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Intermittent fasting-induced amelioration of thyroid hormone sensitivity was associated with improvements in insulin sensitivity independent of weight loss in steatotic liver disease

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Abstract

Aim: This study aimed to evaluate the effect of the intermittent fasting (IF) intervention on metabolism and thyroid hormone sensitivity (THS) in patients with steatotic liver disease (SLD) and to further investigate the association between changes in THS and alterations in metabolic parameters during the intervention.

Methods: A total of 78 patients with SLD underwent a 5:2 IF intervention for 8 weeks. Metabolic outcomes and THS, measured by the thyroid feedback quantile-based index (TFQI), thyrotroph thyroxine resistance index, thyroid-stimulating hormone index (TSHI), and free triiodothyronine to free thyroxine ratio (FT3/FT4), were assessed at baseline and after the intervention. Multiple regression analysis was performed to examine relationships between changes in THS and metabolic parameters during the intervention.

Results: Average hepatic fat content was 15.02% at baseline and decreased by 3.79% after the 8-week IF intervention, accompanied by significant reductions in body weight, blood glucose, serum lipids, fasting insulin, homeostatic model assessment of insulin resistance (HOMA-IR), and adipose tissue insulin resistance index (Adipo-IR). After the intervention, THS improved: TFQI, thyrotroph thyroxine resistance index, and TSHI all decreased, while FT3/FT4 increased. Significant positive correlations were observed between Δ TFQI and Δ TSHI



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and changes in fasting insulin, HOMA-IR, and Adipo-IR. In multivariate models adjusted for age, sex, and weight loss, Δ TFQI and Δ TSHI remained significantly correlated with Δ insulin, Δ HOMA-IR, and Δ Adipo-IR.

Conclusion: IF-induced improvement in THS was associated with enhanced insulin sensitivity independent of weight loss in patients with SLD. These findings suggest that THS may play a role in metabolic improvements and could inform therapeutic strategies for SLD.

Keywords: Steatotic liver disease, 5:2 intermittent fasting, thyroid hormone sensitivity, insulin sensitivity, weight loss

INTRODUCTION

Steatotic liver disease (SLD) has become one of the most common chronic liver diseases. Patients with SLD often present with metabolic dysfunctions, such as obesity, dyslipidemia, and insulin resistance, which place a substantial burden on healthcare systems^[1]. However, very few FDA-approved drugs are available specifically for the treatment of SLD. Therefore, understanding the pathogenesis and identifying new therapeutic targets for SLD is critically important.

Current evidence suggests a potential link between SLD and thyroid function. Thyroid hormones (THs) are proposed to influence hepatic lipid homeostasis through various mechanisms^[2]. Researchers have suggested hypothyroidism as an independent risk factor for SLD^[3]. However, current studies present conflicting findings regarding the association between thyroid dysfunction and SLD. D'Ambrosio *et al.* found no statistically significant association between hypothyroidism and simple hepatic steatosis and steatohepatitis^[4].

There is a belief that THs alone may not fully explain the association between SLD and thyroid function. Laclaustra *et al.* proposed the thyroid feedback quantile-based index (TFQI), also known as the resistance to TH index, which more accurately reflects central sensitivity to TH^[5]. This index presents greater stability than the thyrotrophin thyroxine resistance index (TT4RI) and thyroid-stimulating hormone index (TSHI) in abnormal thyroid gland responsiveness to thyroid-stimulating hormone (TSH). During the last few years, emerging clinical studies investigated the relationship between TH sensitivity (THS) and metabolic health and showed that impaired THS represented by increased levels of TFQI, TT4RI, and TSHI significantly correlated with diabetes, hypertension, metabolic syndrome, obesity, hyperuricemia, and cardiovascular disease risk^[5]. The previous results in our research group also uncovered that reduced THS was associated with vitamin D deficiency, high remnant cholesterol levels, and elevated homocysteine levels^[6]. As for SLD, Zhang *et al.* showed that among patients with newly diagnosed type 2 diabetes, TFQI and TT4RI were increased in patients with SLD than those without SLD, and the risk of SLD and liver fibrosis was increased as the THS indices rose^[7]. Wan *et al.* also found that reduced central THS was associated with metabolic dysfunction-associated SLD and fibrosis in euthyroid populations^[8]. However, whether impaired THS is an independent risk factor for metabolic disorders and SLD is not fully understood. Prospective studies examining the relationships among changes in THS, glucose and lipid metabolism, and SLD are scarce and would provide valuable evidence.

Intermittent fasting (IF) is characterized by recurring periods with little or no energy intake, resulting in weight loss, energy stress, and positive metabolic adaptations. Published evidence has demonstrated that 5:2 IF is a popular intervention used to fight against metabolic diseases^[9]. An umbrella review of randomized clinical trials concluded that IF engaged benefits on weight loss, improved blood lipid profiles and glucose levels, increased insulin sensitivity, and decreased blood pressure in patients with overweight, obesity, or

SLD^[10]. Most previous IF studies in metabolic or liver disease have been conducted in relatively small cohorts. For example, an early time-restricted feeding study done in men with prediabetes only enrolled eight patients and demonstrated improvements in insulin sensitivity^[11]; an alternate-day fasting randomized clinical trial enrolled 100 adults with obesity and reported significant reductions in body weight and fat mass, as well as improvements in cardiovascular risk markers^[12]; a 4-h/6-h time-restricted feeding randomized trial in 58 participants showed reductions in body weight and systolic blood pressure, with favorable changes in insulin resistance^[13]. An intermittent energy restriction trial in overweight women has typically included cohorts of roughly 100 participants and demonstrated decreases in body weight and improvements in insulin sensitivity comparable to those with continuous energy restriction^[14]. However, the effects of IF on THS and whether changes in THS correlated with metabolic improvements in patients with SLD remain unknown.

