RESEARCH ARTICLE

Role of oral hypoglycaemic drugs in preventing complication in non-alcoholic fatty liver disease with type 2 diabetes mellitus

Museera Zahid[1], Samia Perwaiz Khan[2], Sana Ershad[3], Safia Izhar[4], Rizwana Warraich[5], Ali Asghar[6]

Abstract

Objective: To determine the prevalence of non-alcoholic fatty liver disease, and the effect of oral hypoglycaemic drugs and lifestyle modifications in reducing fatty liver changes and liver enzymes in these patients.

Method: The comparative, observational study was conducted at the Department of Pharmacology, Sohail University, Karachi, from October 2022 to October 2023, and comprised patients of either gender having elevated liver enzymes and ultrasound finding of fatty liver changes along with raised glycated haemoglobin, transaminases, total cholesterol and triglycerides. The participants were prescribed oral hypoglycaemic agents by endocrinologists. Those given empaglifazolin + metformin were in group A, empaglifazolin + linglaptin in group B, sitaglaptin + metformin in group C, metformin alone in group D and sitaglaptin alone in group E. Lifestyle modifications were advised in all the treatment groups, while control group F was only advised lifestyle modifications. The intervention lasted 3 months. Investigations included B-mode ultrasound liver, liver enzymes and glycated haemoglobin, which were done at baseline and after the intervention. Data was analysed using SPSS 25.

Result: Of 200 patients, 40 were males and 160 were females in ratio of 1:4. The overall mean age was 48±16 years. There were 154(77%) patients who had non-alcoholic fatty liver disease with type 2 diabetes mellitus, while 46(23%) had only fatty liver changes. There were 50(25%) patients in group A, 30(15%) in group B, 30(15%) in group C, 40(20%) in group D, 10(5%) in group E and 40(20%) in group F. Post-intervention improvement was noted in 48(24%) patients, with 20(41.7%) of them being in group A.

Conclusion: The prevalence of non-alcoholic fatty liver disease with type 2 diabetes was high. Combination of empagliflozin + metformin along with lifestyle modifications was highly effective in reducing fatty changes and the level of liver enzymes.

Keywords: Non-alcoholic fatty liver diseases, Metformin, SGLT2- inhibitor, Type 2 diabetes mellitus, AST, ALT.

(JPMA 74: 1654; 2024) **DOI: https://doi.org/10.47391/JPMA.11151**

Introduction

Non-alcohol fatty liver disease (NAFLD) is one of the chronic liver diseases[1,2] and has shown to be related to metabolic syndrome (MS) which may be caused by accumulation of fats in the liver. This is associated with type 2 diabetes mellitus (T2DM), raised body mass index (BMI) and spike in triglyceride (TG) levels which increase the risk of hepatic and cardiovascular diseases. Although, NAFLD initially affected the Western countries,[3] it has now been reported in developing nations, such as Pakistan.[1,2] The patients may develop aggressive fatty liver changes that are observed as liver inflammation, and lead to cirrhosis and liver failure. According to a study,1 the patients having T2DM for >5 years and have high alanine transaminase (ALT) levels had NAFLD prevalence rate of 56% on the basis of liver biopsy1. In another study among 26 T2DM patients, the prevalence rate was 75%.[3] NAFLD prevalence has generally ranged 35-72% in diagnosed T2DM patients with high glycated haemoglobin (HbAIc) level.[3]

Sudies3-5 have shown that there is a bidirectional relationship between T2DM and NAFLD. T2DM and obesity are both independently linked with an increased risk of developing NAFLD and cardiac complications.[3] Patients with a baseline diagnosis of NAFLD and T2DM have a greater risk of developing liver cirrhosis and hepatocellular cancer (HCC), and mortality rate is also higher among such patients. Impaired insulin sensitivity and enhanced hepatic glucose production are predictors of NAFLD, and the accumulation of specific lipids in the liver can affect insulin signalling. Increased levels of transaminase are positively linked to the future risk of developing T2DM. Thus, patients with NAFLD have a more than two-fold increased risk of developing T2DM. Given the complex interrelationship between NAFLD and T2DM, it has been recommended that NAFLD should be treated by oral hypoglycaemic drugs

[1]Medicare Cardiac and General Hospital, Sohail University, Karachi, Pakistan; [2,3]Department of Pharmacology, Jinnah Medical and Dental College, Sohail University, Karachi, Pakistan; [4]Department of Radiology, Medicare Cardiac and General Hospital, Jinnah Medical and Dental College, Sohail University, Karachi, Pakistan; [5]Department of Molecular Biology, Jinnah Medical and Dental College, Sohail University, Karachi, Pakistan; [6]Department of Endocrinology, Medicare Cardiac and General Hospital, Jinnah Medical and Dental College, Sohail University, Karachi, Pakistan.

