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Oral Semaglutide for the Treatment of Patients of Type 2 Diabetes with Non-Alcoholic Fatty Liver Disease and Antipsychotic-Associated Weight Gain (AAWG) Not Responding to Metformin – A Case Series

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INTRODUCTION

Prevention and treatment of type 2 diabetes and obesity are problematic for individuals with schizophrenia and other patients on antipsychotic therapy because atypical antipsychotics and mental distress themselves increase appetite, thus promoting subsequent body weight gain and deterioration of glycaemic control. Almost half of patients with schizophrenia have body mass index (BMI) ≥ 25- and 2.5-times higher risk of developing T2D compared to healthy individuals [1]. Antipsychotic (AP) drugs are the cornerstone treatment for schizophrenia and are commonly used for other psychiatric disorders. However, they are associated with severe metabolic adverse effects, including weight gain, dyslipidaemia, and insulin resistance [2]. Particularly, insulin resistance and type 2 diabetes mellitus (T2DM) induce Non-alcoholic fatty liver disease (NAFLD) onset, deterioration of liver inflammation/fibrosis, and development of hepatocellular carcinoma. Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease, accounting for approximately 25% of chronic liver disease cases worldwide [3].

Antipsychotic-associated weight gain (AAWG) has been reported as the most distressing medication-related side-effects; [4] it is associated with poor quality of life [5] and interventions leading to even modest weight loss (i.e. 5% of body weight) has been shown to reduce the cardiometabolic risk in people with type 2 diabetes (T2D) [6] . Even though obesity is highly prevalent and adds significantly to the burden of mental illness, there is a lack of effective treatment options, and metabolic comorbidity remains vastly undertreated [7,8].

There are several pharmacological interventions currently available for adjunctive treatment of AAWG, metformin demonstrates a good safety profile and is not associated with increased dropout rates as compared to placebo. Despite safety profile, and established weight loss properties of metformin in AAWG, published data from a multisite randomized control trial (RCT) show that only approximately 17% of patients lose ⩾5% body weight with metformin, leaving a large majority of patients with unclear subsequent options [9]. Glucagon-like peptide 1-receptor agonists (GLP 1RA)s like liraglutide, exenatide, and the most recent addition, semaglutide, are a newer class of drugs with proven efficacy in the management of obesity in the general population [10].While semaglutide's weight loss properties have been investigated extensively in the general population with obesity and weight-related comorbidities, no studies have investigated semaglutide's efficacy in the mentally ill diabetic patients particularly in reference to NAFLD. In this case series, we retrospectively evaluate the effectiveness of semaglutide for the treatment this group of diabetic population with AAWG and NAFLD in a naturalistic clinical setting.

METHOD

Participents

Charts of all patients attending the VIMHANS JAIPUR, between NOV 2023 and NOV 2024 were reviewed to identify patients who were initiated on ORAL semaglutide, In preference we selected those patients in whom semaglutide was initiated for the first time for T2DM with hemoglobinA1c (HbA1c) levels ≥6.5% despite dietary/exercise therapies and /or other antidiabetic drugs and revealing failure to respond metformin (defined as less than 5% weight loss in 3 months or continuing to meet criteria for metabolic syndrome at the end of 3 months) and fatty liver was diagnosed on their routine ultrasonography abdomen. These Patients were on a stable dose of AP medication (>3 months) and met criteria for adjunctive pharmacological interventions [body mass index (BMI) > 27 kg/m^2 with obesity-related comorbidities like high blood pressure, dyslipidemia, or dysglycemia, or BMI ⩾ 30 kg/m^2, or meet criteria for metabolic syndrome].Such 10 diabetic patients on antipsychotic treatment were selected with NAFLD who received oral semaglutide treatment for the first time for T2DM with hemoglobin A1c (HbA1c) levels ≥6.5% despite dietary/exercise therapies and/or other antidiabetic drugs.