In this 8-week 5:2 IF intervention study, we aim to investigate the influences of IF on metabolism and THS in patients with SLD and to further identify whether the changes in THS correlated with the metabolic benefits induced by IF, which may provide novel evidence for the treatment and management of SLD and related metabolic disturbances.

METHODS

Subjects

A total of 80 subjects with SLD were recruited from the endocrinology clinic at Beijing Chao-yang Hospital, Capital Medical University, China, between September 22, 2020 and April 30, 2021. Inclusion criteria were hepatic fat content (HFC) > 5.0% as evaluated by upper abdominal magnetic resonance imaging-proton density fat fraction (MRI-PDFF) examinations^[15]; age ≥ 18 years, body mass index (BMI) ≥ 18.5 kg/m², and stable body weight (fluctuation < $\pm 10\%$) during the preceding 3 months. Subjects were excluded if their serum aspartate aminotransferase (AST) and alanine amino-transferase (ALT) levels exceeded 2.5 times the upper limit of normal; if their fasting blood glucose (FBG) levels ≥ 7.0 mmol/L or glycated hemoglobin A1c (HbA1c) $\geq 6.5\%$; if taking medications known to affect thyroid function (e.g., levothyroxine, antithyroid drugs, glucocorticoids, amiodarone) or metabolic parameters; or if they had type 1 or type 2 diabetes, heart disease, other hepatic disease (excluding SLD) or renal disease.

This study was registered at ClinicalTrials.gov (NCT04795973) and conducted in accordance with the Declaration of Helsinki (as revised in 2013). The protocol was approved by the Ethics Committee of Beijing Chao-Yang Hospital, Capital Medical University (2021-KE-10), and informed consent was obtained from all participants.

Based on sample size calculations, we estimated that with 68 participants, the study would have more than 90% power to detect a significant difference, assuming a mean reduction in liver fat content of 2%, with a standard deviation (SD) of 5%, at an alpha level of 5%^[16].

Study design

Participants underwent an 8-week 5:2 IF intervention. Metabolic parameters and THS indices were assessed at baseline and after intervention.

Intervention

All subjects received a 5:2 IF. They followed a normal diet for five days per week and practiced IF for two nonconsecutive days^[17]. On normal eating days, women consumed 1,200-1,500 kcal/day and men consumed 1,500-1,800 kcal/day, with macro-nutrient distribution of 45%-50% carbohydrate, 20% protein, and 30%-

35% fat. On fasting days, participants consumed 500 kcal, including at least 50 g of protein. Noncaloric beverages such as water and unsweetened tea were allowed without restriction. Participants received standardized training at baseline on portion-size estimation using visual aids (food models and household measures). They were instructed to keep daily food records on both fasting and non-fasting days. A registered dietitian reviewed the records weekly and provided individualized feedback. Any uncertainties were addressed via telephone or WeChat consultations. Adherence to the 5:2 protocol (fast-day caloric targets and non-fast-day guidance) was summarized weekly; deviations were logged and discussed at follow-up visits.

Compliance monitoring

Dietary compliance was objectively evaluated using daily food diaries, in which participants recorded all food intake on both fasting and non-fasting days. Compliance was quantified as the percentage of scheduled fasting days successfully completed over the 8-week intervention. Noncompliance was defined as energy consumption of 20% or less of the recommended diet on fasting days, failure to adhere to the IF schedules for over a week, and/or fasting days fewer than 8 (noncompliance $\geq 20\%$) during the intervention. Researchers closely monitored all potential adverse effects and participant responses throughout the intervention.

Study measurements

Trained investigators and doctors conducted baseline physical examinations including height, weight, and waist circumference (WC) on all participants following standard procedures. Measurements were repeated after the 8-week dietary intervention. After an overnight fasting, subjects were admitted to the endocrinology clinic at 8 a.m. Peripheral venous blood samples were collected at baseline and after the IF intervention.

The subjects visited the imaging center on a different day. HFC was assessed using MRI-PDFF following established protocols at baseline and after the dietary intervention^[18].

Biochemical analysis

Blood samples were collected the day following a non-fasting day. Triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), free fatty acid (FFA), FBG, uric acid (UA), AST, ALT, γ -glutamyl transferase (GGT), total protein (TP), and albumin (ALB) were measured using routine automated laboratory methods (Hitachi 7060C automatic biochemistry analysis system) at Beijing Chao-yang Hospital.

Free triiodothyronine (FT3), free thyroxine (FT4), and TSH were measured using a lectrochemiluminescence immunoassay on an Abbott Architect i2000 (Abbott Diagnostics, Abbott Park, IL, USA). The reference ranges were 0.55-4.78 $\mu\text{IU/mL}$ for TSH, 3.28-6.47 pmol/L for FT3, and 7.64-16.03 pmol/L for FT4. Fasting insulin levels were assessed using radioimmunoassay. HbA1c was measured using high-performance liquid chromatography (Huizhong MQ-6000, Shanghai, China).

TFQI, TT4RI, and TSHI were calculated to assess central THS. TFQI was assessed as $\text{cdf FT4} - (1 - \text{cdf TSH})^{[5]}$; TSHI was determined using $\ln\text{TSH (mIU/L)} + 0.1345 \times \text{FT4 (pmol/L)}$; TT4RI was computed as $\text{FT4 (pmol/L)} \times \text{TSH (mIU/L)}$. The increase in TFQI, TT4RI, and TSHI indices indicates a decrease in central sensitivity to TH. Peripheral THS was assessed by FT3/FT4. The lower values represent the poorer peripheral THS. Insulin resistance was assessed using the homeostatic model assessment of insulin resistance (HOMA-IR): $\text{HOMA-IR} = \text{fasting insulin } (\mu\text{U/mL}) \times \text{FBG (mmol/L)} / 22.5$. Adipose tissue insulin resistance index (Adipo-IR) was calculated as $\text{fasting insulin } (\mu\text{U/mL}) \times \text{FFA level (mmol/L)}$. The

percentage of excessive weight loss (%EWL) was evaluated using $\%EWL = (\text{baseline weight} - \text{follow-up weight}) / (\text{baseline weight} - \text{ideal weight}) \times 100^{[19]}$. BMI was calculated as weight (kg)/height (m^2).

