Original Article

Efficacy and Safety of Semaglutide in Non-Alcoholic Fatty Liver Disease: A Clinical Based Study

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ABSTRACT

Objective: In the current study, we aimed to find the safety and efficacy of semaglutide in patients having NAFLD.
Study Design: A clinical based study
Place and Duration of Study: This study was conducted at the Department of Medicine, DHQ Hospital, Jhelum Pakistan from 14th February 2020 to 20th November 2022.
Methods: Baseline characteristics of the patients suspected of NAFLD were assessed which included liver-function tests, BMI, age, gender distribution, body weight, lipid profile, and diabetes-related markers. Blood profiling by Mindray protocol was performed and ultrasonography was also done.
Results: Significant improvements were observed in triglycerides (p = 0.001), LDL cholesterol (p = 0.001), HDL cholesterol (p = 0.03), body weight (p = 0.04), fasting plasma glucose (<0.001), BMI (p = 0.0001) and HbA1c (p = 0.42). Reductions in ALT (p = 0.0001) and AST (p = 0.13) in liver function tests. An decrease in triglyceride level (169±6 mg/dl to 163±2 mg/dl) and LDL cholesterol (102±4 mg/dl to 98±3 mg/dl) was observed through Semaglutide, while there was a decrease in HDL cholesterol (43±2 mg/dl to 41±1 mg/dl). A reduction in the level of ALT (27±3 U/L to 21±1 U/L) was observed. Body BMI (38±2 kg/m² to 32.5±1.0 kg/m²) and body weight (225±6 kg to 90.8±1.2 kg) were reduced after treating with semaglutide compared to baseline. Glycemic control was improved through HbA1c levels improvement (5.9±0.1% to 5.5±0.3%), while an increase in fasting glucose level (64±5 mg/dl to 102±5 mg/dl) was observed with Semaglutide.
Conclusion: Semaglutide provides a therapeutic option for NAFLD, but still, collaborative efforts and modifications in lifestyle are required to lessen this burden on human health. An effective improvement was observed in different parameters by comparing Semaglutide activity with baseline measures.

Key Words: Non-alcoholic fatty liver disease, Blood Profiling, Semaglutide treatment

Citation of article: Anwar S, Majid F, Tariq F, Ahmad SA, Ali M. Efficacy and Safety of Semaglutide in Non-Alcoholic Fatty Liver Disease: A Clinical Based Study. Med Forum 2024;35(5):60-64. doi:10.60110/medforum.350513.

INTRODUCTION

Non-alcoholic fatty acid liver disease (NAFLD) is responsible for increasing occurrence of chronic liver disease[1]. NAFLD is found to be alarming situation as it is linked with liver cancer, hepatic fibrosis and cirrhosis. Around 25% of people having worse conditions of liver are found to be affected by this. In some patients, it leads to severe inflammation and scarring of liver[2]. In severe NAFLD, liver cirrhosis and malignancy are the main outcomes. Type 2 diabetes and insulin resistance from NAFLD increase cancer risk, liver inflammation, and scarring[3]. Demographically, women were targeted more. NASH hyped liver transplantation in the US, ranking second to alcohol-related liver disease. The link to metabolic problems like type 2 diabetes makes this situation worse[4]. His persistent condition is hard to diagnose and cure.

Liver issues connected to cardiovascular disease kill individuals[5]. Vitamin E and pioglitazone improve liver health, however NAFLD medicines are not available. Health and weight loss are generally encouraged before NAFLD treatment. Recent investigations found SGLT2 inhibitors and GLP-1 receptor agonsists beneficial for NAFLD[6]. Through GLP-1 RAs like semaglutide, insulin levels can be raised to manage blood sugar. Glucagon secretion decreases with blood sugar[7].

