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THE EFFECT OF MELATONIN, METFORMIN AND URSODEOXYCHOLIC ACID ON NON-ALCOHOLIC FATTY LIVER DISEASE: A RANDOMIZED, DOUBLE-BLINDED CONTROLLED TRIAL

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Objective: *This study was to investigate and compare the effect of melatonin, metformin, and ursodeoxycholic acid (UDCA) on non-alcoholic fatty liver disease(NAFLD).* ***Methods****: In this randomized double-blinded clinical trial, 120 patients with NAFLD who had been referred to Gastrointestinal and Liver Diseases Research Center, Rasht, Iran, between September 2015 and January 2016. Patients were randomly assigned to 4 groups. Each group received melatonin, metformin, UDCA, or placebo in addition to a weight loss diet for 3 months.* ***Results****: A significant reduction was observed in levels of steatosis, alanine aminotransferase, alkaline phosphatase, body weight, BMI, waist circumstance and triacylglycerol among participants in groups with metformin or melatonin administration. In addition a significant decrease in fasting plasma glucose, and total cholesterol concentration was detected following metformin and UDCA administration, respectively.* ***Conclusions****: The present study suggests that the addition of metformin or melatonin to a low-caloric diet may be effective in the treatment of patients with NAFLD.*

Keywords*: Melatonin, Metformin, Ursodeoxycholic acid, Non-alcoholic fatty liver disease*

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common hepatic disorders worldwide, which affects populations in both developed and developing countries[1-3] .NAFLD is defined as evidence of hepatic steatosis without evidence of hepatocellular injury, and ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), with or without fibrosis[4]. The prevalence of NAFLD has proliferated in recent years, attributed to urbanization and changes in lifestyle, and has thus become the third most likely cause of liver transplantation[5].In a cohort study in the north Iran, the prevalence of NAFLD was 44.2 % and 44.2 % and 40.1 % in women, and men respectively[6]. Based on a study in the south of Iran, the prevalence of NAFLD was 21.5 %[7].

If NAFLD is not diagnosed expediently, and subsequently appropriately managed, it can progress to chronic liver damage, such as cirrhosis of the liver and hepatocellular carcinoma (HCC)[8] . Several agents have been proposed for the treatment of NAFLD, however, no consensus on effective medical therapy has been established. Notwithstanding, although lifestyle modification is suggested as a first step in the management of NAFLD, its compliance is often low, and most patients fail to follow recommended guidance[9-11]. For these reasons, it is of contemporary interest and clinical importance that effective medical treatments of NAFLD be established; to that end, several drugs such as metformin, gemfibrozil, UDCA, and melatonin have been proposed as a potentially efficacious treatments[11-14].

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As insulin resistance plays an important role in NAFLD pathogenesis[15&16], agents that possess insulin resistive activity may be of therapeutic value[17]. Metformin (1, 1-dimethylbiguanide hydrochloride), an agent of the biguanide class, is an oral anti-hyperglycemic agent that has, historically, been used in patients with diabetes mellitus to decrease blood glucose levels[18] .Moreover, it acts as an insulin-sensitizing agent against peripheral insulin resistance and reduces endogenous and exogenous insulin requirements, as well as attenuating hepatic glucose production[19&20] Concomitant to insulin resistance, oxidative stress also plays a critical role in the onset and progress of NAFLD[21]. In this regard, several antioxidant agents have been suggested as viable in the treatment of NAFLD[22] Melatonin (N-acetyl-5-methoxytryptamine) is a serotonin-derived neurohormone that is produced by the pineal gland, and has numerous biological functions[23], influencing the immune system, and possesses free radicals scavenging, antioxidative, anti-inflammatory and anti-apoptotic properties[24]. Ursodeoxycholic acid is another agent which has been proposed for the treatment of NAFLD, primarily due to its capability to decrease concentrations of hydrophobic bile acid in biliary and serum, reduce tumor necrosis factor-α levels, and suppress oxidative stress[25-27]. Several animal studies have investigated the aforementioned medications about NAFLD and reported promising findings. However, there is a distinct dearth of empirical evidence from human studies. Therefore, the present study aimed to investigate and compare the effect of melatonin, metformin, and UDCA on NAFLD.

