

Glucagon-like peptide-1 receptor agonists as an effective therapeutic agent for diabetes mellitus and obesity in patients with schizophrenia under treatment with second-generation antipsychotics

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Objectives: Cases of schizophrenia are commonly complicated with obesity and diabetes mellitus partially caused by excessive eating associated with the use of second-generation antipsychotics (SGAs). We aimed to study the efficacy of glucagon-like peptide-1 in patients with schizophrenia under treatment with SGAs.

Methods: Diabetic patients with schizophrenia were included if their HbA1c levels increased more than 1% and/or their weight increased more than 3 kg after treatment with SGAs. Patients who developed diabetes after treatment with SGAs were also included. The participants were treated with GLP-1 receptor agonists for one year, and their changes in weight and HbA1c and any adverse events were evaluated.

Results: Seven patients were treated with GLP-1 receptor agonists; their mean age was 46.1 yrs old (range; 26 to 59), mean body weight was 85.3 kg (65.5 to 96.8), and mean BMI was 33.8 (27 to 38.7). Five of them showed improvement in their HbA1c levels of 1.2% (0.1 to 3.4, $p=0.089$) with a weight loss of 3.7 kg (-9.6 to +3.5, $p=0.14$) on average. The adverse effects observed were all gastrointestinal, but were not severe enough to cause termination of the GLP-1 receptor agonist treatment. The GLP-1 receptor agonist was not effective in one patient, and another patient terminated the treatment in a few months.

Conclusions: Although the number of patients studied was small, GLP-1 receptor agonists seem to be effective for treating diabetes and bringing about weight loss in patients with schizophrenia under treatment with SGAs.

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Key words: GLP-1 receptor agonist, second-generation antipsychotics, schizophrenia, weight gain

Introduction

Schizophrenia (SZ) is a common psychiatric disorder, and patients with SZ are known to live shorter lives and be frequently complicated with non-psychiatric diseases (1,2). Patients with SZ are known to develop obesity more commonly than those without SZ (~60% vs. 20-30%) (3). Obesity may be mediated by illness-related factors, such as the decreased motivation and limited social interactions seen in SZ patients

(4), and also by the antipsychotics used to treat SZ (1,2).

Antipsychotics are known to cause various adverse metabolic effects including obesity, diabetes, and dyslipidemia (5-7). Second-generation antipsychotics (SGAs) such as clozapine and olanzapine can interact with serotonin and histamine receptors, leading to appetite enhancement and weight gain of up to 2 kg per month, and are responsible for the development of diabetes, probably due to their diabetogenic actions (8-10). SGAs are defined as one of the risk

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factors for diabetes, while SZ is defined as an independent risk factor for diabetes in the practical guidelines of the Canadian Diabetes Association (11). The prevalence of diabetes among SZ patients has been shown to increase under chronic medical treatment for SZ (12). Thus, the medical treatment of SZ may be hampered by the adverse effects of obesity and obesity-related disorders including diabetes mellitus.

Glucagon-like peptide-1 (GLP-1) receptor agonists were recently introduced as anti-diabetic agents. These drugs are known to enhance insulin secretion and also to suppress glucagon following food intake (13,14). GLP-1 receptor agonists are also known to suppress appetite (15,16). Thus, treatment with GLP-1 receptor agonists can improve diabetes while reducing weight. GLP-1 receptor agonists were also recently shown to be effective for weight reduction in a limited number of patients with hypothalamic hyperphagia and obesity (17-19), in whom overeating and obesity can be caused by refractory appetite associated with hypothalamic lesions (20,21). These findings may indicate that hyperphagia may be effectively treated with GLP-1 receptor agonists in SZ patients under treatment with SGAs. It has been reported that a single SZ patient with weight gain and diabetes was successfully treated with a GLP-1 receptor agonist (22). GLP-1 receptor agonists were very recently used to treat weight gain in patients with SZ without diabetes (23). More recently, Larsen et al. showed liraglutide, one of the GLP-1 receptor agonists, was effective in improving glucose tolerance and obesity in patients with schizophrenia spectrum disorder under treatment with clozapine or olanzapine, but the participants were not with overt diabetes (24). Here we show our findings regarding the use of GLP-1 receptor agonists to treat SZ patients with obesity and type 2 diabetes undergoing treatment with SGAs.