MRI examination and image post-processing

All subjects underwent upper abdominal examinations using a 3-Tesla whole-body MRI scanner (MAGNETOM Prisma System; Siemens Medical Solutions, Erlangen, Germany) to estimate HFC. Subjects who completed the intervention were reassessed eight weeks later. Subjects experienced a 10–12 h fasting before imaging. Breath-hold scans were done at the end-expiratory phase, covering all upper abdominal organs. The scanning protocol included localizer images followed by a T1 volumetric interpolated breath-hold examination (VIBE) Dixon sequence. The imaging parameters include TE1 1.23 ms, TE2 2.46 ms, TR 3.97 ms, 9° flip angle, 1,040 Hz/Px bandwidth, and 3.0 mm slice thickness.

Post-image processing was performed using Siemens Synovia to acquire the fat fraction images. Hepatic PDFF was estimated by calculating the signal intensity from the regions of interest (ROI) of the liver in a fat fraction image. The measurements were conducted by an experienced radiologist, and the imaging analysis was performed by a senior doctor.

Statistical analysis

Statistical analysis was conducted using IBM SPSS (version 27.0). Continuous data were controlled for normal distribution, with non-normally distributed data log-transformed prior to analysis. Normally distributed data are presented as mean $\pm$ SD and categorical variables are shown as frequency (percentage). All variables were calculated with a delta (Δ) value to show the post-intervention differences from baseline. A paired *t*-test was used to analyze differences between baseline and eight weeks post-intervention. The post-hoc statistical power was derived from the noncentral *t* distribution for a two-sided paired *t*-test at $\alpha = 0.05$. Pearson correlation analysis was performed to evaluate associations between changes in THS indices and changes in metabolic parameters after interventions. Multiple linear regression analysis was conducted to better understand the relationships between THS and metabolic disturbances at baseline and their changes during the intervention after adjusting for age, sex, and other confounding factors. A two-tailed *P*-value < 0.05 was considered statistically significant.

RESULTS

Changes in metabolic parameters and THS indices after the 8-week IF intervention

Of the 80 subjects with SLD, one was excluded at week 1 for not adhering to the dietary protocol, and another withdrew at week 2 for personal reasons. A total of 78 subjects completed the 8-week 5:2 IF intervention and were included in the data analysis. As shown in Table 1, the average HFC was 15.02% at baseline and reduced by 3.79% after the 8-week intervention, accompanied by significant reductions in AST, ALT, and GGT (all $P < 0.05$). The dietary intervention significantly decreased body weight (3.09 ± 2.23 kg) and WC (2.55 ± 3.68 cm), with a corresponding BMI decrease of 1.09 ± 0.75 kg/m^2 (all $P < 0.001$). Insulin sensitivity significantly improved, as represented by an 11% reduction in fasting insulin levels, 13.3% in HOMA-IR, and 17.5% in Adipo-IR from baseline. Meanwhile, all glucose metabolism variables showed significant improvements: FBG decreased from 5.38 ± 0.70 to 5.21 ± 0.70 mmol/L ($P = 0.012$) and HbA1c reduced from 5.78 ± 0.37 to 5.71 ± 0.43 % ($P = 0.003$). Significant improvements were also observed in TG ($P < 0.001$), TC ($P = 0.027$), HDL ($P = 0.002$), and LDL ($P = 0.047$). FFA showed a trend towards an improvement (0.59 ± 0.20 mmol/L vs. 0.64 ± 0.15 mmol/L, $P = 0.054$). UA was also significantly decreased from baseline ($P < 0.001$).

Table 1. Baseline characteristics and changes after the 8-week 5:2 IF intervention