MATERIAL AND METHODS

The present study was performed based on the CONSORT statement recommendation and registered at IRCT (IRCT201407201155N21). Also, the experimental protocol was abided by the principles set out in the Declaration of Helsinki. Also, the present study was approved by Ethics Committee of Guilan University of Medical Sciences (1930231612).

Study participants

This study was a double-blinded randomized controlled trial in which 120 subjects aged 18-70 with NAFLD diagnosed and mild to moderate steatosis were included. Subjects were recruited from the patients who had been referred to Razi hospital or gastrointestinal clinics, Guilan, Iran, between September 2015 and January 2016. NAFLD was diagnosed and confirmed by (assessment of transient elastography) fibroScan and elevated levels of ALT serum concentrations. The sample size was calculated, *a priori*, using a type one error of (α) =0.05 and power =80%. After considering 20% dropout, 30 subjects were calculated as necessary for each group. Patients were excluded if they had a history of chronic disease, including cardiovascular disease, pulmonary coronary disease, inflammatory systemic diseases, diabetes, metabolic syndrome or chronic kidney disease or hepatitis, alcohol consumption, cirrhosis, hereditary hemochromatosis, Wilson's disease Cushing's syndrome, antioxidant supplementation, drug toxicity, and gastrointestinal surgery, or were pregnant/lactating.

Study design

First, all eligible participants, according to inclusion and exclusion criteria, commenced a 2-weeks run-in period and were requested to complete a written informed consent. Next, subjects were randomly assigned into 4 groups by block-randomization (1:1:1:1 ratio), adjusting for age, gender, and level of steatosis. The randomization allocation sequence was performed by a research assistant who was not involved in the study, therefore, researchers were concealed to randomization and allocation, as well as the participants, until final analysis was completed. All participants were instructed to self-administer metformin (500 mg, twice a day)[28], melatonin (10 mg, once a day)[29&30], UDCA (300 mg, twice a day)[31], or placebo along with a standardized weight loss diet for 3-months. Drug therapies and placeboes were pre-packaged and encoded by trained staff. The packages were indistinguishable, and blinding of researcher and participants were guaranteed. The weight loss diet was (500 kcal less than individual estimated energy requirement) specialized for

each patient and prescribed at the first of each month for the following month. Patients were also asked not to take any supplements and not to change their usual lifestyle. The subject's adherence was monitored by phone and monthly face-to-face interviews, in addition to assessments of un-consumed drugs.

Anthropometric and biochemical measurements

Weight, height, and waist circumstances were determined pre and post-intervention, with the participant in a fasted status, with minimal clothes and unshod. The measurements were performed by a trained kinanthropometrist.

A 10 mL overnight fasting blood sample was taken from each participant at baseline and after 12-weeks to determine liver enzymes, serum lipids, fasting plasma glucose (FPG), and HbA1C concentrations. All samples were stored at -70 C before analysis. To determine the level of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), triacylglycerol (TG), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), FPG and HbA1C, routine enzymatic assays were applied by using commercially available kits (Pars Azmoon, Tehran, Iran).

Histopathology

Liver stiffness was assessed by using FibroScan (502 touch, Echosense, France)[32], while participants were in the supine position, and the probe was placed on the right lobe of liver in the intercostal position. The results of the liver stiffness were presented as absent of fibrosis (F0) and perisinusoidal or portal fibrosis (F1), perisinusoidal and portal or periportal fibrosis (F2), septal and bridging fibrosis (F3), and cirrhosis (F4). Cutoff levels of 7.1, 9.5, and 14.5 kPa were set as levels higher than F2, F3, and F4, respectively. Furthermore, steatosis severity was evaluated by controlled attenuation parameter method using the Fibroscan device. The steatosis was determined according to the extent of fat in the liver as the absence of steatosis (S0); fat droplets in <33% hepatocytes (S1); fat droplets in 33-66% hepatocytes (S2) and fat droplets in > 66% hepatocytes (S3). All screening processes and interpretation were performed by a hepatologist who was masked to treatment assignment.

Primary and secondary outcome

The primary outcome was a decrease in fibrosis and steatosis grade as well as reductions in ALT, AST, and ALP serum concentration. Secondary outcome measures included changes in anthropometric, FPG, HbA1C, and lipid profile among participants.