Semaglutide, a GLP-1 receptor agonist, is promising. It aids weight loss and glycemic management. It shows inflammatory marker in obese type 2 diabetics[8]. Treating serious cardiovascular problems in high-risk diabetics was also outstanding. Semaglutide was promising for NAFLD patients with fibrosis[9]. Segaglutide also improves lipids, weight, and HbA1c. Firsocostat, cilofexor, and semaglutide have different

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Received: December, 2023
Accepted: January, 2024
Printed: May, 2024

mechanisms. Firsocostat and cilofexor have direct hepatic effects, while semaglutide is anti-inflammatory. Phase 2 open-label trial. The Markov model predicts a 21% increase in non-alcoholic fatty liver disease (NAFLD) in the US by 2030. This will reach 33.5% by 2030[10]. The best technique to identify liver disease is to test blood ALT and AST levels (Powell et al., 2021). Since it's in the liver, ALT is a better liver damage marker. AST is found in kidneys, heart muscle, lungs, white and red blood cells, skeletal muscle, and heart muscle[11]. The most acceptable method to detect insulin resistance (IR) is Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). It was developed by Matthews et al. Insulin resistance occurs when glucose uptake and utilization is prohibited. Another marker used to look for the severity and the presence of NAFLD is glycosylated hemoglobin (HbA1C) along with the other metrics including body mass index (BMI)[12].

METHODS

The study was approved and conducted at the Department of Medicine, DHQ hospital, Jhelum Pakistan from 14th February 2020 to 20th November 2022.

Blood Profiling: In the blood tests, lipid profile, level pf liver enzymes (AST, ALT) and the markers used as liver function detector (albumin, bilirubin) and some other parameters can be prosecuted to check liver health and other metabolic syndrome.

Biochemical analysis by Mindray BS-430 protocol: Mindray BS-430 was our favorite blood profiling procedure. Medical laboratories employ clinical chemistry analyzers for many blood tests. It measured biomarkers to help diagnose NAFLD. To diagnose liver inflammation or injury, ALT and AST enzymes were measured. But ALT was the predominant liver damage sign. High bilirubin and low albumin indicated hepatic obstruction and impaired liver function, respectively. Dyslipidemia—low HDL cholesterol and high triglycerides—occurs in NAFLD patients.

Clinical and Laboratory Data: Midpoint (weeks) laboratory and clinical data were gathered. Platelets, liver biochemistry (AST, ALT), fasting lipids (Triglycerides, HDL cholesterol, LDL), and diabetes-related tests (HbA1c) were tested in the lab. Weight (kg) divided by height (m2) yielded BMI.

Statistical Analysis: The initial dose escalation schedule for semaglutide was followed subcutaneously by patients. During the 1st four weeks, 0.25 mg dose was given once a week. Then the dose was increased to 0.5 mg during 5 to 8 weeks. It was further followed by an increase to 1mg in the 9th week and onwards.

Ethical Approval: To conduct the study on NAFLD patients, ethical approval was taken from the Department of Medicine, DHQ Hospital in Jhelum. Where the study was performed. Patients were guided about the benefits as well as any potential risks included in the study. It was taken into consideration that the study will be beneficial for NAFLD patients which included evidence from preclinical investigations posing the efficacy of semaglutide. The confidentiality of the patients and the security of the collected data were protected.

RESULTS

Table No.1: Baseline characterization of patients with NAFLD

Parameters	(Unit)	Baseline
Age	years	46±2 (42-58)
Male/Female	N(%)	25(62.5)
Body weight	kg	225±6 (154-251)
BMI	kg/m^2	38±2 (31-42)
L.P		
LDL cholesterol	mg/dl	102±4 (85-145)
HDL cholesterol		43±2 (42-53)
Triglycerides		169±6 (120-250)
LFTs		
ALT	U/L	27±3 (19-50)
AST		21±1(10-45)
D.P		
HbA1c	%	5.9±0.1 (5.81-6.70)
Fasting plasma glucose	mg/ dl	64±5 (55-110)
T.P		
Platelets	$10^{3/}\mu L$	217±26 (150-450)

