyclics/SSRI showed no significant difference. However, mirtazapine seemed to bring more somnolence, appetite, and weight gain than SSRIs, but less nausea, vomiting, or sexual dysfunction.

Some limitations may be present in this report. This case is a 73-year-old male with T2D and depression [29]. He showed clinical efficacy of mirtazapine and oral semaglutide for his physical and psychosomatic improvement. However, adverse effects of mirtazapine may increase his body weight, leading to aggravation of diabetes. Several related factors exist in his clinical progress and then follow-up with close attention will be required for future courses.

In summary, this case showed impressive progress in the light of T2D, Rybelsus, depression, mirtazapine, and others. We hope that these data would become a reference for developing clinical practice and research in the future.

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## Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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