Statistical analysis

All analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 21. Kolmogorov-Smirnov test was applied to verify the normality of data distribution. To determine the difference between the 4 groups at baseline, analysis of variance (ANOVA) was used. The mean change of each variable was calculated by subtracting the endpoint from baseline values. Descriptive data were analyzed in the form of frequency and percentage for qualitative variables and mean ± standard deviation for quantitative variables. Analysis of covariance (ANCOVA) was conducted to compare the change of variables. Furthermore, the Chi-square test or Fisher Exact Test was also used for comparing categorical data between groups. Statistical significance was defined as $P < 0.05$.

RESULTS AND DISCUSSION

Results

Our results showed that 120 NAFLD patients were recruited and randomly divided into one of four groups. There were no incidences of drop-out, all participant's data was used for statistical analysis **(Figure 1)**.

The baseline demographic characteristics of each group are presented in **Table 1**. No significant difference was observed regarding age, anthropometric measures, lipid profile, factors related to glycemic status, as well as liver metabolic and pathological markers at the beginning of the study. No serious adverse effects were observed or reported among participants throughout the trial.

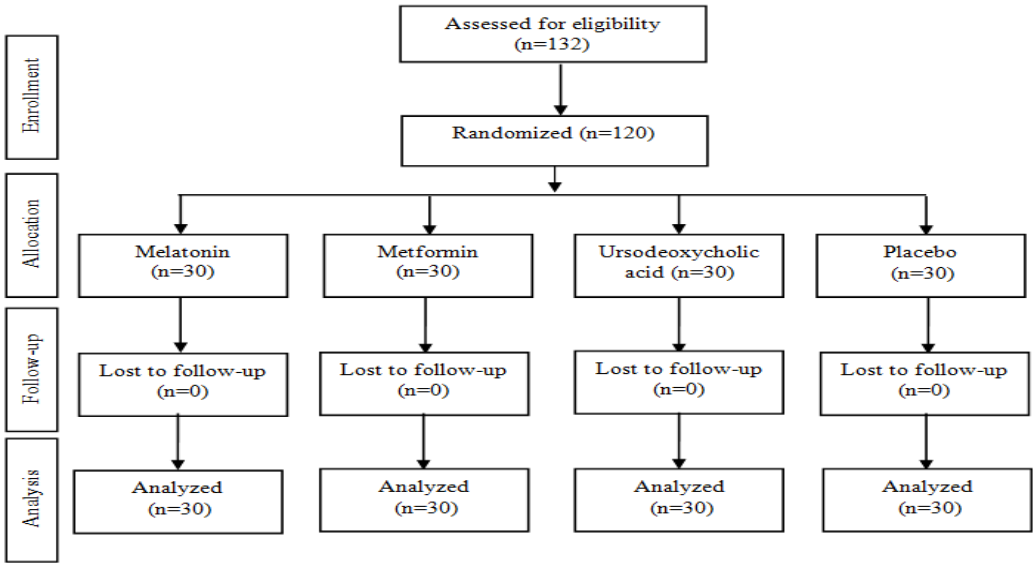

Fig. 1: Participant's flow diagram.

Table 1: General characteristics of NAFLD patients in 4 treatment groups.