Correspondence: Samia Perwaiz Khan. e-mail: samiaphk@gmail.com

ORCID ID: 0000-0003-3154-1785

Submission complete: 26-11-2023 **Review began:** 26-01-2024

Acceptance: 10-07-2024 **Review end:** 15-06-2024

(OHDs). The interrelationship between NAFLD and T2DM suggests that it may be beneficial to take a holistic approach for treating NAFLD as a metabolic disease by focussing on improving insulin sensitivity and hyperglycaemia along with fatty changes in the liver. High incidence of HCC in these patients has been reported even without cirrhosis.[4] Sung et al.[5] found in a cohort study of over 12,000 South Korean adults that obesity, insulin resistance (IR) and ultrasound-diagnosed NAFLD were associated with a doubled risk of developing T2DM. When all the three risk factors were present together, the risk of developing T2DM increased by approximately 14 times. Several studies[5-7] have shown that NAFLD is linked with an approximate doubling of the risk of T2DM, which may lead to hepatic steatosis and liver fibrosis. By combining available evidence and bias analysis[6] higher risk of T2DM in individuals with NAFLD has been confirmed, and suggests a causal link between NAFLD and T2DM.

Studies[7-9] have also shown increased risk of cardiovascular diseases in patients with NAFLD and T2DM even in low to normal body mass index (BMI) groups. Untreated fatty liver diseases lead to complications, like ascites, oesophageal varicose, enlarged spleen, hepatic encephalopathy, liver cancer and liver failure. Raised BMI levels lead to raised TG and low-density lipoprotein (LDL) levels, enhancing the risk of cardiovascular diseases due to dyslipidaemia, hypertension (HTN) and enhanced incidence of T2DM.[8,9]

NAFLD treatment by lifestyle modification[10] and OHDs[11] is used to lower BMI, blood glucose levels, and target the underlying pathophysiological mechanisms that are common in T2DM and NAFLD. These mechanisms include dysfunction of the adipose tissue which is associated with obesity and IR. The use of anti-hyperglycaemic drugs aims at improving insulin sensitivity and regulate glucose metabolism, showing the interconnections between T2DM and NAFLD.[11,12] A study[12] has shown that OHDs like metformin, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium glucose co-transporter-2 (SGLT-2) inhibitors are effective, having better outcome, with weight-loss and lower BMI. Thus, it is very important to treat NAFLD associated with T2DM because together they increase the progress of fatty liver changes. Up till now, lifestyle modifications[10] and glucose-lowering agents, like peroxisome proliferator-activated receptor (PPAR) agonists, GLP-1R agonist and SGLT2 inhibitor[11] are considered useful in the treatment of NAFLD. Metformin is extensively used for lowering blood glucose levels in individuals with T2DM who do not have diabetes-associated complications. Metformin mainly exerts its clinical effects by moderately reducing bodyweight and inhibiting hepatic gluconeogenesis. However, the effects of metformin on NAFLD are not conclusive.[10] Metformin is a widely recommended and effective medication for the treatment of T2DM. It is considered safe, and also reduces HbA1c levels by approximately 0.5% to 1%. Metformin works by improving hepatic glucose metabolism, increasing glucose uptake in muscle cells, and influencing cellular energy charge and other mechanisms.[10] SGLT2 inhibitors are a class of drugs used to treat T2DM. They work by reducing renal tubular glucose reabsorption, leading to a decrease in hyperglycaemia and bodyweight, while these factors contribute to reduction in the risk of cardiovascular diseases in patients with T2DM.[11] In terms of these effects on NAFLD, SGLT2 inhibitors have been found beneficial.

