International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 8, No. 3, 2024

Effect of Combined Action of Triglyceride and Uric Acid on Nonalcoholic Fatty Liver

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Abstract: Objective: To explore whether there is synergistic effect of hyperuric acid and hyperTGemia on the pathogenesis of non-alcoholic fatty liver disease (NAFLD). Methods: In phase one, the hydro-alcoholic extraction of the peel of 750 kg of pomegranate (Punica granatum L.) was performed by the soaking method. Then, in phase two, NAFLD patients received 1500 mg of placebo (n = 37) or pomegranate peel capsules (n = 39) with a 500-kcal deficit diet for 8 weeks. Gastrointestinal intolerance, dietary intake, lipid and glycemic profiles, systolic and diastolic blood pressure, body composition, insulin resistance indexes, and elastography-evaluated NAFLD changes were followed. Results: The mean age of participants was 43.1 ± 8.6 years (51.3% female). Following the intervention, the mean body weight (mean changes: -5.10 ± 2.30 kg), waist circumference (-7.57 ± 2.97 cm), body mass index (-1.82 ± 0.85 kg/m2), body fat index (-1.49 ± 0.86), and trunk fat (- 3.93 ± 3.07%), systolic (-0.63 ± 0.29 cmHg) and diastolic (-0.39 ± 0.19 cmHg) blood pressure, total cholesterol (-10.51 ± 0.77 mg/dl), triglyceride (-16.02 ± 1.7 mg/dl), low-density lipoprotein cholesterol (-9.33 ± 6.66 mg/dl; all P < 0.001), fat free mass (- 0.92 ± 0.90 kg; P < 0.003), and fasting blood sugar (-5.28 ± 1.36 mg/dl; P = 0.02) decreased significantly in PP in contrast to the placebo group in the raw model and when adjusted for confounders. Also, high-density lipoprotein cholesterol (5.10 ± 0.36 mg/dl), liver steatosis and stiffness (- 0.30 ± 0.17 and - 0.72 ± 0.35 kPa, respectively, all P < 0.001) improved in the PP group. However, fasting insulin (P = 0.81) and homeostatic model assessment for insulin resistance (HOMA-IR) (P = 0.93) were not significantly different when comparing two groups during the study in the raw and even adjusted models. Conclusion: The interaction between hyperuric acid and hyperTGemia on the onset of NAFLD is synergistic.

Keywords: Dyslipidemia; Fatty Liver; Hyperuricemia.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a metabolic stress-related liver disease characterized by fatty degeneration of liver cells, which may progress to fibrosis, cirrhosis, and even hepatocellular carcinoma [1]. In the past, NAFLD was mainly involved in western developed countries and was one of the most common chronic liver diseases causing abnormal liver enzymology [2]. In recent years, the number of cases of NAFLD in China has been increasing and showing a trend of low aging, and has now surpassed chronic hepatitis to become the first major chronic liver disease in China[2,3]. Due to the insidiousness of onset and lack of specific clinical symptoms, it is necessary to identify potential risk factors for NAFLD. Epidemiological studies have found that NAFLD is closely related to a variety of metabolic factorsp [4]. Studies at home and abroad have found that overweight and obese people have a significantly increased risk of NAFLD, and other studies have found that elevated TG levels are closely related to the occurrence and development of NAFLD. However, previous studies only focused on the independent effects of the two factors, and there is still a lack of research conclusions on whether abdominal obesity and hyperTGemia interact with NAFLD and how strong the interaction is The Kailuan Study is a prospective cohort study that started in 2006 and is still ongoing based on functional community population risk factor investigation and intervention [3,4]. Participants were followed up every two years, including anthropometric indicators and serum biochemical tests, and the incidence of chronic diseases such as NAFLD was also followed up. This provides an opportunity to explore the combined effect of mid-abdominal obesity and TG on the pathogenesis of NAFLD in the Kailuan cohort [5,6].