Variables	Baseline	8 weeks	Changes	% Δ from baseline	P	Post-hoc power (%)
n	78	78	NA	NA	NA	NA
Sex (male, %)	35 (44.9%)	35 (44.9%)	NA	NA	NA	NA
Age (yr)	42.13 ± 11.81	42.13 ± 11.81	NA	NA	NA	NA
Weight (kg)	81.40 ± 15.31	78.31 ± 14.65	-3.09 ± 2.23	-3.8	< 0.001	100.0
BMI (kg/m ²)	28.95 ± 4.53	27.86 ± 4.38	-1.09 ± 0.75	-3.8	< 0.001	100.0
WC (cm)	97.41 ± 10.50	94.86 ± 10.19	-2.55 ± 3.68	-2.6	< 0.001	100.0
HFC (%)	15.02 ± 9.47	11.23 ± 8.56	-3.79 ± 5.72	-25.2	< 0.001	100.0
FBG (mmol/L)	5.38 ± 0.70	5.21 ± 0.70	-0.17 ± 0.59	-3.2	0.012	72.1
HbA1c (%)	5.78 ± 0.37	5.71 ± 0.43	-0.07 ± 0.20	-1.2	0.003	87.1
Insulin (μU/mL)	18.54 ± 10.33	16.51 ± 8.07	-2.04 ± 6.25	-11.0	0.005	82.2
HOMA-IR (mg/dL·μU/mL)	4.44 ± 2.57	3.85 ± 2.00	-0.59 ± 1.67	-13.3	0.002	87.7
TG (mmol/L)	2.15 ± 1.25	1.46 ± 0.50	-0.68 ± 1.08	-31.6	< 0.001	100
TC (mmol/L)	5.15 ± 0.94	4.90 ± 0.99	-0.25 ± 0.98	-4.9	0.027	61.5
HDL (mmol/L)	1.03 ± 0.16	1.10 ± 0.17	0.07 ± 0.19	-6.8	0.002	90.2
LDL (mmol/L)	3.28 ± 0.79	3.10 ± 0.66	-0.18 ± 0.78	-5.5	0.047	53.1
FFA (mmol/L)	0.64 ± 0.15	0.59 ± 0.20	-0.05 ± 0.22	-7.8	0.054	51.9
Adipo-IR (mmol/L·μU/mL)	12.04 ± 8.36	9.93 ± 6.14	-2.11 ± 6.43	-17.5	0.005	82.6
UA (μmol/L)	367.91 ± 81.69	355.40 ± 81.08	-12.51 ± 31.65	-3.4	< 0.001	93.7
ALT (U/L)	37.14 ± 28.35	31.36 ± 24.83	-5.78 ± 23.25	-15.6	0.031	59.3
AST (U/L)	31.11 ± 16.80	25.20 ± 12.61	-5.91 ± 13.59	-19.0	< 0.001	97.0
GGT(U/L)	42.15 ± 22.18	34.77 ± 19.08	-7.39 ± 15.72	-17.5	< 0.001	98.6
TP (g/L)	74.76 ± 5.17	75.29 ± 3.87	0.54 ± 4.55	0.7	0.301	18.1
ALB (g/L)	47.84 ± 3.04	47.12 ± 3.14	-0.71 ± 4.00	-1.5	0.120	34.7
FT3 (pmol/L)	4.96 ± 0.59	5.09 ± 0.53	0.13 ± 0.52	2.6	0.029	59.8
FT4 (pmol/L)	16.57 ± 2.10	16.21 ± 2.23	-0.35 ± 1.58	-2.1	0.051	49.9
LnTSH	0.80 ± 0.46	0.49 ± 0.34	-0.30 ± 0.30	-37.5	< 0.001	100.0
TFQI	0.107 ± 0.355	-0.173 ± 0.354	-0.281 ± 0.243	-262.6	< 0.001	100.0
TT4RI	40.45 ± 19.26	28.11 ± 10.45	-12.35 ± 14.00	-30.5	< 0.001	100.0
TSHI	3.03 ± 0.48	2.68 ± 0.45	-0.35 ± 0.35	-11.6	< 0.001	100.0
FT3/FT4	0.30 ± 0.05	0.32 ± 0.05	0.02 ± 0.05	6.7	0.004	94.2

Data was presented as mean ± SD or frequency (percentage) and was analyzed by paired *t*-test. Non-normally distributed data was log-transformed prior to analysis. Δ shows the post-intervention differences from baseline. IF: Intermittent fasting; NA: not applicable; BMI: body mass index; WC: waist circumference; HFC: hepatic fat content; FBG: fasting blood glucose; HbA1c: glycated hemoglobin A1c; HOMA-IR: homeostatic model assessment of insulin resistance; TG: triglyceride; TC: total cholesterol; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; FFA: free fatty acid; Adipo-IR: adipose tissue insulin resistance index; UA: uric acid; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: γ-glutamyl transferase; TP: total protein; ALB: albumin; FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid-stimulating hormone; TFQI: thyroid feedback quantile-based index; TT4RI: thyrotroph thyroxine resistance index; TSHI: thyroid-stimulating hormone index; SD: standard deviation.

During eight weeks, the IF intervention significantly reduced the TSH level (LnTSH, $P < 0.001$) and showed a trend toward decreased FT4 levels (16.21 ± 2.23 vs. 16.57 ± 2.10 pmol/L, $P = 0.051$), while significantly increasing FT3 levels (5.09 ± 0.53 vs. 4.96 ± 0.59 pmol/L, $P = 0.029$). Correspondingly, THS improved: TFQI, TT4RI, and TSHI all decreased and FT3/FT4 increased (-0.173 ± 0.354 vs. 0.107 ± 0.355 , $P < 0.001$; 28.11 ± 10.45 vs. 40.45 ± 19.26 , $P < 0.001$; 2.68 ± 0.45 vs. 3.03 ± 0.48 , $P < 0.001$; 0.32 ± 0.05 vs. 0.30 ± 0.05 , $P = 0.004$, respectively).

Associations between changes in THS and changes in metabolic variables during the intervention

At baseline, we evaluated whether THS was an independent risk factor for SLD and related metabolic disorders. HFC and HOMA-IR were significantly positively correlated with TFQI and TG was positively correlated with TT4RI after adjusting for age, sex, BMI, and HbA1c (all $P < 0.05$) [Supplementary Table 1].

Thereafter, we examined the correlations between changes in metabolic variables and alterations in THS indices [Table 2]. Δ BMI, Δ WC, and EWL were significantly correlated with alterations in THS indices (Δ TFQI and Δ TSHI), while Δ HFC had no significant association with changes in THS. Δ LDL positively correlated with Δ TFQI and Δ TSHI. Changes in glucose metabolic measures (Δ FBG and Δ HbA1c), Δ TG, Δ TC, Δ HDL, Δ FFA, Δ UA, Δ ALT, Δ AST, and Δ GGT showed no correlation with changes in any THS indices. For insulin sensitivity measures, Δ insulin and Δ HOMA-IR were significantly correlated with Δ TFQI and Δ TSHI (both $P < 0.05$); Δ Adipo-IR positively correlated with changes in all three central THS indices (Δ TFQI, Δ TT4RI, and Δ TSHI) (all $P < 0.05$).