NAFLD was diagnosed by (i) evidence of fat deposition on ultrasonography; (ii) daily alcohol consumption of <30 g for men and <20 g for women; and (iii) absence of other chronic liver diseases, such as viral hepatitis B or C, autoimmune hepatitis, primary biliary cholangitis, Wilson's disease, and hemochromatosis.

The main exclusion criteria were as follows: (i) age <20 years; (ii) new administration of vitamin E or antidiabetic drugs within 12 weeks prior to oral semaglutide treatment; (iii) weight loss ≥5% within 12 weeks prior to oral semaglutide treatment; (iv) decompensated cirrhosis; and (v) pregnancy or lactation.

The participants received oral semaglutide treatment over 24 weeks. Treatment was initiated at a dose of 3 mg once daily for the first 4 weeks, after which the dose was increased to 7 mg daily for the next 4 weeks, followed by an increase to 14 mg daily for another 4 weeks, all the while monitoring for any adverse events. The dose was then maintained at 14 mg daily for the remaining 12 weeks of the study.

No changes in antidiabetic or anti-dyslipidemic medications including dosage were made during the observation period .

Clinical and laboratory data

Clinical and laboratory data were collected at the midpoint (12 weeks) and the conclusion (24 weeks) of the treatment. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Laboratory analyses included complete blood count, routine liver biochemistry (aspartate aminotransferase [AST], alanine aminotransferase [ALT], albumin, and gamma glutamyl transpeptidase [γ-GTP]), kidney biochemistry (urea nitrogen, creatinine, and estimated glomerular filtration rate), fasting lipids (triglyceride, high-density lipoprotein [HDL] cholesterol, and low-density lipoprotein [LDL] cholesterol), diabetes-related tests (fasting plasma glucose, HbA1c, and immunoreactive insulin), and uric acid.

Laboratory analyses included complete blood count, routine liver biochemistry (aspartate aminotransferase [AST], alanine aminotransferase [ALT], albumin, and gamma glutamyl transpeptidase [γ-GTP]), kidney biochemistry (urea nitrogen, creatinine, and estimated glomerular filtration rate), fasting lipids (triglyceride, high-density lipoprotein [HDL] cholesterol, and low-density lipoprotein [LDL] cholesterol), diabetes-related tests (fasting plasma glucose, HbA1c, and immunoreactive insulin), and uric acid.

The fibrosis-4 (FIB-4) index was calculated to estimate the degree of liver fibrosis, as previously reported [11], Liver stiffness measurement (LSM) [12] and controlled attenuation parameter (CAP) were assessed through transient elastography , using FibroScan 502 equipped with the M-probe (Echosens SA, Paris, France) at the initiation and 24 weeks of oral semaglutide treatment **(Figure-1).**

