



Influence of liraglutide, dulaglutide versus conventional treatment on fatty liver index and fibrosis-4 score in Egyptian patients with type 2 diabetes mellitus and non-alcoholic fatty liver disease

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Abstract:

Background: Non-alcoholic fatty liver disease (NAFLD) represents a major public health challenge in patients with type 2 diabetes mellitus (T2D). It may progress to non-alcoholic steatohepatitis (NASH), cirrhosis, and carcinoma. Our aim was to detect the changes of the fatty liver index (FLI) and FIB-4 score six months after treatment with liraglutide, or dulaglutide; novel antidiabetic medications in the Egyptian market versus the conventional therapy in Egyptian patients with T2D and co-existent NAFLD. **Methods:** A non-concurrent retrospective cohort study conducted at the outpatient department of authors' institution (Mansoura University hospitals) during the period from October 2019 to March 2020, included three matched groups of patients composed of Egyptian patients with T2D with age range from 35-65 years old, HbA1c level above 7.5%, body mass index (BMI) above 25 kg/m², estimated glomerular filtration rate (eGFR) \geq 60 mL/min/1.73 m² and with concomitant NAFLD (diagnosed with hepatic ultrasonography and fatty liver index >30). Clinical history, examination with anthropometric measures, CBC, HBA1c, serum lipid, ALT, AST, GGT, serum creatinine and thyroid profile were measured before and after 24 weeks of treatment. The fatty liver index (FLI) and the FIB-4 score were used to assess hepatic steatosis and fibrosis respectively. **Results:** There was a significant improvement of the FIB-4 and FLI values in the patients who used liraglutide and dulaglutide compared to the conventional treatment and with better results in the liraglutide group. Moreover, there was a significant reduction of the body weight, waist circumference, BMI, SBP, DBP, GGT, ALT, AST, HBA1c, triglyceride, total cholesterol, LDL-C and VLDL-C values in the liraglutide and dulaglutide groups versus the conventional treatment group. FLI, AST and platelet count changes were the significant predictors of the change in log FIB-4 score. However the change in log FLI was

independently affected by ALT changes. **Conclusion:** the addition of the liraglutide or dulaglutide exhibited many clinical and metabolic beneficial effects in the patients with concomitant T2D and NAFLD.

Keywords: NAFLD, Fatty liver index, FIB-4 score, GLP1-RAs.

Introduction

Non-alcoholic fatty liver disease (NAFLD) represents a major public health challenge. Approximately, one-fourth of the adult population and more than half of those with type 2 diabetes mellitus (T2D) suffer from NAFLD¹. It may progress to inflammation, fibrosis, and carcinoma². Obesity, dyslipidemia, insulin resistance (IR), increased apoptosis, mitochondrial dysfunction, oxidative stress and pro-inflammatory genes induction are the most patho-logical features associating NAFLD^{3,4}. Clinically, It is usually under diagnosed; representing a serious clinical challenge⁵. Several diagnostic non-invasive methods have been used for the prediction of steatosis and fibrosis as the fatty liver index (FLI) and the FIB-4 score^{6,7}. Glucagon-like peptide-1 receptor agonists (GLP1-RAs) are novel incretin-based licensed anti-diabetic drugs for T2D. Despite the metabolic benefits of GLP1-RAs, a lack of strong evidence of their use in treatment of NAFLD in T2D still exists^{8,9}. We aimed to compare the metabolic effects of the liraglutide, dulaglutide that recently introduced in the Egyptian market versus the conventional antidiabetic medications for the treatment of T2D complicated with NAFLD.

Patients and Methods

This cohort study conducted at the outpatient department of Mansoura University hospitals during the period from October 2019 to March