Patients

We recruited patients with SZ under treatment with SGAs with diabetes mellitus in Koseikai Michinoo Hospital from April 2014 to April 2015. The inclusion criterion were the patients' SZ being stable as judged by their psychiatrists and under medical treatment including SGAs (risperidone, aripiprazole, perospirone, and blonanserin), with an increase in HbA1c of more than 1% and/or a body weight gain of more than 3 kg if the patients had diabetes, or having developed diabetes after treatment with SGAs. Patients with age less than 18 years old, eating disorders, type 1 diabetes, pregnancy, or malignancy were excluded from the study. It should be noted that the atypical antipsychotics quetiapine and olan-

zapine are contraindicated for those with diabetes mellitus in our country. Out of 18 candidate patients with SZ, 10 were excluded from the study. The reasons the 10 patients were excluded were as follows: 5 did not agree to the study protocol, 3 were without diabetes, 1 was without weight gain, and 1 was not included because of a history of anorexia nervosa. Eligible patients were given a detailed explanation of the study protocol and the method for self-injecting GLP-1 receptor agonists. Written informed consent was obtained by each patient before participation. One of eight patients treated with GLP-1 receptor agonists was excluded as he was found to be complicated with primary hypothyroidism. The study protocol was approved by the local ethical committee.

Study Protocol

This was a one-year prospective non-randomized study to assess safety and efficacy of GLP-1 receptor agonists in treatment of diabetes in patients with SZ. After each patient's clinical history of SZ and diabetes mellitus, body weight, and laboratory data including HbA1c (NGSP) and lipid profiles were evaluated, the patients were treated with GLP-1 receptor agonists. The GLP-1 receptor agonist used was either liraglutide, exenatide, or long-acting exenatide (exenatide-LAR), and the choice of the GLP-1 receptor agonist was made by discussion with each patient about the frequency of injection and potential side effects of each reagent. Patients who preferred to receive the GLP-1 receptor agonist in the hospital, but not by self-injection, were allowed to choose exenatide-LAR if he/she could visit hospital once a week. Patients were advised to increase the dose of liraglutide from its starting dose of 0.3 mg by 0.3 mg every week up to 0.9 mg. It should be noted that the maximal dose of liraglutide approved in our country is 0.9 mg a day. The doses of exenatide used (10 or 20 µg a day) were adjusted by an investigator (TA) based on the glycemic control and adverse events. The dose of exenatide-LAR was a fixed dose of 2 mg per week. Other diabetic medications were allowed to change if hypoglycemia (plasma glucose ≤ 60 mg/dL) occurs or hyperglycemia (HbA1c $> 7\%$) continues. Participants were planned to visit the hospital at least once a month to have their body weight measured and to have blood tests performed to evaluate the treatment status of their diabetes mellitus. However, most of the participants visited the hospital every two weeks. Blood glucose levels were measured by using a glucose meter to ensure stability of diabetes during the study in patients under insulin therapy. After one-year study period, they were allowed to continue the GLP-1 receptor agonist treatment or

to switch to another treatment depending on the treatment status of his/her diabetes. SGAs can be titrated or switched if considered necessary by psychiatrists.

GLP-1 responders were defined as those who maintained an HbA1c of $\leq 7\%$ if their pretreatment HbA1c level was $\leq 7\%$ or who improved their HbA1c level $\geq 1\%$ if their pretreatment HbA1c was $> 7\%$. Patients who did not fulfill these criteria were defined as non-responders. Patients were allowed to add other anti-diabetic agents if his/her HbA1c remained $> 7.0\%$ and were also allowed to add or switch to insulin treatment if it was considered impossible to treat his/her diabetes using mainly GLP-1 receptor agonists.