***Lipid profile (L.P), Liver function tests (LFTs), Diabetes Profile (D.P), Thrombocytes Profile (T.P)**

Table No.2: Semaglutide activity in patients with NAFLD

Parameter	Unit	Semaglutide 2.4 mg
Age, years	years	51±4 (50-58)
Male/Female	n(%)	15 (37.5)
Body weight	kg	90.8±1.2 (76.5-105.6)
BMI	kg/m^2	32.5±1.0 (30.6−36.8)
L.P		
LDL cholesterol	mg/dl	98±3 (83-130)
HDL cholesterol		41±1 (36-54)
Triglycerides		163±2 (103-232)
LFTs		
ALT	U/L	21±1 (19-50)
AST		19±1 (10-45)
D.P		
Fasting plasma glucose	mg/ dl	102±5 (55-110)
HbA1c	%	5.5±0.3 (5.81-

		6.70)
HOMA-IR	u/L	1.4±0.5 (1.0-2.5)
T.P		
Platelets	$10^{3/}$□L	198±17 (150-450)

***Lipid profile (L.P), Liver function tests (LFTs), Diabetes Profile (D.P), Thrombocytes Profile (T.P)**

The study included 25 patients, 62.5% male and 37.5% female. Patients ages ranged from 42 to 58 years, with an average of 46±2 years. The patient's weight ranged from 154 to 251 kg, averaging 225±6 kg. The patients' BMI ranged from 31 to 42 kg/m2, with an average of 38±2 kg/m2. The patients' lipid profile revealed LDL levels ranging from 85 to 145 mg/dl, with an average of 102±4 mg/dl. The average HDL level was 43±2mg/dl, ranging from 42 to 53mg/dl. The triglyceride readings were 120-250mg/dl, with an average of 169±6 mg/dl. An average of 27±3 U/L was seen in ALT levels, whereas AST levels ranged from 10 to 45U/L with an average of 21±1U/L. The HbA1c ranged from 5.81% to 6.70%, averaging 5.9±0.1%, whereas fasting plasma glucose levels ranged from 955 to 110mg/dl, averaging 64±5mg/dl (table 1). The platelet count in the hematological profile was 150-450 103/μL, with an average of 217±26 103/μL.

Table No.3: Comparison of Baseline and Semaglutide activity in patients with NAFLD

Parameter	Unit	Baseline	Semaglutide	P-values
Age, years	years	46±2 (42-58)	51±4 (50-58)	0.0001
Male/Female	n(%)	25(62.5)	15 (37.5)	0.0001
Body weight	kg	225±6 (154-251)	90.8±1.2 (76.5-105.6)	0.04
BMI	kg/m^2	38±2 (31-42)	32.5±1.0 (30.6−36.8)	0.0001
Lipid profile				
LDL cholesterol	mg/dl	102±4 (85-145)	98±3 (83-130)	0.001
HDL cholesterol		43±2 (42-53)	41±1 (36-54)	0.03
Triglycerides		169±6 (120-250)	163±2 (103-232)	0.001
Liver function tests				
ALT	U/L	27±3 (19-50)	21±1 (19-50)	0.0001
AST		21±1(10-45)	19±1 (10-45)	0.13
Diabetes Profile				
Fasting plasma glucose	mg/ dl	64±5 (55-110)	102±5 (55-110)	<0.001
HbA1c	%	5.9±0.1 (5.81-6.70)	5.5±0.3 (5.81-6.70)	0.42
HOMA-IR	U/L	1.4±0.5 (1.0-2.5)	--	0.001
Thrombocytes Profile				
Platelets	$10^{3/}$□L	211±8 (150-450)	198±7 (150-450)	0.000

***Lipid profile (L.P), Liver function tests (LFTs), Diabetes Profile (D.P), thrombocytes Profile (T.P)**

DISCUSSION

For the treatment of non-alcoholic fatty acid liver disease (NAFLD), semaglutide is found to be a promising drug. It is potentially approved by the FDA. The major cause of chronic liver disease (CLD) was found to be NAFLD[13-15]. In the trials performed, the safety profile of semaglutide was found to be consistent with the previous findings in the patients being overweight or obese, and having type 2 diabetes[16]. Brief gastrointestinal symptoms and mild to moderate incidents were noted with treatment. No adverse effects were identified on renal or hepatic function.

