Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i8.7465

EFFICACY AND SAFETY OF SEMAGLUTIDE IN NON-ALCOHOLIC FATTY LIVER DISEASE

Taqdees Zahra[1], Tahira[2], Samreen Bugti[3*], Tariq Mehmood[4]

[1,2,3*]Assistant Professor, Department of Medicine, Bolan Medical College/ Bolan Medical Complex Hospital, Quetta - Pakistan
[4]Medicine PGMI/Sheikh Khalifa Bin Zayyed al Nehan Hospital, Quetta - Pakistan

***Corresponding author:** Samreen Bugti
*Email: dr.sbugti@gmail.com

ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease, with an estimated worldwide prevalence of 32.4%. The prevalence and disease burden of NAFLD are projected to exponentially increase, with mathematical models forecasting a 168% increase in the incidence of decompensated cirrhosis and a 178% increase in NAFLD-related deaths between 2015 and 2030.

Objective: To determine the Efficacy and Safety of Semaglutide in Non-Alcoholic Fatty Liver Disease

Methodology: This clinical based study was carried out at the Department of medicine, Bolan medical college/ Bolan medical complex hospital Quetta. The study duration was one year from January 2023 to January 2024. This study approval was given by the ethical committee of the hospital. To diagnose liver inflammation or injury, ALT and AST enzymes were measured. 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. All the data was analyzed by using SPSS version 23.

Results: In the current study, a total of 40 patients were included. There were 24 (60%) males and 16 (40%) females in our study. The mean (SD) of the patients was 48 (±12) years with minimum age of 45 and maximum age of 60 years. Significant improvements were observed in triglycerides ($p = 0.002$), LDL cholesterol ($p = 0.002$), HDL cholesterol ($p = 0.000$), body weight ($p = 0.03$), fasting plasma glucose (<0.001), BMI ($p = 0.001$) and HbA1c ($p = 0.42$). Reductions in ALT ($p = 0.0001$) and AST ($p = 0.13$) in liver function tests.

Conclusion: Our study concludes that 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: Efficacy; Safety; Semaglutide; Non-Alcoholic Fatty Liver Disease

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease, with an estimated worldwide prevalence of 32.4%[1,2]. The prevalence and disease burden of NAFLD are projected to exponentially increase, with mathematical models forecasting a 168% increase in the

incidence of decompensated cirrhosis and a 178% increase in NAFLD-related deaths between 2015 and 2030. These projections highlight the significant healthcare expenditures and lower health-related quality of life associated with the disease[3-5]. NAFLD is a spectrum of liver disease characterized by hepatic steatosis in the absence of excessive alcohol consumption[6]. The majority of patients with NAFLD have NAFL, of which approximately 20% will develop non-alcoholic steatohepatitis (NASH) and have a risk of further progression to cirrhosis, hepatocellular carcinoma, and end-stage liver disease[3]. Although lean NAFLD is increasingly recognized, the majority of patients with NAFLD have one or more components of metabolic syndrome, which is also independently strongly associated with fibrosis progression[7,8]. GLP-1 receptor agonists (RAs) offer promising therapeutic options in NAFLD due to their beneficial glycemic and weight loss effects. GLP-1 receptors have been detected on human hepatocytes, and it is hypothesized that their activation by GLP-1 RAs can have positive effects on hepatic steatosis, lipotoxicity, fatty acid oxidation, and cytokines involved in hepatic inflammation and fibrosis[9,10]. Moreover, GLP-1 RAs may have indirect hepatoprotective benefits through increased insulin secretion in response to hyperglycemia, decreased glucagon secretion, delayed gastric emptying, and significant weight loss[11,12]. Among the GLP-1 RAs, semaglutide has demonstrated the greatest glycemic and weight loss benefits[13]. In a recent phase three trial of patients with overweight or obesity, semaglutide showed a significant decrease in body weight by 14.9% compared to 2.4% with placebo [14]. Additionally, semaglutide has shown reduced rates of major adverse cardiovascular events and a lower risk of adverse renal outcomes in patients with type 2 diabetes (T2DM)[15]. It has since been approved for the treatment of T2DM and chronic weight management. Several randomized clinical trials have also demonstrated the beneficial effects of semaglutide in patients with NAFLD. A previous systematic review with meta-analysis was conducted to assess the impact of semaglutide on biochemical and radiologic measures of NAFLD[16]. However, more than 85% of the study's patients had diabetes or obesity rather than confirmed NAFLD. Additionally, no histological outcomes were reported, which are considered the gold standard for diagnosing and managing NAFLD. Since its publication, a recent randomized controlled trial (RCT) by Loomba *et al*[17] has been performed, focusing on semaglutide in patients with NASH and compensated cirrhosis. The purpose of this systematic review and meta-analysis is to provide an updated review on the efficacy and safety of semaglutide, focusing on patients with NAFLD, in order to more specifically reflect the NAFLD population and expand the current understanding of semaglutide in NAFLD.