Variables	Melatonin (N=30)	Metformin (N=30)	Ursocholic acid (N=30)	Placebo (N=30)	P-value*
Age (year)	43.66±11.01	42.85±10.55	44.72±11.07	43.12±10.87	0.91
Sex (Male/Female)	12/18	11/19	12/18	12/18	0.93
Weight (Kg)	88.54±15.06	91.96±16.81	90.10±13.16	93.05±10.33	0.59
BMI	31.39±2.82	32.26±3.12	31.83±2.79	32.57±2.55	0.39
Waist circumstance (cm)	99.83±7.43	104.57±11.44	103.58±9.77	105.02±10.17	0.16
ALT (IU/L)	76.13±32.23	70.71±34.82	67.75±32.41	73.88±28.16	0.75
AST(IU/L)	47.10±27.69	44.67±25.04	42.44±24.63	38.11±24.31	0.57
ALP(IU/L)	79.26±18.36	87.31±25.83	89.62±37.40	87.46±32.08	0.53
Bilirubin Total (mg/dL)	0.90±0.24	0.95±0.32	0.96±0.27	0.95±0.30	0.84
Bilirubin Direct (mg/dL)	0.23±0.06	0.27±0.10	0.26±0.09	0.26±0.08	0.82
PTT	31.63±1.88	31.03±4.28	31.65±1.91	31.50±2.76	0.82
INR	1.07±0.07	1.05±0.05	1.06±0.06	1.05±0.06	0.52
Albumin (g/dL)	4.35±0.37	٤,٤1±0.31	4.43±0.36	4.38±0.45	0.85
TG (mg/dl)	199.32±74.21	182.58±91.33	218.85±98.61	202.61±85.47	0.46
TC (mg/dl)	185.70±26.53	190.14±28.58	201.89±27.91	191.22±25.93	0.13
HDL (mg/dl)	40.03±5.83	38.78±5.71	37.86±4.98	39.91±5.63	0.38
LDL (mg/dl)	107.63±21.24	120.51±27.55	121.79±25.89	118.44±23.18	0.10
FPG (mg/dl)	97.26±28.60	100.85±27.82	96.01±26.00	95.31±33.89	0.88
HbA1C (%)	4.44±0.53	4.54±0.42	4.51±0.46	4.40±0.48	0.65
Steatosis score (CAP)	294.7±21.9	288.4±30.2	283.6±32.4	303.2±28.1	0.14
<33% (S1)	11	10	8	11	0.94**
33-66% (S2)	17	19	21	18	
>66% (S3)	2	1	1	1	
Fibrosis score (Kpa)	6.91±2.44	6.76±2.21	7.01±2.38	6.84±2.25	0.97
Absent	6	4	2	4	0.66**
Perisinusoidal/pericellular	16	18	20	17	
Periportal	7	6	8	6	
Bridging	1	2	-	3	
Cirrhosis	-	-	-	-	

Data are presented as mean ± SD; * P-Value was obtained from ANOVA. ** P-value was calculated by Chi-square test.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; TG: triacylglycerol; TC: total-cholesterol; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; FPG: Fasting plasma glucose; BMI: Body mass index.

Primary outcomes

The result of present study demonstrated a significant improvement in the level of steatosis (melatonin: -47.92±20.92; metformin: -55.14±25.78; UDCA: -21.06±28.64; placebo: -17.85±27.53; P=0.001), ALT (melatonin: -19.73±18.81; metformin: -25.96±19.97; UDCA: -11.02±27.12; placebo: -10.50±18.02; P=0.01) and ALP (melatonin: -17.83±13.02; metformin: -18.59±13.19; UDCA: -9.58±19.61; placebo: -9.13±17.93; P=0.03) among metformin or melatonin participants in comparison to the control or UDCA acid group. The change in Fibrosis (melatonin: -0.86±1.39; metformin: -1.03±1.38; UDCA: -0.54±1.38; placebo: -0.52±1.34; P=0.39) or AST (melatonin: -14.40±23.59; metformin: -15.14±18.46; UDCA: -10.82±21.33; placebo: -8.66±17.37; P=0.57) levels was not significant between the 4 groups. Moreover, we did not detect any meaningful change in the aforementioned parameters after UDCA administration in comparison with the control group **(Figure 2 & Table 2)**.