2020; over 24 weeks. Our study includes three groups of diabetic patients with NAFLD with matched age and gender; group (1) control group; patients administered the conventional treatment (metformin +/- sulfonylurea) without sodium glucose co-transporter 2 inhibitors (SGLT2i), GLP1-RAs or thiazolidinediones (TZDs) composed of 65 patients (41 male 63.1% and 24 female 36.9%); group (2); patients administered liraglutide (1.8 mg/daily) via subcutaneous injection added to their treatment, composed of 79 patients (49 male 62.0% and 30 female 38%) and group (3) included patients administered dulaglutide 1.5 mg subcutaneous injection once weekly added on their treatment, composed of 80 patients (54 male 67.5% and 26 female 32.5%). The included Egyptian patients with T2D were (35-65) years old with HbA1c level above 7.5%, body mass index (BMI) above 25 kg/m², estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m² with concomitant NAFLD (diagnosed with hepatic ultrasonography and fatty liver index >30). A written informed consent was obtained from all patients with the Institutional Review Board (IRB) approval. Detailed medical history and clinical examination with anthropometric measures were recorded in the patients' files. Following a 12-h overnight fast, venous blood was collected from each patient to estimate the glycosylated hemoglobin (HbA1c), blood lipid (serum total cholesterol [TC], triglyceride [TG], low-density lipoprotein cholesterol [LDL-C], very low-density lipoprotein cholesterol [VLDL-C] and high-density lipoprotein cholesterol [HDL-C]), complete blood count, liver enzymes (aspartate transaminase [AST], alanine transaminase [ALT], and gamma-glutamyl transferase [GGT]), renal function tests and thyroid profile before and after 24 weeks of treatment. The extent of the hepatic steatosis was estimated with the fatty liver index (FLI)⁶. As well as, the FIB-4 score was used to diagnose hepatic fibrosis⁷. Participants' follow up visits were every 8 weeks for 24 week. Adverse events were recorded on each visit and the severity assessed according to the Common Terminology Criteria for Adverse Events Version 4.0. We excluded patients with other causes of chronic liver disease like viral hepatitis, autoimmune hepatitis, history of alcohol consumption, drug-induced liver injury, biliary diseases, liver cell failure, hepatocellular carcinoma, history of diabetic ketoacidosis, concurrent administration of medications that may alter liver function tests as (NSAIDs, statin, TZDs, etc), patients with advanced cardiac, respiratory, and/or renal dysfunction, history of GLP1-RAs hypersensitivity, intolerance, pancreatitis, history of active cancer or family history of medullary thyroid

carcinoma, patients with severe gastrointestinal disease or GERD and patients with pregnancy or planning for pregnancy.

Study outcome

Our primary endpoint was the detection of the FLI and FIB-4 score changes at the end of the study period. Secondary endpoints were the detection of the significant changes in clinical and metabolic parameters between the three groups as well as the detection of any outcome variation between the liraglutide versus the dulaglutide group.

Statistical analysis

Data were analyzed using IBM SPSS Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Qualitative data were described using number and percent. Quantitative data were described using median with inter quartile range for non-parametric data and mean with standard deviation for parametric data after testing normality using Kolmogorov-Smirnov test. Significance of the obtained results was judged at the (0.05) level. Data analysis was done using Monte Carlo test for comparison of 2 or more groups of categorical variables. Student t-test & One Way ANOVA test were used to compare parametric variables. Mann-Whitney U test & Kruskal Wallis test were used to compare independent groups for non-parametric variables. The comparison between pre and post treatment results was tested with Paired t-test and Wilcoxon signed rank test. The Spearman's rank-order correlation is used to determine the strength and direction of a linear relationship between two non-normally distributed continuous variables and/or ordinal variables. Multiple linear regression analysis was used to detect predictors of change in FIB4 & FLI after log transformation.

Results

Three groups of participants were included in the analysis; group (1); patients treated with conventional treatment alone, group (2); patients administered liraglutide added on their conventional treatment and group (3); patients administered dulaglutide added on their conventional treatment. **Tables (1 & 2)** show the demographic, clinical and laboratory characters of the participants of different groups before and after 6 months of treatment. We found a significant reduction of median FIB-4 score in the liraglutide and dulaglutide groups versus the conventional treatment group (p-value <0.001) with significant lower values in the liraglutide group than the dulaglutide group (p-value =0.027), **tab. (2)** and **fig. (1)**. Also, a significant reduction of mean FLI was achieved in the liraglutide and



dulaglutide groups versus the conventional treatment group (p-value <0.001) but without significant differences in-between the GLP1-receptor agonists groups (P- value =0.102), **tab. (2)** and **fig. (2)**. GGT, ALT and AST were significantly reduced after liraglutide and dulaglutide use than the conventional treatment (p-value <0.001). However, GGT was significantly lower in the liraglutide than the dulaglutide (p-value <0.001), **tab. (2)**. Administration of liraglutide and dulaglutide achieved a significant HBA1c reduction than the conventional treatment (p-value <0.001) but with better results in the liraglutide group than the dulaglutide group (p- value <0.001), **tab. (2)**. There was a significant improvement of the lipid profile (TG, TC, LDL-C, VLDL-C) in the patients administered GLP-1 receptor agonists than the patients used the conventional treatment (p-value <0.001). VLDL-C was significantly lower in the liraglutide