Significant positive correlations were observed between Δ TFQI and Δ TSHI and changes in insulin sensitivity indices, including fasting insulin, HOMA-IR, and Adipo-IR, after adjusting for sex, age, and EWL during the intervention (all $P < 0.05$) [Figure 1A-L]. In a multivariate model adjusted for age, sex, and EWL, Δ TFQI and Δ TSHI were still significantly associated with Δ insulin ($\beta = 0.265$, $P = 0.017$; $\beta = 0.245$, $P = 0.028$, respectively), Δ HOMA-IR ($\beta = 0.262$, $P = 0.019$; $\beta = 0.232$, $P = 0.040$, respectively), and Δ Adipo-IR ($\beta = 0.312$, $P = 0.004$; $\beta = 0.257$, $P = 0.019$, respectively). Δ TFQI explained 18%, 17%, and 23% of the variance in insulin, HOMA-IR, and Adipo-IR, respectively, across the models. Δ TSHI explained 17%, 16%, and 20% of the variance in insulin, HOMA-IR, and Adipo-IR, respectively [Table 3]. Δ F3/FT4 was negatively correlated with Δ insulin after adjusting for age, sex, and EWL, explaining 17% of the variance in insulin in the full model.

DISCUSSION

In this prospective 5:2 IF intervention study, we demonstrated that an 8-week IF regimen significantly decreased HFC and improved glucose and lipid metabolism and THS in patients with SLD, with amelioration of THS being associated with improvements in insulin sensitivity independent of weight loss. Our findings provide additional support for refining therapeutic strategies for SLD, suggesting that appropriate dietary interventions could help improve TH resistance in individuals with SLD, thereby contributing to improved insulin resistance. Notably, the present trial enrolled 78 patients, a relatively large sample compared with most previous IF studies in metabolic or liver disease populations^[11-14], which strengthens the reliability of our findings and highlights the novelty of investigating THS in this clinical context.

THs participate in regulating glucose and lipid metabolism, including modulating hepatic insulin sensitivity, inhibiting hepatic gluconeogenesis, and promoting lipolysis, lipid exportation, and lipogenesis. It is plausible and well-known that thyroid dysfunctions are closely correlated with metabolic disturbances and SLD. The proposal of THS indices and acquired resistance to TH by Laclaustra *et al.* partially explains the previous controversy about abnormal thyroid function and SLD and related metabolic disorders^[5]. With Dr. Laclaustra first proposing the association between THS and diabetes and metabolic syndrome, a growing body of studies in the past five years have revealed that impaired THS correlated with visceral adiposity, insulin resistance, dyslipidemia, and SLD in euthyroid populations or patients with subclinical hypothyroidism^[20]. Lai *et al.* explored the relationship between THS and non-alcoholic SLD in 4,610 Chinese subjects for the first time and discovered that THS indices positively correlated with dyslipidemia and SLD even after controlling for confounding factors^[21]. Another cross-sectional study performed on

Table 2. Univariate correlation analysis between changes in THS indices and changes in metabolic parameters after the 8-week 5:2 IF intervention

Variables	Δ TFQI		Δ TT4RI		Δ TSHI		Δ FT3/FT4	
	r	P	r	P	r	P	r	P
Δ BMI (kg/m ²)	0.326	0.004	0.148	0.197	0.253	0.026	-0.253	0.025
Δ WC (cm)	0.278	0.014	0.136	0.234	0.244	0.031	-0.170	0.136
Δ HFC (%)	0.157	0.169	0.081	0.480	0.129	0.260	-0.165	0.148
EWL (%)	0.221	0.052	0.146	0.203	0.232	0.041	-0.179	0.116
Δ FBG (mmol/L)	0.067	0.560	0.072	0.530	0.045	0.693	0.053	0.647
Δ HbA1c (%)	0.212	0.063	0.173	0.131	0.187	0.101	-0.182	0.110
Δ Insulin (μ U/mL)	0.272	0.016	0.133	0.244	0.242	0.033	-0.167	0.143
Δ HOMA-IR (mg/dL· μ U/mL)	0.272	0.016	0.147	0.200	0.232	0.041	-0.145	0.206
Δ TG (mmol/L)	-0.036	0.756	0.221	0.052	0.072	0.522	-0.065	0.569
Δ TC (mmol/L)	0.018	0.878	-0.027	0.812	-0.073	0.525	0.115	0.315
Δ HDL (mmol/L)	-0.097	0.397	-0.026	0.824	-0.042	0.712	0.038	0.743
Δ LDL (mmol/L)	0.245	0.031	0.161	0.159	0.236	0.038	-0.178	0.118
Δ FFA (mmol/L)	0.101	0.377	0.122	0.287	0.053	0.647	0.109	0.341
Δ Adipo-IR (mmol/L· μ U/mL)	0.314	0.005	0.205	0.017	0.249	0.028	-0.087	0.449
Δ UA (μ mol/L)	0.201	0.078	0.095	0.408	0.137	0.231	-0.027	0.812
Δ ALT (U/L)	0.091	0.428	0.013	0.910	0.099	0.388	-0.030	0.793
Δ AST (U/L)	0.074	0.522	0.161	0.160	0.101	0.378	-0.002	0.984
Δ GGT (U/L)	0.074	0.520	0.097	0.397	0.047	0.680	-0.083	0.471

Data was analyzed by Pearson correlation. Δ shows the post-intervention differences from baseline. THS: Thyroid hormone sensitivity; IF: intermittent fasting; TFQI: thyroid feedback quantile-based index; TT4RI: thyrotroph thyroxine resistance index; TSHI: thyroid-stimulating hormone index; FT3: free triiodothyronine; FT4: free thyroxine; BMI: body mass index; WC: waist circumference; HFC: hepatic fat content; EWL: excessive weight loss; FBG: fasting blood glucose; HbA1c: glycated hemoglobin A1c; HOMA-IR: homeostatic model assessment of insulin resistance; TG: triglyceride; TC: total cholesterol; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; FFA: free fatty acid; Adipo-IR: adipose tissue insulin resistance index; UA: uric acid; ALT: alanine amino-transferase; AST: aspartate aminotransferase; GGT: γ -glutamyl transferase.