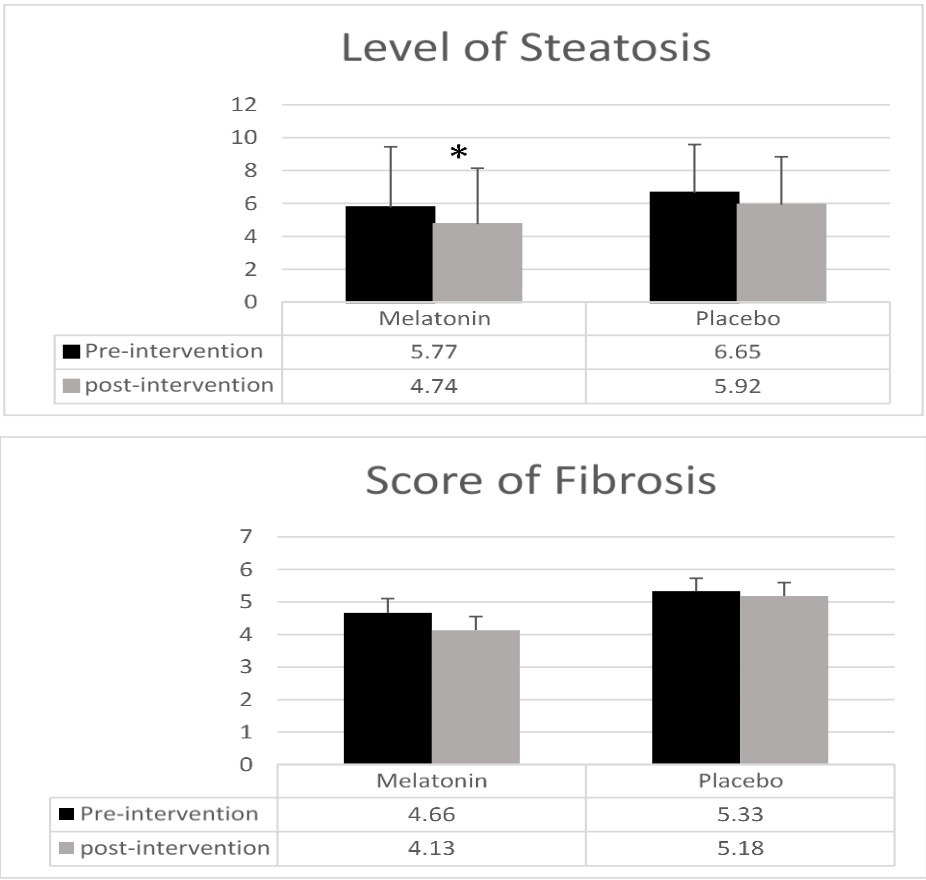

Fig. 2: The effect of melatonin on levels of steatosis and score of fibrosis among patients with NAFLD. Data expressed as mean ± SE. * P-value <0.05 in compare to placebo.

Table 2: Change from baseline to post 3 months treatment in anthropometrics, serum lipids, glycemic, and liver biochemical parameters by treatment groups.

Variables		Melatonin	Metformin	Ursocholic acid	Placebo	P-value
ALT	Pre	76.13±32.23	70.71±34.82	67.75±32.41	73.88±28.16	
	Post	56.40±30.66	44.75±31.93	56.73±30.78	63.38±29.81	
	Change	-19.73±18.81	-25.96±19.97	-11.02±27.12	-10.50±18.02	0.01
AST	Pre	47.10±27.69	44.67±25.04	42.44±24.63	38.11±24.31	
	Post	32.70±28.08	29.53±27.36	31.62±24.73	29.45±26.14	
	Change	-14.40±23.59	-15.14±18.46	-10.82±21.33	-8.66±17.37	0.57
ALP	Pre	79.26±18.36	87.31±25.83	89.62±37.40	87.46±32.08	
	Post	61.43±16.26	68.72±22.71	80.04±32.12	78.33±28.43	
	Change	-17.83±13.02	-18.59±13.19	-9.58±19.61	-9.13±17.93	0.03
Weight	Pre	88.54±15.06	91.96±16.81	90.10±13.16	93.05±10.33	
	Post	82.32±12.44	86.20±12.86	86.98±13.20	89.50±11.10	
	Change	-6.23±4.27	-6.76±3.26	-3.12±3.90	-3.55±3.12	0.001
BMI	Pre	31.39±2.82	32.26±3.12	31.83±2.79	32.57±2.55	
	Post	29.19±2.14	30.24±2.64	30.74±2.16	31.33±2.63	
	Change	-2.20±1.09	-2.02±1.93	-1.09±1.11	-1.24±1.01	0.002
Waist circumstance	Pre	99.83±7.43	104.57±8.44	103.58±9.77	105.02±10.17	
	Post	97.13±6.30	101.56±8.63	102.17±8.69	106.22±9.02	
	Change	-2.70±2.02	-3.00±2.48	-1.41±2.25	-1.2±2.11	0.002
TG	Pre	199.32±74.21	182.58±91.33	218.85±98.61	202.61±85.47	
	Post	176.60±52.36	156.30±71.35	208.39±81.11	193.40±74.13	
	Change	-22.72±17.63	-26.28±18.20	-10.46±21.72	-9.21±21.42	0.001
TC	Pre	185.70±26.53	190.14±28.58	201.89±27.91	191.22±25.93	
	Post	162.59±25.76	165.65±26.18	165.65±28.6	173.03±24.82	
	Change	-23.11±21.26	-24.49±23.21	-36.24±20.92	-18.19±22.21	0.01
HDL	Pre	40.03±5.83	38.78±5.71	37.86±4.98	39.91±5.63	
	Post	39.91±5.69	39.80±5.47	38.48±5.20	41.11±4.98	
	Change	-0.12±4.52	1.02±4.87	0.62±4.52	1.2±4.09	0.79
LDL	Pre	107.63±21.24	120.50±27.55	121.79±25.89	118.44±23.18	
	Post	100.32±18.34	108.80±20.51	105.93±21.28	111.06±21.29	
	Change	-7.31±13.25	-11.70±19.90	-15.86±17.25	-7.38±16.74	0.16
FPG	Pre	97.26±28.60	100.85±27.82	96.01±26.00	95.31±33.89	
	Post	91.77±20.28	89.99±17.62	92.15±16.34	92.23±22.15	
	Change	-5.49±10.25	-10.86±9.42	-3.85±10.77	-3.08±12.52	0.02
HbA1C	Pre	4.44±0.53	4.54±0.42	4.51±0.46	4.40±0.48	
	Post	4.35±0.46	4.42±0.43	4.59±0.52	4.46±0.54	
	Change	-0.09±0.44	-0.12±0.38	0.08±0.41	0.06±0.45	0.15