2. Data and Methods

2.1. The Study Subjects

from 2006 to 2007 (referred to as 2006) were enrolled in 11 branches of Kailuan General Hospital, Kailuan Linxi Hospital, Kailuan Zhaogezhuang Hospital, Kailuan Tangjiazhuang Hospital, Kailuan Fangezhuang Hospital, Kailuan Lujiatuo Hospital, Kailuan Jinggezhuang Hospital, Kailuan Linnancang Hospital, Kailuan Qianjiaying Hospital, Kailuan Majjiagou Hospital and Kailuan Hospital A hospital conducted the first physical examination of the current and retired employees of Kailuan Group, and collected the contents of epidemiological investigation, anthropometric indicators, biochemical indicators and abdominal ultrasound including liver ultrasound data. Then, in 2008-2009, 2010-2011, 2012-2013 (referred to as 2008, 2010, 2012 respectively), the medical personnel who participated in the first physical examination conducted the first medical examination on the same population in the same place according to the time order of the first physical examination

The epidemiological investigation contents, anthropometric indicators and biochemical indicators of the 2, 3 and 4 health examinations were the same as those of the first health examination[7]. The physical examination data of 2006 were used as the baseline data of this study. A total of 101,510 active and retired employees of Kailuan Group participated in and completed the health examination in 2006[9]. one

Inclusion criteria: (1) active and retired employees of Kailuan Group who have reached the age of 18 and participated in the 2006 health examination; (2) Complete data of height, waist circumference and TG in physical examination; (3) Respondents who completed the questionnaire during the physical examination. Exclusion criteria: (1) Patients with NAFLD disease or absence of hepatobiliary ultrasound data in baseline data; (2) Patients with previous malignant tumor diseases; (3) Incomplete interviewers.

2.2. Inclusion Criteria and Exclusion Criteria Inclusion Criteria

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2.3. Data Collection

Smoking was defined as smoking an average of at least one cigarette a day in the last 1 year; Alcohol consumption was defined as an average daily consumption of 100 ml of liquor (alcohol content ≥ 50%) for at least 1 year; Physical exercise is defined as exercise ≥3 times per week, each duration ≥30 min. Set TG≥2. 3 mmol/L was defined as hyperTGemia with TG < 2. 3 mmol/L idine.Meaning non-hyperTGemia, male blood uric acid >420μmol/L[16,17]. Finally, the subjects were divided into 4 groups: normal uric acid combined with non-hyperTGemia group, normal uric acid combined with hyperTGemia group, hyperuric acid combined with non-hyperTGemia group, and hyperuric acid combined with hyperTGemia group. Fasting abdominal ultrasonography was performed by imaging doctors with many years of clinical experience[18,19]. The data were collected from July 1, 2006 to December 31, 2020, and the end time of follow-up was the time of death or the last follow-up for those with no event, and the end time of follow-up for those with event was the time of diagnosis[20,21].

2.4. Statistical Methods

Adopt SAS9. 4 Statistical software for analysis. The measurement data conforming to normal distribution were expressed as x ± s, and one-way analysis of variance was used for comparison among groups[1,2,3]. Measurement data of non-normal distribution were represented by M (P25 ~ P75), and were compared among multiple groups Test with Kruskal-Wallis H. The Chi-square test was used to compare the data groups. Pearsn correlation was used to analyze the linear relationship between WHtR and TG[12,13,15] .Person-time incidence of NAFLD in each group was calculated. Kaplan-Meier method was used to calculate the cumulative incidence of endpoint events in different groups, and the differences in the cumulative incidence of NAFLD in each group were compared by log-rank test. The hazard ratio (HR) and 95% confidence interval (95% CI) for NAFLD were further analyzed by Cox proportional risk model[20,21,23]. Finally, Cox regression model was used to analyze the relationship between abdominal obesity, hyperTGemia and NAFLD, and to analyze whether there was interaction between the two on the incidence of NAFLD [20]. In Cox and interaction models, the corrected variables included sex, age, BMI, serum TC, ALT, TBil, hypersensitive C-reactive protein (hs-CRP), smoking, hypertension, diabetes, physical exercise, education, and per capita household income. P < 0. The difference of 05 was statistically significant [27.28.30].

3. Result

Table 1 shows the sociodemographic characteristics of participants according to tertiles of changes of adherence to the MedDiet at baseline. No differences between groups were registered in the considered sociodemographic and clinical parameters.