Dipeptidyl-peptidase IV (DPP-4) inhibitors, which inhibit the degradation of the incretins, GLP-1 and glucose-dependent insulin tropic peptide (GIP), inhibit glucagon release and increase insulin secretion, decrease gastric emptying, and decrease blood glucose levels. DPP-4 inhibitors have not been shown to decrease bodyweight or improve cardiovascular outcomes in the context of NAFLD.[11,12]

The current study was planned to determine the prevalence of fatty liver disease with T2M, and the impact of OHD therapy along with lifestyle modification in reducing fatty changes in liver and liver enzymes levels.

Patients and Methods

The comparative, observational study was conducted at the Department of Pharmacology, Sohail University, Karachi, from October 2022 to October 2023 and comprised patients of either gender having elevated liver enzymes and ultrasound finding of fatty liver changes along with raised HbA1c, transaminases, total cholesterol (TC) and TGs. The sample was raised using convenience sampling technique from among the patients visiting Sohail Trust Hospitals and Medicare Cardiac and General Hospital, Karachi. Patients with bile duct disease, hepatitis, jaundice, liver cancer, haemochromatosis, Wilson's disease and those who were alcoholics were excluded. After approval from the institutional ethics review committee, the sample size was calculated using OpenEpi online calculator,[13] where N was the required sample size, with 95% level of confidence and 5% chance of error.

Patients with complaints of anorexia, nausea, increased BMI, with or without T2DM were approached at the diabetic outpatient department (OPD). After taking written informed consent, the patients were advised blood test to check liver enzyme levels, and ultrasound to rule out sonographic fatty liver changes. The blood tests advised included serum glutamic pyruvic transaminase [SGPT], serum glutamic-oxaloacetic transaminase [SGOT], TC, TG,

HbA1C and urine test for glucose. The participants were then prescribed OHDs by the endocrinologist.

In the radiology department, the sonologist performed ultrasound of all patients referred by the endocrinologist. The ultrasound of abdomen was performed on ultrasound machine (Samsung HS-40 Japan) after 6-8 hours of fasting. The patients were in a supine position and that the liver and gall bladder could be seen with 2.5-3.5MHz convex probe (curvilinear transducer). The size of liver was taken as normal up to 15cm in females and up to 16cm in males. Beyond that, the eco-texture of liver was observed to see whether or not the liver was hyper-echoic. In NAFLD patients, liver echogenicity was raised, indicating fatty infiltration in the liver.

Blood samples were obtained from these patients after 12 hours of fasting. They were then referred back to the endocrinologist to prescribe OHDs, according to fatty changes and the level of liver enzymes. Those given empaglifazolin+metformin were in group A, empaglifazolin +linglaptin in group B, sitaglaptin+metformin in group C, metformin alone in group D, and sitaglaptin alone in group E. Lifestyle modifications were advised in all the treatment groups, while control group F was only advised lifestyle modifications. The intervention lasted 3 months. Baseline investigations were repeated at the end of the intervention.

Data was analysed using SPSS 25. Descriptive statistics were used for determining mean±standard deviation. Inferential statistics were used with t-test. P<0.05 was considered significant.

Table-1: Patient characteristics (n=200).

Characteristics	Fatty liver Changes+type 2 DM n=154	Fatty changes only n = 46	*p*-value
Age (years)			
20-40	30	03	> 0.05
40-60	104	40	
60- 80	20	03	
Gender M: F - 1:4	31: 123	9:37	> 0.5
Mean BMI (kg/m²)	27±5	20±2	>0.001
Type 2 DM HbAlc (%)	154	46	>0.001
Mean Lipid profile			
Cholesterol	205±5	200±6	> 0.05
Triglycerides	130±4	70±5	
Mean Liver Enzymes			
SGPT/	150±5	0±3	> 0.05
SGOT	50 ±5	30±3	
U/S Changes			
Grade -I	60	30	> 0.001
Grade -II	94	16	

DM: Diabetes mellitus, BMI: Bod mass index, HbA1c: Glycated haemoglobin,
SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic-oxaloacetic transaminase.