Data was presented as mean ± SD; P value was obtained by ANCOVA adjusted for age, sex and baseline BMI.

Secondary outcomes

Compared to the control group, a significant reduction in body weight (melatonin: -6.23±4.27; metformin: -6.76±3.26; UDCA: -3.12±3.90; placebo: -3.55±3.12; P=0.001), BMI (melatonin: -2.20±1.09; metformin: -2.02±1.93; UDCA: -1.09±1.11; placebo: -1.24±1.01; P=0.002), WC (melatonin: -2.70±2.02; metformin: -3.00±2.48; UDCA: -1.41±2.25; placebo: -1.2±2.11; P=0.002), TG (melatonin: -22.72±17.63; metformin: -26.28±18.20; UDCA: -10.46±21.72; placebo: -9.21±21.42; P=0.001) was observed in both metformin and melatonin groups. In addition, FPG concentrations (melatonin: -5.49±10.25; metformin: -10.86±9.42; UDCA: -3.85±10.77; placebo: -3.08±12.52; P=0.02) was significantly decrease in metformin group in compared to control. We did not find a significant change in any variable, except TC (melatonin: -23.11±21.26; metformin: -24.49±23.21; UDCA: -36.24±20.92; placebo: -18.19±22.21; P=0.01), following UDCA treatment when compared with the placebo group. No significant difference was detected in HbA1C, TC, LDL and HDL between all 4 groups **(Table 2)**.

Discussion

The present study indicates that treatment with metformin or melatonin, in addition to a low-caloric diet, for 3 months among NAFLD patients may have a beneficial effect on hepatic steatosis, ALT, ALP, TG, and weight loss, as compared with UDCA plus low-caloric diet or low-caloric diet alone. In addition, administration of UDCA and metformin resulted in improved TC and FPG concentrations, respectively. However, no significant difference was detected in liver fibrosis score, AST, HbA1C, LDL, and HDL between groups.

Attributed to the ever-increasing global prevalence of diabetes, metabolic syndrome, and obesity, the incidence of NAFLD is inexorably rising[33&34] NAFLD is well reported to be an independent risk factor for fatal and non-fatal cardiovascular disease events[35], further demonstrating that NAFLD treatment prevention remain a strong, the contemporary focus for clinical care, globally. The present study demonstrated that metformin in addition to a low-caloric diet may be an efficacious therapy in NAFLD treatment. In concordance with the present study, several investigations have shown favorable effects following metformin administration in improving NAFLD. Lin et al[36] showed that metformin can reduce hepatomegaly and hepatic steatosis, and reverse fatty liver disease in ob/ob mice. A 48-week clinical trial, in which 28 patients with non-alcoholic steatohepatitis were treated with 2000 mg/day metformin, indicated an improvement in liver histology, decreases in ALT levels among 30% of patients. Also, an intervention consisting of metformin, plus dietary restriction of lipids and complex carbohydrates, was compared with dietary restrictions alone, and highlighted a preferential improvement in ALT levels, insulin resistance, and severity of steatohepatitis[37].