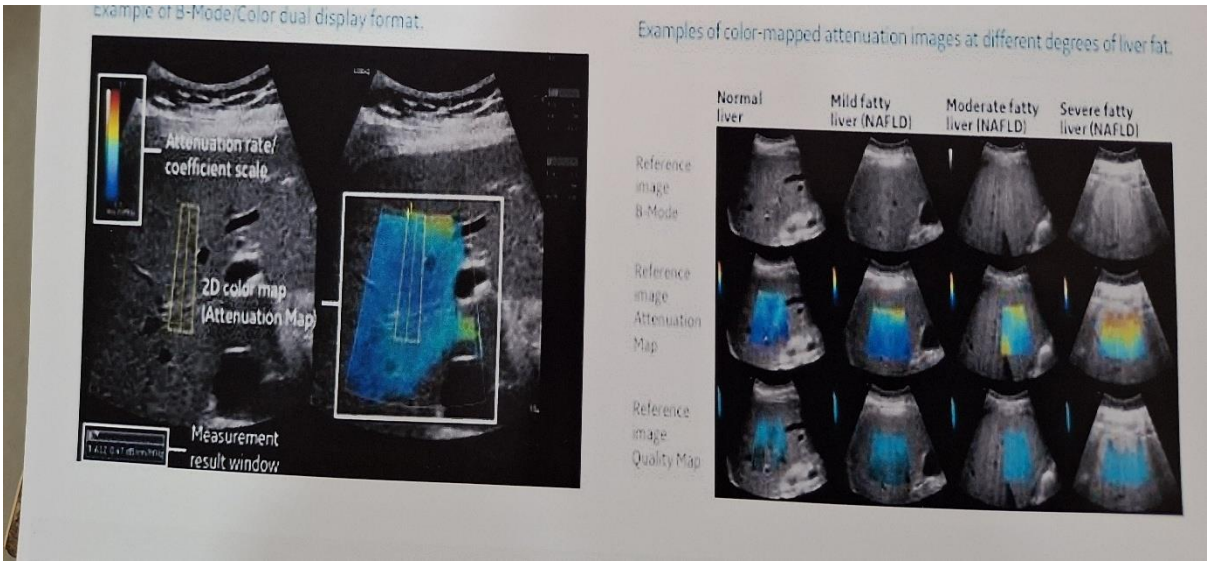

Figure 1. Attenuation Image Of Liver Fat Deposits

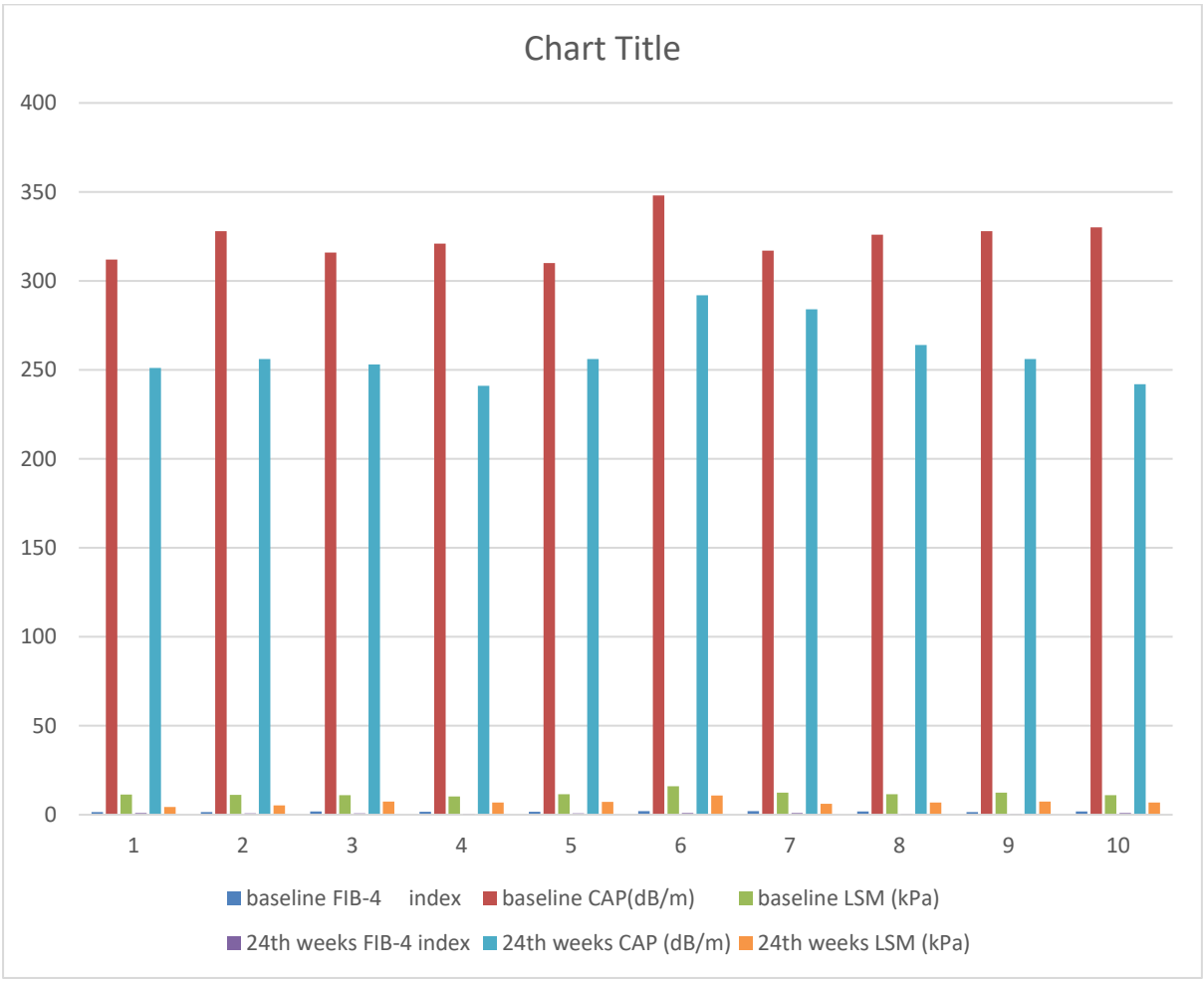

Figure 2. Baeline Compared With 24 Weeks-Cap, Fib-4 Index And Lsm

RESULTS

Among the OPD patients visited in VIMHNS during the time period of NOV.2023 to NOV. 2024; the final review sample consisted of 10 patients (who met the inclusion criteria. Half were female; the average age was 38.09 ± 9.2 years. Baseline data were available for 10 patients at the pre-designated time points of 3 months, and at 6 months. Major depressive disorder (MDD) was the primary psychiatric diagnosis in four patients, bipolar disorder in four patients, schizophrenia spectrum disorder (SSD) and borderline personality disorder each one patient. All 10 patients were on second-generation AP medications. All patients had a diagnosis of diabetes and were on standard oral-antidiabetic agents (especially metformin-1500 to2000 mg/day) with psychotropic medication at the time of initiation of semaglutide **(Table 1).**

Table-1 Clinical and demographic features of patients included in the case series at baseline visit

Patient	Age (y)/sex	sex	Primary clinical diagnosis	Antipsychotic medication (APs)	Average dose of APs (mg)	Psychotropic medications	BMI (kg/m^2)	WC (cm)	HbA1c (%)	Metformin dose (mg)	AE