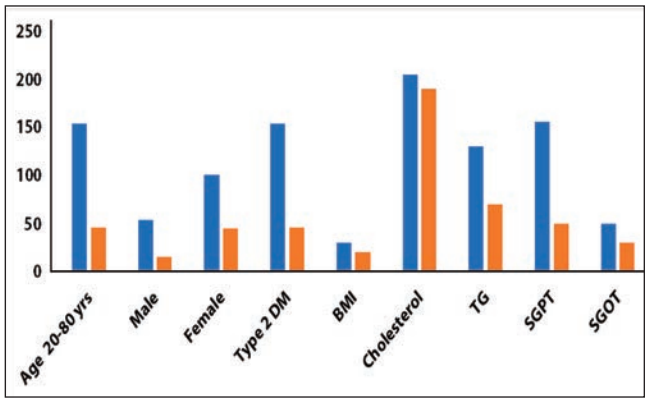

Figure: Characteristics of patients having non-alcoholic fatty liver disease (NAFLD) with type 2 diabetes mellitus (T2DM) (blue bar), and patients with NAFLD alone (orange bar).

Table-2: Post-intervention improvement (n=200).

Therapy	Number of patients	Ultrasound improvement (Grade – I) n (%)
Empagliflozin/metformin	50	20 (10)
Empagliflozin/linagliptin	30	10 (5)
Metformin	40	8 (4)
Sitagliptin and metformin	30	5 (3)
Sitagliptin	10	2 (1)
Lifestyle modification only	40	3 (2)
	200	48 (24)

Results

Of 200 patients, 40 were males and 160 were females in ratio of 1:4. The overall mean age was 48±16 years. There were 154(77%) patients who had NAFLD with T2DM, while 46(23%) had only fatty liver changes (Table 1). Characteristics of patients having non-alcoholic fatty liver disease (NAFLD) with type 2 diabetes mellitus (T2DM) (blue bar), and patients with NAFLD alone (orange bar), given in (Figure.1)

There were 50(25%) patients in group A, 30(15%) in group B, 30(15%) in group C, 40(20%) in group D, 10(5%) in group E, and 40(20%) in group F. Post-intervention improvement was noted in 48(24%) patients, with 20(41.7%) of them being in group A (Table 2).

Discussion

The current study Comprised 200 patients of both genders who had been diagnosed with NAFLD. Of them, 154(77%) patients had T2DM, while 46(23%) had pre-diabetics. Empagliflozin+metformin had significantly positive impact on BMI, TG and liver enzyme levels.

Several studies[14-17] have shown the increased association of NAFLD with T2DM, with obesity having a significant role in enhancing the risk of cardiovascular diseases in such patients. Study[3] DPP-4 inhibitors sitagliptin or vildagliptin as a therapy for non-alcoholic fatty liver in diabetics did not

show considerable improvement in HbAIc, and not much improvement in fatty liver changes. Another study[18] showed that 3 months of therapy led to reduction in fatty liver changes, BMI, TG, LDL levels. Studies18-20 have reported NAFLD as an epidemic, and the treatment of choice being OHDs. Others have reported lifestyle modifications and pharmacotherapy using insulin secretagogues having definite benefits in the management of this condition.[19-21] On comparing low-bodyweight NAFLD patients with obese or overweight patients, a study reported 20% of even the slim patients had high fibrosis scores as well as carotid atherosclerosis.[17] OHDs, such as metformin, were ideal for lowering BMI, HbAIC and bodyweight in such patients.[17]

Studies[20,21] conducted in adults with biopsy-proven NAFLD showed that metformin had a modest effect on liver enzymes and HbA1c levels, but did not significantly impact liver steatosis, inflammation, resolution of non-alcoholic steatohepatitis (NASH) or liver fibrosis. Although metformin is generally well-tolerated, but gastrointestinal symptoms and vitamin B12 deficiency can occur in some individuals. Combination of metformin (insulin secretagogues) and sitagliptin has beneficial effects on HbAIc level, BMI and insulin sensitivity21. A recent study[22] reported better outcome with SGLT2 inhibitors in the management of NAFLD and T2DM. Metformin and SGLT2 inhibitors have shown significant decrease in HbAIc levels and blood glucose levels,[23-25] and have been studied for better outcomes in NAFLD. Pioglitazone improved fatty changes in the liver, but increased bodyweight, enhancing the cardiovascular risk.[26] Metformin and SGLT2 inhibitors have been reported to be beneficial in obese patients as they reduce BMI, HbAIc and liver enzyme levels.[27,28]

A study showed that the combination of empagliflozin and metformin had better outcome as it reduced IR, BMI, HbAIc and bodyweight.[29]

The current study had limitations, as a number of patients were lost to follow-up, and, therefore, data could not be collected for all the patients post-intervention.