Several mechanisms have been putatively suggested regarding the functionality of metformin. It seems that metformin can influence metabolism through activation of adenosine monophosphate (AMP)-activated protein kinase in both the liver and muscles[38]. The activation of AMP kinase acts to reduce lipogenesis and gluconeogenesis along with enhancing glucose and fatty acid uptake by hepatic and peripheral tissue, either directly or indirectly through serine–threonine kinase known as LKB1[39]. By improving insulin actions, metformin can also exhibit a weight-lowering effect[40&41]. In a study conducted by Loomba et al, patients following a metformin treatment regimen reported that they could better control their appetite, as compared to no treatment; the author further suggested that it might be due to fact that AMP kinase is also present in the hypothalamus and may regulate food intake, appetite, and satiety[39].

The results of the present studies indicated that administration of melatonin plus weight-loss diet is efficacious in the treatment of NAFLD. In line with our study, several animal and human study have reported the positive influence of this agent. A study on mice with NAFLD, induced by high fat diet, demonstrated that administration of melatonin for 12 weeks significantly reduces body weight, FPG, ALT and, LDL. In addition, liver steatosis and inflammation markers in NAFLD mice was decreased after melatonin treatment[42]. In a study conducted by Gonciarz

et al, patients with non-alcoholic steatohepatitis that followed a 24-week melatonin administration had significant attenuation in elevated liver enzymes[43]. Further, Celinski et al conducted a study in which patients with NAFLD consumed melatonin 10 mg/day for 14 months; in this study, participants in the melatonin group experienced a reduction in pro-inflammatory cytokines and improvement in some parameters of fat metabolism. However, no significant reduction in liver enzymes was reported[44].

Although animal studies have shown that melatonin significantly attenuates weight gain and reduces body weight and visceral adiposity[45-47], clinical trials in humans have not indicated any change in anthropometric measures manifest from melatonin administration[48&49]. The maximum dosage of melatonin which has been investigated on weight loss in human studies is 6 mg/day[50]; however, this amount of melatonin is small in comparison with those used in animal models (4-10 mg/kg body weight)[45-47].

The exact hepatoprotective mechanism of melatonin is not well-understood; tentatively, it has been suggested that the main role of melatonin in NAFLD treatment is attributable to decreases in oxidative stress, which is one of the main pathophysiological mechanisms of NAFLD[51]. It has been suggested that melatonin can decrease oxidative stress by improving SOD and GSH-Px activities, and can improve hepatic steatosis, inflammation and elevated liver enzymes[51&52]. On the other hand, obesity and insulin resistance are considered to be important risk factors in the onset and development of NAFLD. Contemporary evidence suggests that melatonin has a role in body weight, and metabolism regulation[53]. Melatonin can regulate the metabolism of carbohydrates and retain brown adipocytes, as well as elevate its metabolic activity[54]. Melatonin has receptors (MT1 and MT2) in the islets of Langerhans which indicates the insulin production and secretion partially controlled by melatonin[55]. Studies have suggested that melatonin administration may lead to suppression in insulin secretion and enhance insulin sensitivity in the peripheral tissue[56] and central nervous system[57]; moreover, these effects on metabolism could explain why melatonin regulates body weight and improves glucose hemostasis. However, it appears that melatonin does not alter insulin sensitivity and glucose metabolism, only acting when a metabolic disturbance occurs[45].

The results of the present study did not demonstrate any significant effect of UDCA on NAFLD in comparison with the control group. Although a favorable impact of this agent has been shown on liver histology and functions by smaller open-label clinical studies[58&59], a double-blinded trial with 2-years follow-up and 166 participants did not find any significant improvement in liver histology or laboratory data by UDCA treatment at doses ranging from 13 to 15 mg/kg[60]. Furthermore, high dose therapy with UDCA (23-28 mg/kg/day) on non-alcoholic steatohepatitis for 18-months failed to improve overall histology and laboratory data, except gamma-glutamyl transferase[61]. In this case, is apparent that ursodeoxycholic acid should not be prioritised in the treatment of NAFLD, in comparison with other options.