Materials and Methods

This clinical based study was carried out at the Department of medicine, Bolan medical college/ Bolan medical complex hospital Quetta. The study duration was one year from January 2023 to January 2024. This study approval was given by the ethical committee of the hospital. Mindray BS-430 was blood profiling procedure in our study. 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 high 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. Platelets, liver biochemistry (AST, ALT), fasting lipids (Triglycerides, HDL cholesterol, LDL), and diabetes- related tests (HbA1c) were tested in the lab. 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. All the data was analyzed by using SPSS version 23. Frequency and percentages were determined for the variable like gender and means and standard deviation were calculated for the variables like age and laboratory tests.

Results

In the current study, a total of 40 patients were included. There were 24 (60%) males and 16 (40%) females in our study. The mean (SD) of the patients was 48 (±12) years with minimum age of 45 and

maximum age of 60 years. The baseline characteristics of these patients were as follow. The patient's weight ranged from 159 to 245 kg, with the average of 220±4 kg. The patients' BMI ranged from 30 to 40kg/m2, with an average of 39±1 kg/m2. The patients' lipid profile revealed LDL levels ranging from 84 to 141 mg/dl, with an average of 101±5mg/dl. The average HDL level was 41±4mg/dl, ranging from 41 to 51mg/dl. The triglyceride readings were 121-254mg/dl, with an average of 173±3 mg/dl. Average ALT levels were 27±3 U/L, whereas AST levels ranged from 10 to 45U/L with an average of 21±1U/L. The HbA1c ranged from 5.83% to 6.73%, averaging 5.8±0.1%, whereas fasting plasma glucose levels ranged from 48 to 115mg/dl, averaging 69±4mg/dl The platelet count in the hematological profile was 153-455 $10^3/\mu L$, with an average of 223±21 $10^3/\mu L$ (table 1). The semaglutide activity in patients with NAFLD is shown in table 2. Significant improvements were observed in triglycerides (p = 0.002), LDL cholesterol (p = 0.002), HDL cholesterol (p = 0.000), body weight (p = 0.03), fasting plasma glucose (<0.001), BMI (p = 0.001) and HbA1c (p = 0.42). Reductions in ALT (p = 0.0001) and AST (p = 0.13) in liver function tests. (Table 3)

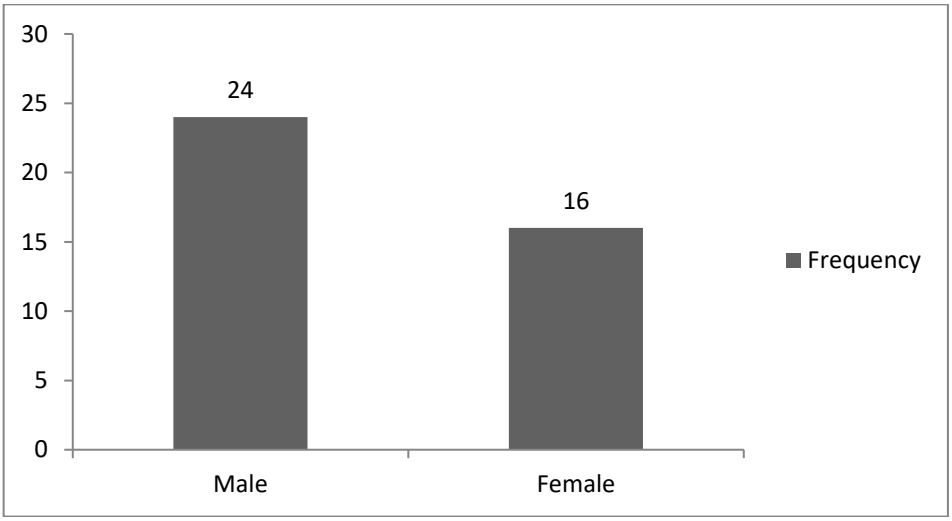

Figure 1: Gender wise distribution of patients

Table 1: Baseline characteristics of the patients

Parameter	Mean±Sd (Range)
Age	48 ±12, (45-60 years)
Body weight	220±4 kg (159 to 245 kg)
BMI	48 ±12 (45-60) years
LDL cholesterol	101±5mg/dl, (84 to 141 mg/dl,)
HDL cholesterol	41±4mg/dl, (41 to 51mg/dl.)
triglycerides	173±3 mg/dl. (121-254mg/dl)
ALT	27±3 U/L (18-51) U/L
AST	21±1U/L (10 to 45U/L)
HbA1c	5.8±0.1%, (5.83% to 6.73%)
Fasting plasma glucose	69±4mg/dl (48 to 115mg/dl)
Platelets	223±21 $10^3/\mu L$ (153-455 $10^3/\mu L$)