Conclusions

Fatty liver could be managed with OHDs, but the most improvement was seen in patients on empagliflozin+ metformin therapy, followed by those on metformin alone.

Limitations: The current study had limitations, as a number of patients were lost to follow-up, and, therefore, data could not be collected for all the patients post-intervention.

Acknowledgement: We are grateful to the Dean, Faculty of Health Sciences, and the staff of the Radiology Department, Medicare Cardiac and General Hospital, for facilitating the study.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

References

1. Seetlani NK, Memon AR, Tanveer S, Ali A, Ali P, Imran K, et al. Frequency of Non-Alcoholic Steatohepatitis on Histopathology in Patients of Type 2 Diabetes Mellitus with Duration of More than 5 Years. J Coll Physicians Surg Pak 2016;26:643-6.
2. Abbas Z, Zaheer R. Non-alcoholic fatty liver disease: A real threat in Pakistan. J Pak Med Assoc 2020;70(B):2437-40. doi: 10.5455/JPMA.95891
3. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol 2013;10:330-44. doi: 10.1038/nrgastro.2013.41.
4. Targher G, Corey KE, Byrne CD, Roden M. The complex link between NAFLD and type 2 diabetes mellitus - mechanisms and treatments. Nat Rev Gastroenterol Hepatol 2021;18:599-612. doi: 10.1038/s41575-021-00448-y
5. Sung KC, Yoo TK, Lee MY, Byrne CD, Zheng MH, Targher G. Comparative Associations of Nonalcoholic Fatty Liver Disease and Metabolic Dysfunction-Associated Fatty Liver Disease With Coronary Artery Calcification: A Cross-Sectional and Longitudinal Cohort Study. Arterioscler Thromb Vasc Biol 2023;43:482-91. doi: 10.1161/ATVBAHA.122.318661
6. Ali A, Amin MJ, Ahmed MU, Taj A, Aasim M, Tabrez E. Frequency of non-alcoholic fatty liver disease (NAFLD) and its associated risk factors among Type-2 diabetics. Pak J Med Sci 2022;38:28-33. doi: 10.12669/pjms.38.1.4968
7. Ishido S, Tamaki N, Takahashi Y, Uchihara N, Suzuki K, Tanaka Y, et al. Risk of cardiovascular disease in lean patients with nonalcoholic fatty liver disease. BMC Gastroenterol 2023;23:211. doi: 10.1186/s12876-023-02848-7
8. Rashid A, Zafar S, Bashir A, Bakht K, Bhalli AU. Presence of non-alcoholic fatty liver disease in patients of uncontrolled and controlled type 2 diabetes mellitus. Pak Armed Forces Med J 2019;69:822-25.
9. Lu H, Zeng L, Liang B, Shu X, Xie D. High prevalence of coronary heart disease in type 2 diabetic patients with non-alcoholic fatty liver disease. Arch Med Res 2009;40:571-5. doi: 10.1016/j.arcmed.2009.07.009
10. Ezpeleta M, Gabel K, Cienfuegos S, Kalam F, Lin S, Pavlou V, et al. Effect of alternate day fasting combined with aerobic exercise on non-alcoholic fatty liver disease: A randomized controlled trial. Cell Metab 2023;35:56-70. doi: 10.1016/j.cmet.2022.12.001
11. 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;8:179-91. doi: 10.1016/S2468-1253(22)00338-7
12. Cui J, Philo L, Nguyen P, Hofflich H, Hernandez C, Bettencourt R, et al. Sitagliptin vs. placebo for non-alcoholic fatty liver disease: A randomized controlled trial. J Hepatol 2016;65:369-76. doi: 10.1016/j.jhep.2016.04.021.
13. Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version: 3.01. [Online] 2013 [Cited 2024 July 11]. Available from URL: https://www.openepi.com/Menu/OE_Menu.htm
14. Bhatt HB, Smith RJ. Fatty liver disease in diabetes mellitus.