1	36	M	BD	Aripiprazole	22	Lithium, pregabalin	42.5	112	6.9	2500	Nil
2	35	F	BPD	Quetiapine, loxapine	425; 12.5	Citalopram, valproate, clonazepam	38.7	120	7.2	1000	Nil
3	31	M	Schizophrenia	Aripiprazole, aripiprazole LAI	15; 400		31.2	103.5	7.7	2000	N, V
4	58	F	MDD	Risperidone	0.25	Lorazepam, venlafaxine	31.4	94	7.2	2000	N
5	23	F	BD	Olanzapine	15	Lithium	32.9	99	8.1	1500	N, V
6	36	M	BD	Brexiprazole	3	Valproate, zopiclone	38.3	119	7.1	2500	Nil
7	44	F	MDD	Lurasidone, loxapine	40; 25	Sertraline, pregabalin, lorazepam, trazodone	40.7	128	6.6	2000	N, V
8	22	M	MDD	Risperidone	2	Sertraline, trazodone	42.7	156.2	6.5	2000	Nil
9	59	M	MDD	Quetiapine, aripiprazole	25; 7	Moclobemide	36	117	6.3	1000	Nil
10	36	F	BD	Aripiprazole	17.5	Lithium	38	130	6.2	2000	Nil
SD	9.4						3.492	12.77	0.48		
MEAN	38						37.24	117.87	6.98		

AE, adverse events; BD, bipolar disorder; BMI, body mass index; BPD, borderline personality disorder; D, diarrhea; HbA1c, glycosylated hemoglobin; Kg, kilograms; LAI, long-acting injectable; MDD, major depressive disorder; N, nausea; SAD, schizoaffective disorder; SSD, schizophrenia spectrum disorder; TGL, fasting triglyceride; V, vomiting; WC, waist circumference.