group than the dulaglutide group (p-value =0.014), **tab. (2)**. SBP and DBP showed significant lower readings in the liraglutide and the dulaglutide groups than the conventional treatment group (p-value <0.001), with better values in the liraglutide group than the dulaglutide (p-value <0.001), **tab. (1)**. Body weight, waist circumference and BMI were significantly reduced in the liraglutide and the dulaglutide groups than the conventional treatment group (p-value <0.001). However, the dulaglutide group showed better BMI values than the liraglutide group (p-value <0.001), **tab. (1)**. With multiple linear regression analysis of our data; FLI, AST and platelet count changes were the significant predictors of the change in log FIB-4 with 69.5% of FIB4 change was predicted by the combination of these factors. ALT change was the only significant predictor of log FLI change, **tab., (3 & 4)**.

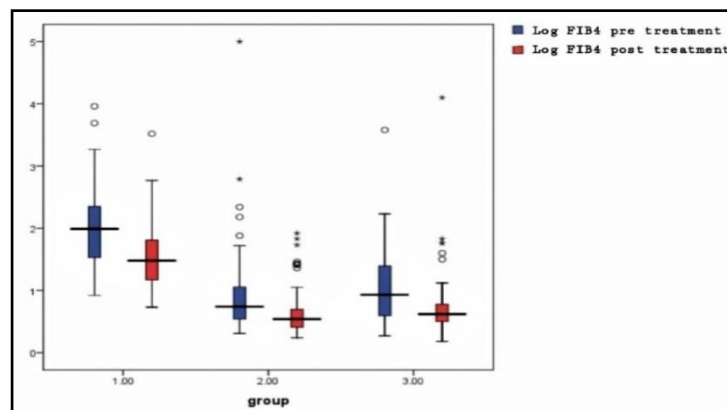
Table 1. Demographic and clinical characteristics between studied groups pre and post treatment

	Group 1 G1 n=65	Group 2 G2 n=79	Group 3 G3 n=80	Test of significance	G1 Vs G2	G1 Vs G3	G2 Vs G3
Age/years Mean±SD	51.45±6.82	49.89±6.69	51.70±7.59	F=1.35 P=0.26	0.214	0.838	0.127
Sex N(%)							
Male	41(63.1)	49(62.0)	54(67.5)	MC	0.89	0.58	0.47
Female	24(36.9)	30(38.0)	26(32.5)	P=0.75			
Duration/years Median (IQR)	9.0(6.0-11.0)	10.0(7.0-16.0)	11.0(7.25-17.75)	KW P=0.001*	0.007*	<0.001*	0.48
Systolic blood pressure 1	151.0±10.87	153.16±9.65	154.63±9.70	F=2.35 P=0.09	0.199	0.03*	0.36
Systolic blood pressure 2	145.52±8.96 P<0.001*	131.58±8.15 P<0.001*	137.25±9.31 P<0.001*	F=44.7 P<0.001*	<0.001*	<0.001*	<0.001*
Diastolic blood pressure 1	92.92±6.67	93.16±6.0	95.94±6.75	F=5.12 P=0.0007*	0.824	0.006*	0.007*
Diastolic blood pressure 2	90.92±5.29 P<0.001*	77.91±5.86 P<0.001*	81.75±8.65 P<0.001*	F=66.54 P<0.001*	<0.001*	<0.001*	<0.001*
Weight/kg 1	98.96±14.33	102.02±18.75	101.54±15.76	F=0.688 P=0.504	0.27	0.35	0.85
Weight / kg 2	104.7±14.09 P<0.001*	88.48±17.03 P<0.001*	89.35±13.31 P<0.001*	F=25.83 P<0.001*	<0.001*	<0.001*	0.715
Height/cm	168.02±8.74	168.06±9.05	169.15±8.46	F=0.413 P=0.66	0.97	0.438	0.435
BMI 1(Kg/m ²)	35.0±3.98	36.06±5.39	35.53±5.05	F=0.838 P=0.434	0.197	0.518	0.495
BMI 2(Kg/m ²)	37.16±4.12 P<0.001*	31.26±5.09 P<0.001*	31.24±4.30 P<0.001*	F=38.91 P<0.001*	<0.001*	<0.001*	<0.001*
Waist Circumference 1/cm	114.78±12.86	115.85±16.04	116.69±13.61	F=0.318 P=0.728	0.656	0.426	0.712
Waist Circumference 2/cm	121.48±13.24 P<0.001*	102.41±14.22 P<0.001*	102.81±11.12 P<0.001*	F=49.43 P<0.001*	<0.001*	<0.001*	0.847