euthyroid participants also reported a positive association between THS indices and the prevalence of metabolic dysfunction-associated SLD and indicated that the TG glucose index, a surrogate index of insulin sensitivity, partly mediated this relevance^[22]. Zhang *et al.* revealed the same correlation between THS and metabolic dysfunction-associated SLD in patients with newly diagnosed type 2 diabetes; however, the relationship was not significant when they adjusted for BMI and HOMA-IR in euthyroid populations^[7], which indicated that other metabolic factors might mediate the association between THS and SLD. However, evidence on the relationship between THS and metabolism in patients with SLD is limited. Only one cross-sectional study conducted in 129 Chinese subjects with biopsy-proven euthyroid SLD by Li *et al.* showed that resistance to TH assessed by FT3/FT4, TFQI, TT4RI, and TSHI correlated with advanced liver fibrosis^[23]. To the best of our knowledge, this is the first study to demonstrate that reduced THS is associated with increased HFC, elevated TG levels, and decreased insulin sensitivity, even after adjusting for factors such as age, sex, BMI, and HbA1c in participants with SLD. Therefore, we propose that THS is an independent risk factor for HFC and insulin sensitivity in SLD patients.

Approved pharmacological agents for SLD are largely limited. Noninvasive weight-loss approaches, such as fasting-based dietary interventions, have gained considerable attention in the fields of obesity and metabolic diseases and have been effective in improving glucose and lipid metabolism, with the 5:2 IF regimen being among the most popular^[10]. Only a few studies have investigated the benefits of 5:2 IF on SLD and related pathologies. Holmer *et al.* showed that 12-week 5:2 IF significantly reduced body weight, hepatic steatosis