At baseline, BMI was 37.24 ± 3.49 kg/m2, with a mean waist cir cumference of 117.87 ± 12.77 cm. Demographics and clinical characteristics are provided in detail in Table 1. Metformin was continued in all

patients . A weight loss of 4.56 ± 3.15 kg ($p < 0.001$), 5.16 ± 6.27 kg ($p = 0.04$), and 8.67 ± 9 kg ($p = 0.04$) was seen at 3, 6, and 12 months, respectively, after initiation of semaglutide. The participants received semaglutide as mentioned in study design.

Significant decreases in body weight and BMI were observed as the mean BMI at 12^{th} weeks and 24^{th} weeks was 34.22 (±3.02) and 31(±2.2) and mean waist circumference at 12^{th} and 24^{th} weeks was 99.4(±6.8) and 3.7(±5.3), respectively **(Table-2)**.

Table-2 comparison of BMI and WC of patients included in the case series at baseline visit,12 weeks and 24 weeks.

			BMI (kg/m2)			WC		
	Patient	primary clinical diagnosis	BASELINE	12 weeks	24 weeks	BASELINE	12 weeks	24 weeks
	1	BD	42.5	40.2	34	112	106	101
	2	BPD	38.7	38	33	105	100	95
	3	SSD	31.2	31	28	94	91	87
	4	MDD	31.4	28	27	91	87	84
	5	BD	32.9	31	27	95	91	85
	6	BD	38.3	35	33	106	101	95
	7	MDD	40.7	35	32	115	109	102
	8	MDD	42.7	38	33	118	115	102
	9	MDD	36	33	32	102	98	93
	10	BD	38	33	31	101	96	93
		SD	3.492	3.02	2.2	7.3	6.8	5.3
		MEAN	37.24	34.22	31	103.9	99.4	93.7
	; BD, bipolar disorder; BMI, body mass index; BPD, borderline personality disorder; ; HbA1c, glycosylated hemoglobin; Kg, kilograms; MDD, major depressive disorder;r; SSD, schizophrenia spectrum disorder; TGL, fasting triglyceride; WC, waist circumference.							

The mean ALT, and triglycerides values were 89.4 (±5.4) U/L, and 185.5 (±17.9) mg/dL, respectively at baseline also revealed significant improvement at 12th and 24th weeks. Mean triglycerides was almost normal at the end of 24th weeks (127±8.4mg/dL).

The mean values for fibrosis markers at baseline, as FIB-4 index was1.75 (±0.17), mean CAP and LSM values were 323.6 (±8.4) dB/m and 11.8 (±1.64) kPa, respectively. More detailed information regarding each patient is presented in **(Table-3)**. The median CAP values significantly decreased to 259.5 (±12.3) dB/m at week 24.

			Table-3 Changes in ALT,triglyceride and ficoscan 10 patients who received oral semaglutide for 24weeks											
								transient elastography-FibroScan 502						
Patient	Pimary Clinical. Diagnosis		ALT (U/L)			Triglyceride (mg/dL)		baseline			24th weeks			
		baseline	12 weeks	24 weeks	baseline	12 weeks	24 weeks	FIB-4 index	CAP(dB/m)	LSM (kPa)	FIB-4 index	CAP (dB/m)	LSM (kPa)	
1	BD	85	65	52	210	156	113	1.48	312	11.4	0.93	251	4.4	
2	BPD	76	66	54	185	152	134	1.56	328	11.2	0.74	256	5.2	
3	SSD	92	78	68	154	133	114	1.92	316	10.9	0.82	253	7.4	
4	MDD	83	63	56	168	148	118	1.64	321	10.2	0.65	241	6.9	
5	BD	90	78	48	203	168	132	1.66	310	11.6	0.74	256	7.2	
6	BD	102	76	56	210	172	136	2.01	348	16	0.99	292	10.8	
7	MDD	96	78	62	198	168	138	1.99	317	12.4	0.91	284	6.2	
8	MDD	94	82	61	196	166	140	1.78	326	11.5	0.53	264	6.9	
9	MDD	87	67	42	162	140	126	1.56	328	12.5	0.64	256	7.4	
10	BD	89	69	49	169	145	125	1.92	330	10.9	0.93	242	6.9	
SD		5.4	6.2	5.8	17.9	11.2	8.4	**0.172**	8.4	1.064	0.128	12.3	1.016	
mean		89.4	72.2	54.8	185.5	154.8	127.6	**1.752**	323.6	11.86	0.788	259.5	6.93	