Group 1= control, group 2= liraglutide, group 3= dulaglutide. 1= before treatment & 2= after treatment. Parameters described as mean ± standard deviation, used tests:

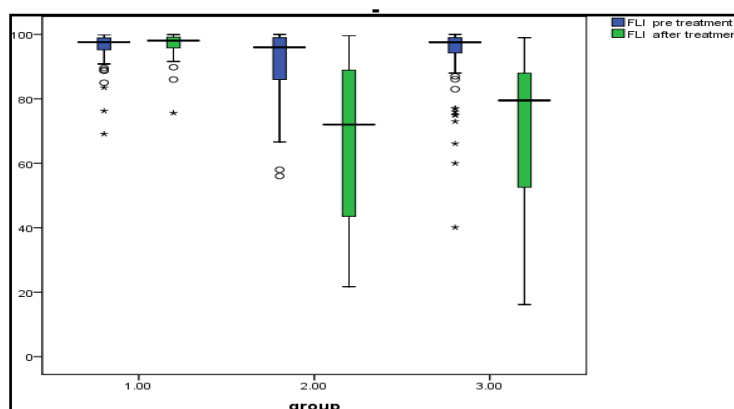
Table 2. Laboratory results of the studied groups pre and post-treatment

	Group 1 G1 n=65	Group 2 G2 n=79	Group 3 G3 n=80	Test of significance	G1Vs G2	G1 Vs G 3	G2 Vs G 3
GGT1	91.83±16.66	60.29±24.45	80.73±31.29	F=29.19 P<0.001*	<0.001*	0.009*	<0.001*
GGT2	79.49±19.94	26.89±13.36	37.91±16.60	F=193.32 P<0.001*	<0.001*	<0.001*	<0.001*
	P<0.001*	P<0.001*	P<0.001*				
TG1	276.85±82.24	236.04±101.84	275.36±163.98	F=2.68 P=0.07	0.05	0.94	0.046*
TG2	224.77±90.2	153.14±77.65	180.21±94.93	F=11.96 P<0.001*	<0.001*	0.003*	0.053
	P<0.001*	P<0.001*	P<0.001*				
ALT1	89.0(75.5-99.5)	75.0(66.0-89.0)	83.5(74.0-94.0)	KW P<0.001*	<0.001*	0.053	0.009*
ALT2	78.0(64.0-92.5)	36.0(29.0-42.0)	39.5(31.0-45.0)	KW P<0.001*	<0.001*	<0.001*	0.072
	P=0.959	P<0.001*	P<0.001*				
AST1	77.25±16.99	43.56±19.22	53.3±23.05	F=51.98 P<0.001*	<0.001*	<0.001*	0.003*
AST2	57.05±14.61	24.41±10.36	27.55±12.1	F=147.98 P<0.001*	<0.001*	<0.001*	0.109
	P<0.001*	P<0.001*	P<0.001*				
Platelet 1	224.88±62.52	308.18±68.26	302.13±66.22	F=34.37 P<0.001*	<0.001*	<0.001*	0.563
Platelet 2	225.06±60.29	337.37±72.93	335.48±71.38	F=60.22 P<0.001*	<0.001*	<0.001*	0.863
	P=0.931	P<0.001*	P<0.001*				
TC 1	204.66±36.36	208.61±35.27	201.05±33.81	F=0.923 P=0.399	0.502	0.538	0.176
TC 2	199.09±39.69	165.1±40.72	176.53±40.59	F=11.34 P<0.001*	<0.001*	0.001*	0.16
	P=0.418	P<0.001*	P<0.001*				
HDL 1	40.03±6.88	41.89±11.07	39.89±11.51	F=1.27 P=0.28	0.279	0.706	0.124
HDL 2	42.82±10.93	43.96±14.0	42.33±12.76	F=0.344 P=0.71	0.59	0.818	0.418
	P=0.11	P=0.062	P=0.015*				
LDL 1	108.63±34.79	117.57±33.06	103.98±40.58	F=2.85 P=0.06	0.144	0.444	0.019*
LDL 2	110.23±41.16	90.88±41.96	93.33±40.94	F=4.49 P=0.012*	0.006*	0.015*	0.71
	P=0.816	P<0.001*	P=0.02*				



Group1(control), Group2(liraglutide), Group3(dulaglutide).