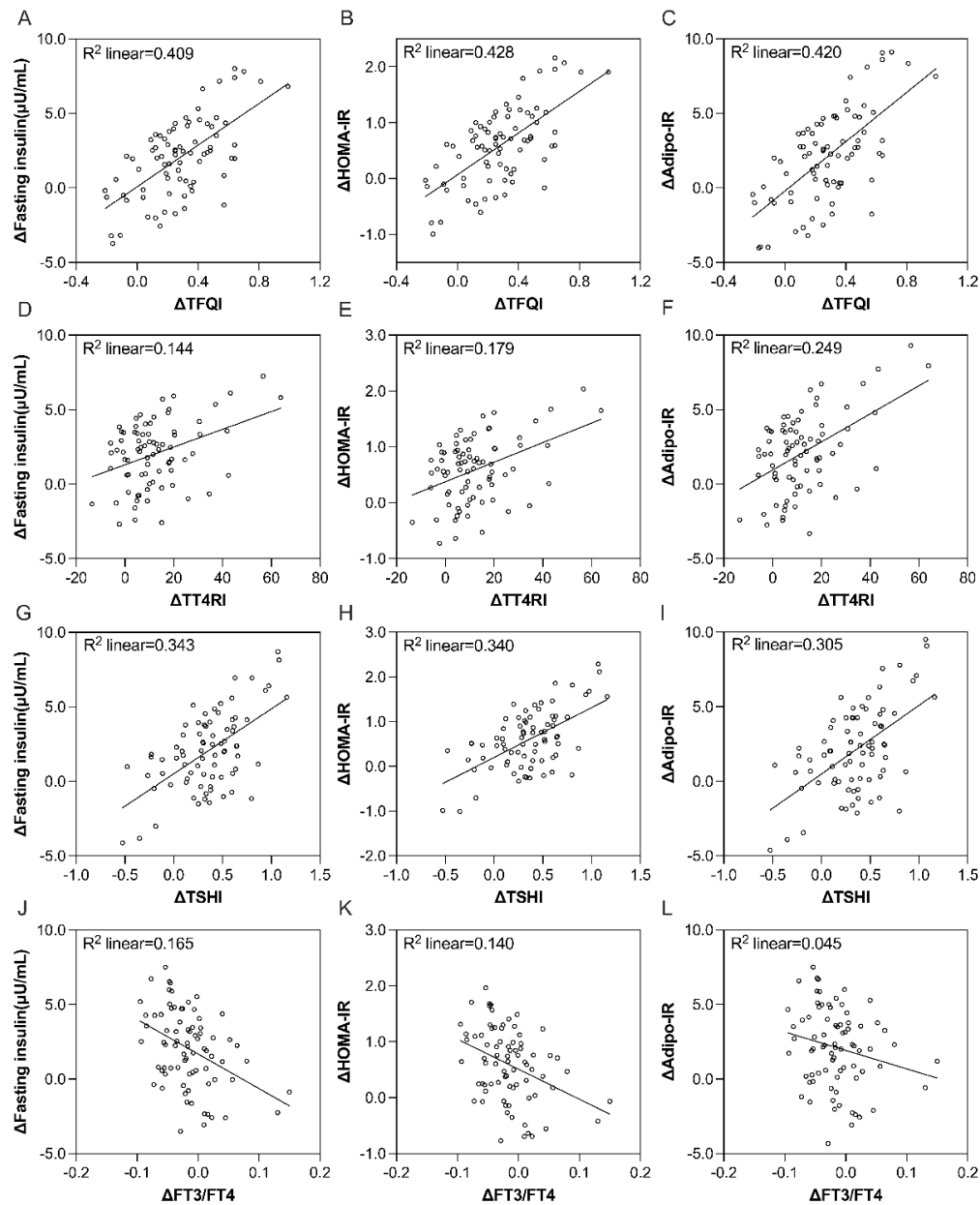


Figure 1. Correlations between in-patient changes in insulin sensitivity indices and THS indices during an 8-week 5:2 IF intervention after adjusting for age, sex, and EWL. (A) Δ TFQI and Δ fasting insulin; (B) Δ TFQI and Δ HOMA-IR; (C) Δ TFQI and Δ Adipo-IR; (D) Δ TT4RI and Δ fasting insulin; (E) Δ TT4RI and Δ HOMA-IR; (F) Δ TT4RI and Δ Adipo-IR; (G) Δ TSHI and Δ fasting insulin; (H) Δ TSHI and Δ HOMA-IR; (I) Δ TSHI and Δ Adipo-IR; (J) Δ FT3/FT4 and Δ fasting insulin; (K) Δ FT3/FT4 and Δ HOMA-IR; (L) Δ FT3/FT4 and Δ Adipo-IR. Δ shows the post-intervention differences from baseline. THS: Thyroid hormone sensitivity; IF: intermittent fasting; EWL: excessive weight loss; TFQI: thyroid feedback quantile-based index; HOMA-IR: homeostatic model assessment of insulin resistance; Adipo-IR: adipose tissue insulin resistance index; TT4RI: thyrotroph thyroxine resistance index; TSHI: thyroid-stimulating hormone index; FT3: free triiodothyronine; FT4: free thyroxine.

measured by magnetic resonance spectroscopy, liver stiffness, HOMA-IR, HbA1c, and serum TC and LDL in 74 participants with SLD for the first time^[24]. Kord Varkaneh *et al.* performed a randomized controlled study to compare the effects of 12-week 5:2 IF ($n = 21$) and control diet ($n = 23$) on SLD. They also observed significant reductions in liver steatosis score and fibrosis score and dramatic decreases in serum TG, AST, ALT, insulin levels, and inflammatory biomarkers such as high-sensitivity C-reactive protein and

Table 3. Multiple regression analysis with changes in fasting insulin, HOMA-IR, or Adipo-IR as the dependent variable and changes in THS indices as independent variables after controlling for age, sex, and EWL in patients with fatty liver disease undergoing an 8-week IF intervention

Variables	Δ Insulin		Δ HOMA-IR		Δ Adipo-IR	
	β	P	β	P	β	P
Δ TFQI	0.265	0.017	0.262	0.019	0.312	0.004
EWL	0.143	0.205	0.149	0.189	0.134	0.219
	$R^2 = 0.181$		$R^2 = 0.173$		$R^2 = 0.234$	
Δ TT4RI	0.099	0.378	0.114	0.311	0.170	0.123
EWL	0.184	0.111	0.187	0.106	0.174	0.121
	$R^2 = 0.124$		$R^2 = 0.120$		$R^2 = 0.169$	
Δ TSHI	0.245	0.028	0.232	0.040	0.257	0.019
EWL	0.146	0.195	0.155	0.175	0.145	0.190
	$R^2 = 0.171$		$R^2 = 0.158$		$R^2 = 0.204$	
Δ FT3/FT4	-0.246	0.031	-0.215	0.062	-0.172	0.131
EWL	0.170	0.128	0.179	0.113	0.181	0.107
	$R^2 = 0.169$		$R^2 = 0.150$		$R^2 = 0.168$	

Data was analyzed by multiple linear regression. Δ shows the post-intervention differences from baseline. R^2 values were for the entire model including changes in THS indices, age, sex, and EWL. HOMA-IR: Homeostatic model assessment of insulin resistance; Adipo-IR: adipose tissue insulin resistance index; THS: thyroid hormone sensitivity; EWL: excessive weight loss; IF: intermittent fasting; TFQI: thyroid feedback quantile-based index; TT4RI: thyrotroph thyroxine resistance index; TSHI: thyroid-stimulating hormone index; FT3: free triiodothyronine; FT4: free thyroxine.

cytokeratin-18 after 12-week IF intervention^[25]. Gallage *et al.* recently validated the effects of 5:2 IF on SLD and steatohepatitis in a preclinical model induced by a Western diet and showed that fasted mice gained less body weight and presented improvements in fasting glucose levels and hepatic steatosis and inflammation, which is independent of the total calorie intake^[26]. In line with the above studies, our study also found that 8-week 5:2 IF significantly reduced HFC assessed by MRI-PDFF, body weight, WC, serum lipid profiles, FBG, insulin, HOMA-IR, and Adipo-IR in patients with SLD. Meanwhile, we observed that serum FT3 and the FT3/FT4 ratio increased, whereas FT4, TSH, TFQI, TT4RI, and TSHI decreased following the 5:2 IF intervention.

Lines of evidence have demonstrated that fasting influences the hypothalamus-pituitary-thyroid (HPT) axis. Fasting-induced downregulation of hypothalamus thyrotropin-releasing hormone (TRH) and pituitary TSH has been shown in animal models, in which fasting-altered leptin and neuromedin B might play some roles. Meanwhile, animal studies also showed that serum T3 and T4 levels were decreased following 24-hour fasting^[27]. However, few studies explored the effects of long-term IF on thyroid function, especially in humans. Moro *et al.* analyzed the changes in thyroid function after 8-week time-restricted fasting (8 h) in 34 resistance-trained men and showed that T3 significantly decreased but TSH did not change after IF intervention^[28]. In animal experiments, a recent study suggested that 3-week IF decreased body weight, promoted white fat browning, and increased serum T3 levels along with elevated TRH expression in the hypothalamus in stressed rats^[29]. Differences in IF intervention regimens, intervention duration, and study populations or animal models might contribute to the inconsistencies among the published studies. Moreover, we speculate that heterogeneity in THS may also partially decipher the different results among the studies. In our study, 8-week 5:2 IF elevated serum FT3 levels but reduced TSH and FT4 levels in SLD patients. Central THS measured by TFQI, TT4RI, and TSHI and peripheral THS assessed by FT3/FT4 were both improved by IF. More large-scale clinical studies and animal experiments were required to validate the results and our hypothesis and to reveal the involved biological mechanisms.