Anti-fibrotic effect of oral semaglutide.is highlighted as FIB-4 index significantly decreased to 0.788(±0.128). LSM values did not show significant changes from baseline to 24 weeks of the treatment.

DISCUSSION

This case series reports the real-world effectiveness of semaglutide in the treatment of AAWG, —we found that 24-week oral semaglutide treatment in patients with NAFLD complicated by T2DM with AAWG improved

insulin resistance, diabetes mellitus, hypertriglyceridemia, impaired liver function, and hepatic steatosis, while also decreasing body weight. To our knowledge, this is the first case-series on the efficacy and safety of oral semaglutide treatment in patients of T2DM with AAWG and complicated with NAFLD in a naturalistic small subset of individuals who failed to respond to metformin.

Five RCTs (exenatide and liraglutide) to date have examined the efficacy of GLP-1-RAs on weight loss among people on APs with schizophrenia spectrum disorders (SSDs) [13] . GLP-1 RAs, including semaglutide, are anti-diabetic drugs classified as incretin mimetics, which promote insulin secretion in a blood glucose-dependent manner by acting on the pancreatic β cells and decrease blood glucose levels by suppressing glucagon secretion. Additionally, GLP-1 RAs promote a feeling of fullness by activating GLP-1 receptors in the hypothalamus, thus reducing appetite by delaying gastric emptying, leading to weight reduction [14,15].

In this study, we found significant correlations between changes in body weight and levels of ALT or CAP. These findings suggest that semaglutide may have indirect effects on hepatic steatosis and inflammation by improving obesity and insulin resistance, which are the key drivers of NAFLD onset and progression. Preclinical studies have shown the direct effects of GLP-1 RAs on liver function, such as suppression of de novo lipogenesis[16] , promotion of fatty acid β-oxidation, improvement of insulin signals, [17] and anti-inflammatory actions. [18]

Liver biopsy is the gold standard for evaluating liver fibrosis; however, it has several limitations, such as invasiveness, risk of complications, and sampling errors. Transient elastography, using FibroScan 502 equipped with the M-probe (Echosens SA, Paris, France) at the initiation and 24 weeks of oral semaglutide treatment - NON-INVASIVE test showed an improvement in the FIB-4 index may be attributable to the normalization of AST and ALT levels, that a decrease in the FIB-4 index could indicate an improvement in liver fibrosis. GLP-1 RA treatment may prevent these complications and improve the prognosis of patients with NAFLD. In this study, we found no significant changes in LSM values after oral semaglutide treatment. Therefore, a large-scale, long-term study is required to investigate whether GLP-1 RA treatment improves liver fibrosis and extrahepatic complications and, consequently, the prognosis in patients with NAFLD complicated by T2DM on AAWG. This case series demonstrates initial evidence of real-world effectiveness of semaglutide in redu ing weight in patients with AAWG with improvement in NAFLD.

In conclusion, the 24-week oral semaglutide treatment was effective and safe in patients with NAFLD complicated by T2DM. Oral semaglutide treatment significantly improved impaired liver function, hypertriglyceridemia, insulin resistance, and hepatic steatosis, as well as improving diabetic status and reducing body weight, despite AAWG.. Although this pilot study had numerous limitations, the results suggest a potential benefit of semaglutide in the treatment of liver fibrosis, and further investigation is warranted.

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