Adverse effects of GLP-1 treatment

Potential adverse effects during GLP-1 receptor agonist treatment were monitored at every visit. Psychological events observed during GLP-1 receptor agonist treatment were recorded in the medical record. Mental status was also assessed by the Brief Psychiatric Rating Scale (BPRS) upon participation in the study, and at 3, 6, and 12 months after the initiation of GLP-1 receptor agonists in most of the participants.

Results

We were able to include 7 patients with SZ who gained weight and/or developed/exacerbated diabetes mellitus while under medical treatment with SGAs (Tables 1 and 2). The mean age of the participants was 46.1 yrs old (range; 26 to 59) with a mean body weight of 85.3 kg (range; 65.5 to 96.8) and a mean BMI of 33.8 (range; 27 to 38.7). These patients gained significant weight and developed/exacerbated diabetes mellitus after atypical psychotics use. It should be noted that all the participants were under SGAs for longer than 4 years. The disease duration of diabetes mellitus was relatively short in some of the patients, and the precedent anti-diabetic reagents used were mainly DPP-4 inhibitors. Four of the participants were treated with liraglutide (0.9 mg a day), two with exenatide (20 ug a day), and one with exenatide-LAR (2 mg per week). The atypical antipsychotics used were continued with dosage adjustments throughout the year.

We monitored HbA1c as a hallmark of the GLP-1 receptor agonist treatment. We found that five patients were GLP-1 responders, with an improvement in HbA1c of 1.2 % on average (range; 0.1 to 3.4) (Table 1). In contrast, one patient

had no apparent benefit from GLP-1 receptor agonists, and one patient stopped her GLP-1 receptor agonist treatment by herself (Table 2). Four of the five GLP-1 responders also showed reductions in body weight. There was a rebound weight gain in one of the responders (patient 1 in Table 1). The anti-diabetic drugs concomitantly used were metformin in one and metformin plus basal insulin in the other (patient 1 and 3 in Table 1). Five subjects, including two non-responders, were treated only with GLP-1 receptor agonists.

When the maximal reductions in HbA1c and weight caused by GLP-1 receptor agonists were compared to data obtained before the GLP-1 receptor agonist treatment among GLP-1 responders, there were no significant differences in HbA1c ($p=0.089$) or body weight ($p=0.14$). There were no remarkable changes in the lipid profiles of the responders (data not shown).

The adverse effects associated with GLP-1 receptor agonists were all gastrointestinal (Tables 1 and 2) and mainly observed within one month of the initiation of GLP-1 receptor agonists, and these were not severe enough to terminate the GLP-1 receptor agonist treatment. We also observed psychiatric events, such as wrist cuts and mental irritability. These events did not reoccur during the study period and had been observed before the GLP-1 receptor agonist treatment. Thus, we did not consider these psychiatric events were related to GLP-1 agonist treatment. There were no remarkable differences in BPRS. It should be also noted that the doses of SGAs used were not increased during the study period and rather decreased in some patients (Tables 1 and 2).

Discussion

We administered GLP-1 receptor agonists to SZ patients under treatment with SGAs as a therapy for diabetes mellitus. We showed that the HbA1c improved and the body weight decreased in most of the patients, although the difference did not reach statistical significance. The adverse events observed were those commonly seen in diabetes patients without SZ, and the psychiatric events observed during the study did not seem to be related to the GLP-1 receptor agonist treatment. There was no apparent exacerbation of SZ in our patients.

There may be several possible ways to counteract weight gain in patients with SZ under treatment with atypical psychotics. It has been shown that weight loss can be achieved by a strict program involving diet and intensive physical training during hospitalization (4) or during short treatment periods (25). However, the maintenance of such an ideal lifestyle for longer periods would be challenging. Anti-obe-

sity drugs such as topiramade and sibutramine are shown to reduce body weight marginally (up to 2.5 kg), but with an exacerbation of psychiatric symptoms in some reagents, according to a recent meta-analysis (26). SGAs can be changed to other antipsychotics that are known to cause less of an increase in weight as recommended by clinical guidelines (8). However, the clinical effectiveness of SGAs may make such a decision difficult.