Figure 1. Log FIB-4 score changes before and after treatment in study groups.



Group1 (control), Group2 (liraglutide), Group3 (dulaglutide).

Figure 2. FLI changes before and after treatment in study groups.

Table (3) Multiple linear regression for prediction of log FIB-4 changes

Log FIB-4	β	t	P-value
(Constant)		-10.953	<0.001*
FLI change	.214	3.343	<0.001*
AST change	-.642	-10.640	<0.001*
PLT change	.198	3.094	.002*
R²=0.695			
F=14.82			
P<0.001*			

Table (4) Multiple linear regression for prediction of log FLI changes.

Log FLI	β	t	P-value
(Constant)		.592	.558
ALT change	-.335	-	.028*
		2.303	
R²=0.626			
F=1.87			
P=0.082			

Discussion

Lifestyle modifications of diet, exercise, and weight loss represent the keystone of treatment of NAFLD and NASH. Scarce approved therapeutic options for NAFLD treatment represent a major clinical challenge particularly for patients with T2D¹⁰. Despite the growing promising metabolic effects of GLP1-RAs in T2D patients, the American Association for the Study of Liver Diseases (AASLD) and the National Institute for Health and Care Excellence (NICE) recommendations reported scarcity of the strong evidence to support the use of GLP-1 analogues to specifically treat liver disease in patients with NAFLD^{11,12}. We found a significant reduction of median FIB-4 score and mean FLI in

patients who used liraglutide and dulaglutide versus the conventional treatment. With post-hoc analysis, FIB-4 score was significantly lower in the liraglutide group than the dulaglutide group; however, FLI showed no significant difference in-between the liraglutide and dulaglutide groups. Moreover, there was a significant reduction of ALT, AST and GGT in patients who administrated liraglutide and dulaglutide versus the conventional treatment. Our findings were in accordance with Vilsbøll et al.¹³ who studied the effect of GLP1 receptor agonists on weight status and found a favorable effect of GLP1-RAs on overweight and liver enzymes in pre-marketing studies. Many studies demonstrated



that, a direct action of GLP-1 receptor agonists on GLP-1 receptors located on the hepatocytes enhancing weight-loss and insulin sensitivity even in the absence of diabetes^{14,15}. However, it is unclear whether the beneficial effects of GLP-1 receptor agonists are attributed to hepatic de novo lipogenesis reduction or hepatic fat oxidation increase. In vitro, GLP-1 receptors were found on hepatocytes and the direct interaction with GLP-1 receptor agonists alleviated hepatic steatosis by reducing hepatic lipogenesis as well as enhancing fatty acid consumption¹⁶. Gupta et al. found that, GLP-1 receptor agonists use in murine NASH models led to an improvement of liver enzymes, oxidative stress, liver histology as well as weight and diabetic control¹⁷. As well as, Fan et al. that demonstrated the insulin-sensitizing effect of liraglutide through its direct action on GLP-1 receptors expressed on hepatocytes in obesity and diabetes mice leading to a significant improvement of fasting plasma glucose levels, HOMA-IR and hepatic steatosis¹⁸. Our results in the liraglutide group agreed with Tong et al.¹⁹ who studied the effect of liraglutide on the rate of gastric emptying and found a significant weight loss with improvement of insulin sensitivity and hepatic steatosis. Also, Matikainen et al.²⁰ found a significant reduction of both visceral and subcutaneous adipose tissue estimated by the bioimpedance analysis (BIA) method with subsequent improvement of hepatic fat content after 16 weeks of treatment with liraglutide, however our study was of longer duration and different methodology. Also, Armstrong et al.²¹ studied the effect of liraglutide on insulin resistance and lipotoxicity in patients with nonalcoholic steatohepatitis (NASH) and found beneficial metabolic effects of liraglutide through decreasing de-novo lipogenesis although their study was carried out on 14 patients for 12 weeks only. Despite different methodology and study design, our findings agreed with the LEAN trial that was carried out on patients with biopsy-proven NASH, liraglutide administered subcutaneously once-daily for 48 weeks resulted in enhanced greater histological resolution of NASH and delayed fibrosis progression⁹. Eguchi et al.²² and Petit et al.²³ studied the effect of liraglutide in different population and found a significant improvement of the NAFLD activity score, which agreed with our findings despite different methodology and ethnicity. Our findings may be attributed to the significant improvement of glycaemic control and weight reduction. However, Yang et al. attributed the liraglutide induced amelioration of hepatic steatosis in NAFLD patients to the up-regulation of the IRS2/PI3K/Akt signaling mediators which enhanced the expression and activation of insulin signaling proteins²⁴. In contrary to, Luo et al.²⁵ who explained the positive effect of liraglutide on hepatic