Semaglutide treatment led to increased triglycerides (169±6 mg/dl to 163±2), LDL cholesterol (102±4 mg/dl to 98±3 mg/dl), and decreased HDL cholesterol (43±2 mg/dl to 41±1 mg/dl), consistent with previous findings of improved liver fat content with GLP-1 receptor agonists[17]. In particular, ALT levels improved[17]. Our investigation showed a decrease in ALT levels (27±3 U/L to 21±1 U/L). In NAFLD patients, semaglutide activity had distinct discernible effects than baseline characteristics. Due to these changes, reaction or treatment selection may affect demographics. After treatment with semaglutide, body weight and BMI decreased somewhat compared to baseline, comparable with prior findings[18,19]. This revealed how semaglutide can improve NAFLD and other metabolic problems. Obesity is a risk factor for NAFLD, thus our study's weight and BMI reductions are notable. Semaglutide may reduce metabolic abnormalities that cause NAFLD by encouraging weight loss. Lifestyle changes and collaboration in NAFLD management are also highlighted by our findings. Semaglutide may cure NAFLD, however more research is needed to confirm its efficacy and safety. Studies are needed to determine the best combination therapy and dose regimes for Semaglutide for NAFLD. A dose-dependent connection exists between NAFLD patients' histological improvement and weight loss 10). Semaglutide's benefits have also been shown in NAFLD trials[20,21]. In Volpe et al.'s 2022 trial, body weight decrease was up to 10%, which may explain semaglutide's advantages. After treatment with semaglutide, we observed a small decrease in body weight (225±6 kg to 90.8±1.2 kg) and BMI (38±2 kg/m^2 to 32.5±1.0 kg/m^2) compared to

baseline, similar with prior findings. Lifestyle changes and collaboration in NAFLD management are also highlighted by our findings. Semaglutide may cure NAFLD, however more research is needed to confirm its efficacy and safety. Studies are needed to determine the best combination therapy and dose regimes for Semaglutide for NAFLD. Previous research shows that Semaglutide improves cardiovascular difficulties in type 2 diabetics with obesity and other metabolic variables. We tested Semaglutide in NAFLD patients to add to the corpus of information[18,19]. Semaglutide improved glycemic control by lowering HbA1c levels (5.9±0.1% to 5.5±0.3%) and increasing fasting glucose levels (64±5 mg/dl to 102±5 mg/dl). However, some patients experienced hypoglycemic episodes with glucose levels of 70 mg/dL[22]. HOMA-IR was not found. Along with this, Semaglutide has been found to impose its beneficial impacts through its antioxidative and anti-inflammatory actions[23]. However, some studies have also provided the data related to the direct impact of GLP1-RAs in cell-culture models of NAFLD on hepatic lipid metabolism[24].

CONCLUSION

Non-alcoholic fatty liver disease (NAFLD) is known as an important global health issue affecting cardiovascular well-being and the health of the liver. Our study was conducted by assessing multiple laboratory and clinical assessments in NAFLD patients. To understand the multifaceted nature of NAFLD, We used ultrasonography, diabetes indicators, liver enzymes, and lipid profiles. Obesity, dyslipidemia, and insulin resistance were key to NAFLD development. The best NAFLD treatment was Semaglutide, which targeted glucagon-like-peptide-1 receptors. Different variables were found by comparing Semaglutide effects to baseline features. Semaglutide lowered BMI and weight. Fasting glucose increased and HbA1c improved, improving glycemic management. Semaglutide increased triglycerides and LDL cholesterol and decreased HDL cholesterol. Lower ALT levels were seen.

Author's Contribution:

Concept & Design of Study:	Saeed Anwar
Drafting:	Fawad Majid, Farhan Tariq
Data Analysis:	Farhan Tariq, Sajid Ali Ahmad, Muhammad Ali
Revisiting Critically:	Saeed Anwar, Fawad Majid
Final Approval of version:	Saeed Anwar

Conflict of Interest: The study has no conflict of interest to declare by any author.

Source of Funding: None

Ethical Approval: No.3092/MSJ dated 14.02.2020.

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