GLP-1 receptor agonists have been repeatedly shown to be effective to reduce body weight in individuals with or without diabetes mellitus (27,28). It has been shown very recently that exenatide-LAR was ineffective for reducing body weight in obese patients with SZ without diabetes (23). This was because similar weight loss was observed in a placebo group for unknown reasons. Larsen et al. (24) showed their promising data that liraglutide was effectively normalizing glucose intolerance and reducing body weight among SZ spectrum disorder with prediabetes and $BMI \geq 27$, but the duration of the study was relatively short (16 weeks). These findings suggested GLP-1 receptor agonists as effective reagents in SZ patients with obesity and prediabetes under SGAs. However, it remained unclear if it was the case in SZ patients with overt diabetes. Although the number of patients included was very small, our data suggested that GLP-1 receptor agonists seemed to be also useful for controlling obesity and diabetes mellitus in SZ patients under treatment with SGAs. Since we did not include control patients who were administered a placebo, we cannot exclude the possibility that the weight loss seen in our patients might have been related to placebo effects. Additional studies will be needed to assess the effect of GLP-1 receptor agonists on weight reduction in SZ patients with overt diabetes.

We experienced a patient in whom the clinical effects of the GLP-1 receptor agonist lasted less than one year in our study (patient 1). Although we did not try, it may be possible to switch to other anti-obesity reagents including topiramade and sibutramine temporarily, and then switch back to GLP-1 receptor agonists to utilize their anorectic effects maximally, as the switching of anti-obesity reagents is recommended in the guideline (29). We also had a patient who showed almost no benefits from the GLP-1 receptor agonist (patient 6). Hyperphagia apparently continued in the patient, since her body weight kept increasing while her HbA1c increased during the study. It was only possible to improve her weight and diabetes during a hospitalization she underwent after the study. Although the precise reasons for GLP-1 non-responsiveness in this patient were not known, we previously reported that one-third of diabetes patients treated with GLP-1 receptor agonists were GLP-1 non-responders (30). There-

fore, we consider that this phenomenon is not specific to patients with SZ.

GLP-1 receptor agonists might have unexpected psychiatric effects in patients with SZ. This study suggested that GLP-1 receptor agonists can be safely used in SZ patients with diabetes, although we observed some psychiatric events during the GLP-1 receptor agonist treatment. These events had been observed even before GLP-1 receptor agonist treatment began, and thus we did not consider them to be related to the GLP-1 receptor agonist treatment, as has also been shown by others (23). This might be supported by the reduction of SGAs doses in SZ patients who had psychiatric events.

The limitations of this study were the small number of the participants and the patients were treated with different kinds of GLP-1 receptor agonists. This study also lacked the control cohort. In addition, liraglutide used in our study was not the maximal dose allowed in the other countries and this might have influence the results of the study.

In conclusion, SZ patients under treatment with SGAs may be treated safely and effectively with GLP-1 receptor agonists for the purpose of improving their diabetes and losing weight. It would be also important to see if the psychiatric events seen in our study can be observed in other study. Since the number of patients included was limited without controls, an additional study with a prospective design is mandatory to confirm our findings.

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Table 1: GLP-1 responders among patients with schizophrenia treated with GLP-1 receptor agonists