steatosis through down-regulating the expression of inflammatory and pro inflammatory cytokines, such as IL-1 β and TNF- α , thereby improving lipid profile and attenuating NAFLD development in diabetic mice. In contrast to our findings, Tang et al.²⁶ found insignificant changes of liver fat content with liraglutide. However, their study included only 35 patients for 12 weeks. In the dulaglutide group, our findings agreed with Cusi et al.²⁷ who carried out Sub-analyses of the AWARD program (AWARD-1, AWARD-5, AWARD-8 and AWARD-9) and found that once-weekly dulaglutide had significantly reduced serum ALT, AST and GGT levels compared with a placebo due to its efficacy in body weight reduction and glycaemic control. We used FLI and FIB-4 score to assess hepatic steatosis and fibrosis but Seko et al.²⁸ used liver biopsy and fibroscan to assess liver steatosis and stiffness and found a significant improvement of liver enzymes and liver stiffness with dulaglutide that coincided with our results. Sumida et al.²⁹ showed the cardioprotective and renoprotective effects of GLP1-RAs that may mediate a beneficial metabolic effect on hepatic steatosis. We found a significant reduction of TG, TC, LDL-C and HBA1c in patients used liraglutide and dulaglutide versus the conventional treatment, but the liraglutide group achieved better values of VLDL-C and HBA1c. In accordance with Matikainen et al.²⁰ and Marso et al.³⁰ who attributed the cardioprotective effects of GLP-1 receptor agonists to the better glycaemic control, weight loss and plasma lipids changes. In our study, liraglutide achieved the highest effect in amelioration of SBP and DBP which were significantly reduced in the liraglutide and the dulaglutide groups versus the conventional treatment. In accordance with Zhao et al.³¹ and Rosso et al.³² who demonstrated the beneficial effect of liraglutide on the arterial blood pressure in individuals with or without hyperglycemia compared with placebo providing additional evidence for cardiovascular protection effect. In this study, a significant reduction of BW, BMI and WC in patients who used liraglutide and dulaglutide versus the conventional treatment, but BMI was significantly lower in the dulaglutide group. In accordance with Inagaki et al.³³ who found the addition of dulaglutide to metformin resulted in higher significant weight loss in patients with T2D. Also, Garg and Kumar reported that the use of dulaglutide as first, second, or third-line therapy in T2D management promotes weight loss with improving β -cell function, blood pressure control, serum lipid levels and cardiovascular benefits³⁴. The major points of strength in our study were that, the use of two different GLP1-receptor agonists (liraglutide and dulaglutide) and reasonable number of participants in each arm. However, we have limitations as it was a single-center study and the ethnicity issue.



Conclusion

GLP-1 receptor agonists exert beneficial effects on hepatic steatosis in Egyptian patients with T2D with better results after liraglutide administration. Further prospective multi-center double blinded trials with invasive histopathology and long term follow up are warranted in the future.

Abbreviations

Non-alcoholic fatty liver disease (**NAFLD**)
Type 2 diabetes mellitus (**T2D**).
Non-alcoholic steatohepatitis (**NASH**)
Thiazolidendions (**TZDs**)
Glucagon like peptide receptor agonists (**GLP1-RAs**)
Sodium glucose co-transporters inhibitors (**SGLT2i**)
Body mass index (**BMI**)
Fatty liver index (**FLI**)
Fibrosis-4 index (**FIB-4**)
Insulin resistance (**IR**)
Body weight (**BW**)
Waist circumference (**WC**)
American Association for the Study of Liver Diseases (**AASLD**)
National Institute for Health and Care Excellence (**UK**) (**NICE**).

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