Table 1. The sociodemographic characteristics of participants according to tertiles of changes of adherence to the MedDiet at baseline

Outcomes	No Changes in Adherence to MedDiet (n = 15)	Moderate Changes in Adherence to MedDiet (n = 56)	High Changes in Adherence to MedDiet (n = 57)	*p* *
Age (y) (mean ± SD)	53.3 ± 7.2	53.5 ± 8.0	52.0 ± 6.9	0.516
Marital Status (n; %)				0.402
Single	0 (0.0)	4 (3.1)	8 (6.3)	
Married/domestic partnership	12 (9.4)	41 (32.0)	44 (33.6)	
Divorced/separated/widowed	3 (2.3)	11 (8.6)	6 (4.7)	
Employment (n; %)				0.338
Working	11 (8.6)	38 (29.7)	44 (34.4)	
Unemployed/retired/housewife	4 (3.1)	18 (14.1)	13 (10.2)	
Education Level (n; %)				0.219
University/post-university	4 (3.1)	4 (3.1)	2 (1.6)	
Secondary education	7 (5.5)	24 (18.8)	24 (18.8)	
Primary education	2 (1.6)	24 (18.8)	29 (22.7)	
None	2 (1.6)	4 (3.1)	2 (1.6)	
Currently smoking (n; %)	0 (0.0)	7 (5.3)	9 (6.8)	0.554
Regular Physical Activity (n; %)				0.246
None	4 (2.9)	23 (16.7)	32 (23.2)	
Light	6 (4.3)	23 (16.7)	19 (13.8)	
Moderate	5 (3.6)	7 (5.1)	10 (7.2)	
Heavy	0 (0.0)	3 (2.2)	6 (4.3)	
T2DM (%)	4 (2.9)	23 (33.8)	11 (16.2)	0.141
High BP (n; %)	4 (2.9)	17 (12.2)	9 (6.5)	0.062

Abbreviations: BP: blood pressure; SD: standard deviation; T2DM: type 2 diabetes mellitus. * By chi-square.

Table 2 shows the clinical features of participants according to the changes of adherence to MedDiet at 6-month follow-up. It was observed an improvement of subjects' clinical parameters on the High changes in the adherence to the MedDiet group. High changes in adherence to the MedDiet group showed a higher decrease in BMI, body weight, WC, SBP, DBP, and IFC than in Moderate changes group and No changes group. TG was slightly higher in High

changes group than in Moderate changes group.

Table 2. Six-month follow-up changes of clinical features according to the changes in adherence to MedDiet

Outcomes		No Changes in Adherence to MedDiet (n = 15)	Moderate Changes in Adherence to MedDiet (n = 56)	High Changes in Adherence to MedDiet (n = 57)	p ‡
BMI (kg/m^2)	Basal	32.6 ± 3.0	33.6 ± 3.5	33.9 ± 3.9	<0.001
	6-months	31.9 ± 2.7	32.1 ± 3.6	30.9 ± 3.9	
	Δ	−0.7 ± 1.2 *c	−1.5 ± 1.6 *b	−3.0 ± 2.0 *bc	
Body weight (kg)	Basal	91.5 ± 14.8	94.7 ± 12.4	96.5 ± 14.5	<0.001
	6-months	89.5 ± 14.5	90.5 ± 12.4	88.1 ± 14.5	
	Δ	−1.9 ± 3.6 c	−4.2 ± 4.6 *b	−8.5 ± 5.8 *bc	
WC (cm)	Basal	110.2 ± 9.4	113.0 ± 9.0	111.4 ± 9.0	0.004
	6-months	108.6 ± 7.4	110.5 ± 17.0	103.1 ± 10.5	
	Δ	−1.6 ± 4.1	−2.5 ± 15.1 b	−8.3 ± 5.6 *b	
SBP (mmHg)	Basal	134.2 ± 19.4	138.0 ± 16.2	134.7 ± 13.9	0.013
	6-months	134.4 ± 16.5	134.1 ± 15.3	126.3 ± 15.0	
	Δ	+0.2 ± 11.7	−4.0 ± 16.7 b	−8.4 ± 14.6 *b	