Hepatobiliary Surg Nutr 2015;4:101-8. doi: 10.3978/j.issn.2304-3881.2015.01.03

15. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73-84. doi: 10.1002/hep.28431
16. Prabhakar A, Ambili NR, Kartha TDU, Renymol B. Prevalence of non-alcoholic fatty liver disease (NAFLD) in patients with type 2 diabetes mellitus and its correlation with coronary artery disease (CAD). Int J Res Med Sci 2017;5:5175-81. doi: 10.18203/2320-6012.ijrms 20175079
17. Adams LA, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut 2017;66:1138-53. doi: 10.1136/gutjnl-2017-313884
18. Tilg H, Moschen AR, Roden M. NAFLD and diabetes mellitus. Nat Rev Gastroenterol Hepatol 2017;14:32-4. doi: 10.1038/nrgastro.2016.147
19. Lin YH, Zhang ZJ, Zhong JQ, Wang ZY, Peng YT, Lin YM, et al. Semaglutide combined with empagliflozin vs. monotherapy for non-alcoholic fatty liver disease in type 2 diabetes: Study protocol for a randomized clinical trial. PLoS One 2024;19:e0302155. doi: 10.1371/journal.pone.0302155.
20. Tan DJH, Ng CH, Lin SY, Pan XH, Tay P, Lim WH, et al. Clinical characteristics, surveillance, treatment allocation, and outcomes of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. Lancet Oncol 2022;23:521-30. doi: 10.1016/S1470-2045(22)00078-X
21. Dos Santos LR, Duarte ML, Peccin MS, Gagliardi ART, Melnik T. Dipeptidyl Peptidase IV Inhibitors for Nonalcoholic Fatty Liver Disease - Systematic Review and Metanalysis. Curr Diabetes Rev 2021;17:e101120187811. doi: 10.2174/1573399816999201110195634
22. Mantovani A, Byrne CD, Scorletti E, Mantzoros CS, Targher G. Efficacy and safety of anti-hyperglycaemic drugs in patients with non-alcoholic fatty liver disease with or without diabetes: An updated systematic review of randomized controlled trials. Diabetes Metab 2020;46:427-41. doi: 10.1016/j.diabet.2019.12.007.
23. Mazza A, Fruci B, Garinis GA, Giuliano S, Malaguarnera R, Belfiore A. The role of metformin in the management of NAFLD. Exp Diabetes Res 2012;2012:716404. doi: 10.1155/2012/716404
24. Ferguson D, Finck BN. Emerging therapeutic approaches for the treatment of NAFLD and type 2 diabetes mellitus. Nat Rev Endocrinol 2021;17:484-95. doi: 10.1038/s41574-021-00507-z
25. Alkabbani W, Gamble JM. Profile of Ipragliflozin, an Oral SGLT-2 Inhibitor for the Treatment of Type 2 Diabetes: The Evidence to Date. Drug Des Devel Ther 2021;15:3057-69. doi: 10.2147/DDDT.S281602
26. Ito D, Shimizu S, Inoue K, Saito D, Yanagisawa M, Inukai K, et al. Comparison of Ipragliflozin and Pioglitazone Effects on Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes: A Randomized, 24-Week, Open-Label, Active-Controlled Trial. Diabetes Care 2017;40:1364-72. doi: 10.2337/dc17-0518
27. Zhou J, Massey S, Story D, Li L. Metformin: An Old Drug with New Applications. Int J Mol Sci 2018;19:2863. doi: 10.3390/ijms19102863
28. Mirarchi L, Amodeo S, Citarrella R, Licata A, Soresi M, Giannitrapani L. SGLT2 Inhibitors as the Most Promising Influencers on the Outcome of Non-Alcoholic Fatty Liver Disease. Int J Mol Sci 2022;23:3668. doi: 10.3390/ijms23073668
29. Caturano A, Galiero R, Loffredo G, Vetrano E, Medicamento G, Acierno C, et al. Effects of a Combination of Empagliflozin Plus Metformin vs. Metformin Monotherapy on NAFLD Progression in Type 2 Diabetes: The IMAGIN Pilot Study. Biomedicines 2023;11:322. doi: 10.3390/biomedicines11020322.

Author Contribution:

MZ: Literature search, study design, questionnaire design, data collection, writing, analysis and interpretation.
SPK: Study design, concepts, data collection, writing, data analysis and drafting.
SE, SI: Data collection, writing and data analysis.
RW: Review of final draft.
AA: Data collection, review of final draft.