In the present study, no serious adverse effects related to the intervention groups were observed among participants. However, antecedents evidence has demonstrated some undesirable effects attributed to drug administration, and, thus, should be considered when prescribed in clinical practice. Common adverse effects among patients with metformin treatment is gastrointestinal complaints such as diarrhea, nausea, and abdominal cramping, in addition to lactic acidosis[62&63]. Furthermore, a mild vitamin B12 malabsorbtion might occur among patients with long-term metformin treatment[64]. Human and animal studies have documented that melatonin is generally safe during short-term intake and only mild unfavorable side effects, including; headache, dizziness, nausea, and sleepiness have been reported[65]. Furthermore, clinical studies have shown the long-term use of melatonin also causes only mild adverse-effects[65&66]. Although empirical evidence has indicated exogenous melatonin can be considered as a safe agent, there is a dearth of evidence on interactions with breast-feeding and pregnancy, and thus should be carefully considered[67&68]. Several rare reactions resulting from ursodeoxycholic acid intake including diarrhea, decompensation of liver cirrhosis in end-stage primary biliary cirrhosis case, and recurrent

right upper quadrant abdominal pain has been reported in small subsets of patients[69-71]. The ursodeoxycholic acid absorption has an interaction with ciclosporin, nitrendipine, dapsone, and cytochrome P4503A substrates, and its absorption is reduced by concurrent uses of colestipol, aluminium hydroxide, colestyramine, colestimide, and smectite[72].

To the best of the authors' knowledge, the present study is the first clinical trial to compare the effect of three common medications on NAFLD. However, several limitations should be considered. First, the duration of the study was relatively short. But, even in this short time, we demonstrated a significant effect of different agents on NAFLD treatment. Second, the participant's respective habitual diet and physical activity were not assessed, however, we a prescribed standard-weight lost diet and asked participants not to change their habitual physical activity, as well as weekly phone interviews during follow-ups to cover this limitation. Finally, there are several unmeasured residual variables such as educational and economic status which maybe act as confounders and affect the results, and as such, should be further investigated.

Conclusion

The present study demonstrates that the addition of metformin or melatonin to a calorie-restricted diet is beneficial in the treatment of NAFLD and significantly better than UDCA plus dietary restriction or dietary restriction alone. This study provides hitherto unseen insight into NAFLD management, and our results highlight some promising results. However, further studies are needed to confirm the veracity of these results, and assimilate the evidence required to translate into clinical practice.

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تأثير الميلاتونين والميتفورمين وحمض أورسوديوكسيكوليك على مرض الكبد الدهني غير الكحولي: تجربة معشاة مزدوجة التعمية ذات شواهد

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الهدف: هدفت هذه الدراسة الى التحقيق ومقارنة تأثير الميلاتونين والميتفورمين وحمض أورسوديوكسيكوليك (UDCA) على مرض الكبد الدهنى غير الكحولى.

الطريقة: في هذه التجربة السريرية المعشاة مزدوجة التعمية ، تمت إحالة ١٢٠ مريضا يعانون من مرض الكبد الدهنى غير الكحولى إلى مركز أبحاث أمراض الجهاز الهضمي والكبد ، رشت ، إيران ، بين سبتمبر ٢٠١٥ ويناير ٢٠١٦. تم تعيين المرضى بشكل عشوائي إلى ٤ مجموعات. تلقت كل مجموعة الميلاتونين أو الميتفورمين أو UDCA أو الدواء الوهمي بالإضافة إلى نظام غذائي لفقدان الوزن لمدة ٣ أشهر.

النتائج: لوحظ انخفاض كبير في مستويات التنكس الدهني ، ألانين أمينوترانسفيراز ، الفوسفاتيز القلوي ، وزن الجسم ، مؤشر كتلة الجسم ، ظرف الخصر وثلاثي الجلسرين بين المشاركين في المجموعات التي يتم فيها إعطاء الميتفورمين أو الميلاتونين. بالإضافة إلى ذلك ، تم الكشف عن انخفاض كبير في نسبة الجلوكوز في البلازما الصائمة ، وتركيز الكوليسترول الكلي بعد إعطاء الميتفورمين و UDCA ، على التوالي.

الاستنتاجات: تشير الدراسة الحالية إلى أن إضافة الميتفورمين أو الميلاتونين إلى نظام غذائي منخفض السعرات الحرارية قد يكون فعالا في علاج المرضى الذين يعانون من مرض الكبد الدهني غير الكحولي.