Pt	1		2		3		4		5		
Age/sex	49/F		41/F		47/F		54/M		59/M		
Duration of SZ (yrs)	14		9		20		25		30		
Duration of DM (yrs)	2		2.5		10		3		Newly diagnosed		
Bw change	+17 kg in 1 yr		+14.5 kg in 4 yrs		-3 kg loss in 1 yr		+8 kg in 3 yrs		+8.5 kg in 4 yrs		
Increase in HbA1c	+1.1 % in 1 yr		0 % in 1 yr		+2.2 % in 1 yr		+0.5% ? in 1 yr		Not available		
Duration of GLP-1 treatment	^{1)Pre}	^{2)Max}	^{3)Post}	Pre	Max/Post	Pre	Max/Post	Pre	Max/Post	Pro	Max/Post
Bw	0	7	12	0	12	0	12	0	12	0	12
BMI	87.2	81.9	84.2	96.8	87.2	65.5	69	73.3	69.8	98.5	94
HbA1c	36.9	35.0	36.0	36.4	32.4	27	28	29	27.6	35.7	34.1
GLP-1 receptor agonist used	Exenatide (20ug)		Liraglutide (0.9 mg)		Liraglutide (0.9 mg)		Exenatide-LAR (2 mg)		Liraglutide (0.9 mg)		
SGAs used											
Before GLP-1	ARI (24mg), RIS (3mg)		ARI (30mg), RIS (8mg)		RIS (3mg)		ARI (24mg)		RIS (3mg)		
After GLP-1	ARI (18mg)		ARI (24mg), RIS (4mg)		RIS (2mg)		ARI (24mg)		RIS (3mg)		
Anti-diabetic medication											
Before GLP-1	None		SG (25mg)		Gla (6 U), GM (2 mg),		VG (100mg)		None		
Along with GLP-1	None		None		LG (5mg), MET (750 mg)		None		None		
Adverse effects											
GLP-1 related	Nausea, Diarrhea		None		None		None		None		
Psychiatric	Wrist cuts		Mental irritability		None		None		None		
BPRS	27	25	29	27	24	28	31	ND	ND	38	37

The clinical courses of five patients with schizophrenia under treatment with SGAs and with diabetes mellitus treated with GLP-1 receptor agonists are shown. ^{1)Pre} indicates pretreatment. ^{2)Max} indicates when the maximum effects were seen in body weight and HbA1c. ^{3)Post} indicates after one year of treatment with GLP-1 receptor agonist in patient 1. The dose per day of each reagent is shown in the parenthesis.

Abbreviations used: SZ, schizophrenia, SGAs; second-generation antipsychotics, DM; diabetes mellitus, Bw; body weight, BMI; body mass index, ARI; aripiprazole, RIS; risperidone, SG; sitagliptin, LG; linagliptin, MET; metformin, Gla; insulin glargine, GM; glimepiride, VG; vildagliptin, BPRS; brief psychiatric rating system, ND; not done.

Table 2: A GLP-1 non-responder and a patient who dropped out

Pt	6			7	
Outcome	Non-responder			Dropped out	
Age/sex	47/F			26/F	
Duration of SZ (yrs)	19			10	
Duration of DM (yrs)	7			Newly diagnosed	
Bw change	+7.4 kg in 1 yr			+35 kg in 6 yrs	
Increase in HbA1c	+2.9 % in 1 yr			Not available	
	¹ Pre	² Max	³ Post	Pre	⁴ Post
Duration of GLP-1 treatment	0	1	12	0	2
Bw	82.5	85.2	88.2	93	91.1
BMI	33	34.1	35.3	38.7	37.9
HbA1c	7.9	6.0	10.1	6.8	5.7
GLP-1 receptor agonist used	Exenatide (20ug)			Liraglutide (0.9mg)	
SGAs used					
Before GLP-1	RIS (4mg)			RIS (1mg), ARI (6mg)	
After GLP-1	RIS (4mg)			ARI (6mg)	
Anti-diabetic medication					
Before GLP-1	SG (50mg)			None	
Along with GLP-1	None			None	
Adverse effects					
GPL-1 related	None			Constipation	
Psychiatric	None			Insomnia	
BPRS	27	ND	28	28	ND

Clinical courses of two patients with schizophrenia under treatment with SGAs and with diabetes mellitus treated with GLP-1 receptor agonists are shown.

¹Pre indicates pretreatment. ²Max indicates when the maximum effects were seen in body weight and HbA1c. ³Post indicates after one year of treatment with GLP-1 receptor agonists. ⁴Data shown are obtained last time the patient visited us to have diabetes treatment. The dose per day of each reagent is shown in the parenthesis.

Abbreviations used: SZ; schizophrenia, SGAs; second-generation antipsychotics, DM; diabetes mellitus, Bw; body weight, BMI; body mass index, ARI; aripiprazole, RIS; risperidone, SG; sitagliptin, BPRS; brief psychiatric rating system, ND; not done.

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