Table 2: Semaglutide activity in patients with NAFLD

Parameter	Mean±Sd (Range)
Body weight	92±3 kg (78 to 107 kg)
BMI	33 ±9 (31-39) years
LDL cholesterol	98±5mg/dl (81 to 130 mg/dl)
HDL cholesterol	40±2mg/dl, (30 to 49mg/dl)
triglycerides	160±1.5 mg/dl. (100-220mg/dl)
ALT	20±3 U/L (19-50) U/L
AST	21±1U/L (10 to 45U/L)
HbA1c	5.4±0.1%, (5.80% to 6.70%)

Fasting plasma glucose	103±4mg/dl (48 to 115mg/dl)
Platelets	196±18 10^3/µL (153-455 10^3/µL)

Table 3: Comparison of Baseline and Semaglutide activity in patients with NAFLD

Parameter	**Semaglutide**	Baseline	P value
	Mean±Sd (Range)	Mean±Sd (Range)	
Body weight	92±3 kg (78 to 107 kg)	220±4 kg (159 to 245 kg)	0.03
BMI	33 ±9 (31-39) years	48 ±12 (45-60) years	0.001
LDL cholesterol	101±5mg/dl (84 to 141 mg/dl)	98±5mg/dl, (84 to 141 mg/dl,)	0.002
HDL cholesterol	40±2mg/dl, (30 to 49mg/dl)	41±4mg/dl, (41 to 51mg/dl.)	0.000
triglycerides	160±1.5 mg/dl. (100-220mg/dl)	173±3 mg/dl. (121-254mg/dl)	0.002
ALT	20±3 U/L (19-50) U/L	27±3 U/L (18-51) U/L	0.0001
AST	21±1U/L (10 to 45U/L)	21±1U/L (10 to 45U/L)	0.13
HbA1c	5.4±0.1%, (5.80% to 6.70%)	5.8±0.1%, (5.83% to 6.73%)	0.42
Fasting plasma glucose	103±4mg/dl (48 to 115mg/dl)	69±4mg/dl (48 to 115mg/dl)	(<0.001
Platelets	196±18 10^3/µL (153-455 10^3/µL)	223±21 10^3/µL (153-455 10^3/µL)	0.000

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 [18-20]. 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[21]. 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 (173±3 mg/dl to 160±1.5 mg/dl), LDL cholesterol (101±5 mg/dl to 98±5mg/dl), and decreased HDL cholesterol (41±4 mg/dl to 40±2 mg/dl), consistent with previous findings of improved liver fat content with GLP-1 receptor agonists [22]. In particular, ALT levels improved [22]. Our investigation showed a decrease in ALT levels (27±3 U/L to 20±3 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 [23, 24]. 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[25,26]. In Volpe et al.'s 2022 trial, body weight decrease was up to 10%, which may explain semaglutide's advantages. 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 . Semaglutide improved glycemic control by lowering HbA1c levels (5.8±0.1% to 5.4±0.1%) and increasing fasting glucose levels (69±4 mg/dl to 103±4 mg/dl). However, some patients experienced hypoglycemic episodes with glucose levels of 70 mg/dL [27]. HOMA-IR was not found. Along with this, Semaglutide has been found to impose its beneficial impacts through its antioxidative and anti-inflammatory actions [28]. 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 [29].