4. Discussion

The results of the present analysis showed an association between an improvement in the adherence to the MedDiet after a 6-month follow-up and better status of MetS features, as well as better values of IFC by MRI [30,31,32]. Subjects with high changes in adherence to the MedDiet showed lower IFC at the 6-month follow-up, and this high adherence to the MedDiet was associated with amelioration of IFC. These findings are consistent with literature pointing out that the MedDiet has preventive effect on NAFLD[31] . A study conducted in Australia found that following the MedDiet for 6 weeks resulted in reversal of NAFLD by lowering intrahepatic lipids (−39%) and decreasing insulin resistance (−1.7 mmol/L, using HOMA-IR); they found that MedDiet decreases the intrahepatic fat contents independently from weight loss. All these findings showed that the MedDiet could be recommended in NAFLD patient[21,22].The current study reported that patients with high changes in adherence to MedDiet had lower body weight, WC, BMI, TG, SBP, DBP and IFC, which are in line with a previous study suggesting that the MedDiet had benefits on MetS, T2DM and cardiovascular diseases, which are pathophysiologically linked with NAFLD[27].According to previous studies, an increased adherence to a MedDiet in patients with NAFLD can improve intrahepatic lipid levels, fibrosis, insulin resistance, inflammatory markers, and other metabolic risk markers[30,31].The current study also showed how specific consumption of food groups has increased or decreased. The soft drinks consumption was lowered as the adherence to the MedDiet increased. Nuts consumption was improved as the adherence to the MedDiet increased, and interestingly, dairy consumption was increased too in the High changes group. The food groups highlighted on high adherence could reverse the intrahepatic fat contents. In addition, this study also verified the conclusion of previous studies: hyperuric acid and hyperTGemia are both risk factors for the onset of NAFLD[31]. The influence of TG on the pathogenesis of NAFLD is consistent with the conclusions of previous domestic and foreign studies. Lee et al., through statistical analysis of the data of 2008 observation subjects in Taiwan, found that TG is a risk factor for NAFLD in both obese and non-obese people (odds ratio = 1. 01, 95% CI: 1. 01 ~ 1. 02), Zhang Yanmin et al. [33] also reached a similar conclusion. At present, the synergistic pathogenesis of abdominal obesity and Hypertriglyceridemia in NAFLD is not clear, but insulin resistance may play an important role in the pathogenesis of NAFLD. On the one hand, obesity, especially in the state of abdominal obesity, increases in free fatty acids, lipid deposition, and activation of inflammatory pathways will affect insulin effect pathways, leading to insulin resistance. On the other hand, Hypertriglyceridemia can affect glucose utilization and metabolism, and also inhibit the binding of insulin to its receptors, resulting in increased insulin levels and decreased biological activity. In obese people, the synthesis and breakdown of liver lipoprotein lipase is enhanced, leading to liver lipid deposition, which leads to the development of NAFLD [17,18]. Through the method of cohort study, this study found that subjects with abdominal obesity combined with Hypertriglyceridemia were more likely to develop NAFLD, and there was a synergistic pathogenic effect between the two factors. With the improvement of China's living standards and the change of lifestyle, the number of obesity and dyslipidemia will continue to increase in the future, and the prevention and control of NAFLD cannot be ignored. Therefore, to prevent the onset of NAFLD, people with abdominal obesity or Hypertriglyceridemia need to be vigilant, especially those with two risk factors co-existing, and should be paid more attention. There are still some defects in this study. First of all, the diagnosis of NAFLD in this study was mainly based on abdominal ultrasound. Although liver biopsy is the current gold standard for the diagnosis of NAFLD, due to the invasive nature of biopsy, it is not suitable for epidemiological investigation of the physical examination population. Abdominal ultrasonography is non-invasive, convenient, quick and easy to implement, with high sensitivity and specificity. Secondly, due to the limited research conditions, other indicators reflecting obesity, such as subcutaneous fat thickness and visceral fat content, could not be measured in this study. Finally, this study only used data from a single measurement, and further studies are needed to determine whether dynamic changes in anthropometric and laboratory data have an impact on the onset of NAFLD.

5. Conclusion

The interaction between hyperuric acid and Hypertriglyceridemia on the onset of NAFLD is synergistic.

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