Conclusion

Our study concludes that 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

References

1. Riazi K, Azhari H, Charette JH, Underwood FE, King JA, Afshar EE, Swain MG, Congly SE, Kaplan GG, Shaheen AA. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2022;7:851–861.
2. Cheemerla S, Balakrishnan M. Global Epidemiology of Chronic Liver Disease. Clin Liver Dis (Hoboken) 2021;17:365–370.
3. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology. 2018;67:123–133.
4. Golabi P, Otgonsuren M, Cable R, Felix S, Koenig A, Sayiner M, Younossi ZM. Non-alcoholic Fatty Liver Disease (NAFLD) is associated with impairment of Health Related Quality of Life (HRQOL) Health Qual Life Outcomes. 2016;14:18.
5. Younossi ZM, Blissett D, Blissett R, Henry L, Stepanova M, Younossi Y, Racila A, Hunt S, Beckerman R. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology. 2016;64:1577–1586.
6. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ American Gastroenterological Association; American Association for the Study of Liver Diseases; American College of Gastroenterologyh. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology. 2012;142:1592–1609.
7. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA. 2015;**313**:2263–2273.
8. Ma J, Hwang SJ, Pedley A, Massaro JM, Hoffmann U, Chung RT, Benjamin EJ, Levy D, Fox CS, Long MT. Bi-directional analysis between fatty liver and cardiovascular disease risk factors. J Hepatol. 2017;66:390–397.
9. Gupta NA, Mells J, Dunham RM, Grakoui A, Handy J, Saxena NK, Anania FA. Glucagon-like peptide-1 receptor is present on human hepatocytes and has a direct role in decreasing hepatic steatosis in vitro by modulating elements of the insulin signaling pathway. Hepatology. 2010;51:1584–1592.
10. Dichtel LE. The Glucagon-Like Peptide-1 Receptor Agonist, Semaglutide, for the Treatment of Nonalcoholic Steatohepatitis. Hepatology. 2021;74:2290–2292.
11. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Diabetes Care. 2022;45:2753–2786.
12. Targher G, Mantovani A, Byrne CD. Mechanisms and possible hepatoprotective effects of glucagon-like peptide-1 receptor agonists and other incretin receptor agonists in non-alcoholic fatty liver disease. Lancet Gastroenterol Hepatol. 2023;8:179–191.
13. Nauck MA, Meier JJ. MANAGEMENT OF ENDOCRINE DISEASE: Are all GLP-1 agonists equal in the treatment of type 2 diabetes? Eur J Endocrinol. 2019;181:R211–R234.
14. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF STEP 1 Study Group. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021;384:989–1002.

15. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016;375:1834–1844.
16. Dutta D, Kumar M, Shivaprasad KS, Kumar A, Sharma M. Impact of semaglutide on biochemical and radiologic measures of metabolic-dysfunction associated fatty liver disease across the spectrum of glycaemia: A meta-analysis. Diabetes Metab Syndr. 2022;16:102539.
17. Loomba R, Abdelmalek MF, Armstrong MJ, Jara M, Kjær MS, Krarup N, Lawitz E, Ratziu V, Sanyal AJ, Schattenberg JM, Newsome PN NN9931-4492 investigators. Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. Lancet Gastroenterol Hepatol. 2023;8:511–522.
18. Petzold G. Role of Ultrasound Methods for the Assessment of NAFLD. J Clin Med 2022;11(15).
19. Miller MJ, Harding-Theobald E, DiBattista JV, Zhao Z, Wijarnpreecha K, Lok AS, et al. Progression to cirrhosis is similar among all ages in nonalcoholic fatty liver disease, but liver-related events increase with age. Hepatol Commun 2023;7(6).
20. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatol 2018;67(1):123–33.
21. Alkhouri N, Almomani A, Le P, Payne JY, Asaad I, Sakkal C, et al. The prevalence of alcoholic and nonalcoholic fatty liver disease in adolescents and young adults in the United States: analysis of the NHANES database. BMC Gastroenterol 2022;22(1).
22. Dufour JF, Scherer R, Balp MM, McKenna SJ, Janssens N, Lopez P, et al. The global epidemiology of nonalcoholic steatohepatitis (NASH) and associated risk factors–A targeted literature review. Endocr Metab Sci 2021;3.
23. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): A multicentre, randomised, placebo- controlled trial. Lancet. 2015;385(9972):956–65.
24. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. N Engl J Med 2021;384(12):1113–24.
25. Okamoto A, Yokokawa H, Nagamine T, Fukuda H, Hisaoka T, Naito T. Efficacy and safety of semaglutide in glycemic control, body weight management, lipid profiles and other biomarkers among obese type 2 diabetes patients initiated or switched to semaglutide from other GLP-1 receptor agonists. J Diabetes Metab Disord 2021;20(2): 2121–8.
26. Nomoto H, Takahashi Y, Takano Y, Yokoyama H, Tsuchida K, Nagai S, et al. Effect of Switching to Once-Weekly Semaglutide on Non-Alcoholic Fatty Liver Disease: The SWITCH-SEMA 1 Subanalysis. Pharmaceutics 2023;15(8).
27. Bækdal TA, Thomsen M, Kupčová V, Hansen CW, Anderson TW. Pharmacokinetics, Safety, and Tolerability of Oral Semaglutide in Subjects with Hepatic Impairment. J Clin Pharmacol 2018; 58(10):1314–23.
28. Niu S, Chen S, Chen X, Ren Q, Yue L, Pan X, et al. Semaglutide ameliorates metabolism and hepatic outcomes in an NAFLD mouse model. Front Endocrinol (Lausanne) 2022;13.
29. Petrovic A, Igrec D, Rozac K, Bojanic K, Kuna L, Kolaric TO, et al. The Role of GLP1-RAs in Direct Modulation of Lipid Metabolism in Hepatic Tissue as Determined Using In Vitro Models of NAFLD. Curr Issues Mol Biol 2023;45(6):4544–56.