Interestingly, multiple regression analysis showed that Δ TFQI and Δ TSHI were significantly associated with Δ insulin, Δ HOMA-IR, and Δ Adipo-IR, and that Δ FT3/FT4 was correlated with Δ insulin in patients with SLD during the 8-week IF intervention, after adjusting for age, sex, and weight loss. Resistance to TH syndrome (RTH) is a rare disease caused by inherited mutations in TH receptor beta (*THR β*) and characterized by both elevated FT4 and TSH levels. Patients exhibited higher levels of intrahepatic fat, HOMA-IR, and FFA. However, another study suggested no changes in skeletal insulin sensitivity evaluated by the hyperinsulinemic-euglycemic clamp in 16 patients with RTH compared with 28 age-, sex-, and BMI-matched controls^[30]. These different manifestations might be induced by variable resistance to the action of THs in different peripheral tissues. Central THS pertains to the HPT axis's responsiveness to variations in circulating FT4^[5]. Participants with reduced central THS also displayed peripheral TH resistance^[5]. A recent study from our research team showed that impaired THS correlated with increased HOMA-IR and Adipo-IR in obese populations, whereas the association between HOMA-IR and THS indices lost significance after adjusting for confounding factors^[31]. THs regulate hepatic glucose output via modulating the expression of glucose-6-phosphatase involved in gluconeogenesis and glycogenolysis and glucose transporter 2 (GLUT2) and through a central sympathetic pathway from the hypothalamic paraventricular nucleus to the liver^[32]. Additionally, resistance to TH was shown to correlate with visceral adiposity and insulin resistance resulting from the inhibition of catecholamine-stimulated lipolysis. Some adipokines such as leptin and inflammatory cytokines including interleukin 6 and tumor necrosis factor- α have been suggested to be mediators of the correlation between THS and adipose insulin resistance^[31]. Liver-directed *THR β* selective agonists resmetirom have gained growing popularity in the treatment of SLD. A randomized, double-blind, placebo-controlled study showed that resmetirom reduced hepatic fat by 37.3% and liver enzymes after a 36-week intervention in patients with non-alcoholic steatohepatitis^[33]. The current study suggested that improvements in THS indices induced by noninvasive 5:2 IF positively correlated with increased insulin sensitivity in patients with SLD for the first time, which is also weight loss independent. Potential mechanisms linking IF to improved THS may involve alterations in peripheral deiodinase activity^[34], changes in leptin signaling during energy restriction^[35], and TH regulation of systemic energy homeostasis^[36]. While speculative, these mechanisms highlight possible biological links between dietary restriction and thyroid-metabolic interactions and warrant further mechanistic investigation in future studies.

From a clinical perspective, these findings suggest that IF may be considered a non-pharmacological option for the management of SLD. Improvements in HFC, insulin sensitivity, and THS highlight its potential to complement existing lifestyle-based strategies^[37]. For patients with concurrent thyroid dysfunction, careful monitoring of thyroid parameters during IF may be particularly important. Compared with other dietary interventions, such as continuous caloric restriction or the Mediterranean diet, the magnitude of metabolic improvements observed in this study is comparable or even greater for certain outcomes, underscoring the potential utility of IF in clinical practice^[38].

Limitations

This study has several limitations that should be considered when interpreting the findings. First, this was a single-center, prospective intervention without a parallel control group or randomization. Accordingly, causal inference is limited, and regression to the mean or secular trends cannot be completely excluded^[39]. Future randomized controlled trials with appropriate comparators are warranted to validate these findings in patients with SLD. Second, the 8-week duration of intervention may be insufficient to assess the sustainability of metabolic and THS improvements. Longer follow-up is required to determine the durability of improvements in HFC, THS, and insulin sensitivity, as well as to evaluate potential rebound after the intervention^[40]. Third, although MRI-PDFF is a validated, noninvasive biomarker of hepatic steatosis, it does not capture histologic features such as inflammation or fibrosis; thus, we could not assess

whether changes in THS were linked to histologic improvement^[41]. Fourth, compliance with fasting days and prescribed macronutrient targets was monitored by dietitian coaching and self-report, which may introduce information bias^[42]. Fifth, we did not collect thyroid autoantibodies, detailed hypothalamic–pituitary–thyroid axis function (e.g., TRH, leptin, neuromedin B), or thyroid imaging assessments (e.g., ultrasonography), which precludes mechanistic dissection of central vs. peripheral pathways and prevents a more comprehensive evaluation of thyroid status in patients with SLD^[43]. This represents a notable limitation, and future studies incorporating comprehensive thyroid axis evaluations and thyroid imaging assessments are needed. Sixth, residual confounding cannot be ruled out despite multivariable adjustment for age, sex, and weight loss; unmeasured factors such as sleep, physical activity, medication changes, or baseline dietary patterns might have contributed to the metabolic responses^[44]. In addition, IF may also influence the gut–liver axis through modulation of gut microbiota and microbial metabolites^[45]. However, our study did not assess these pathways, and therefore we cannot determine whether such effects are independent of THS and insulin resistance. We acknowledge this as an additional potential mechanism, and emphasize that future multi-omics investigations are needed to disentangle the relative contributions of gut microbial pathways vs. THS/IR-mediated pathways. Finally, participants were Chinese outpatients with SLD managed at a tertiary hospital, which may limit generalizability to other populations, ethnicities, or care settings. Future randomized, controlled studies with longer duration, mechanistic profiling, and hard liver outcomes are warranted to validate and extend these results.

Conclusions

This prospective study demonstrated that improvement in THS following an 8-week 5:2 IF intervention was associated with enhanced insulin sensitivity independent of weight loss in patients with SLD. These findings provide new evidence for the metabolic benefits of IF in SLD and may help refine therapeutic strategies for this condition.

DECLARATIONS

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Authors' contributions

Methodology, data curation, and writing - original draft: Zhou L

Visualization, validation, and writing - original draft: Yu Y

Methodology: Jiang L

Resources, conceptualization, methodology, and supervision: Liu J

Funding acquisition, investigation, project administration, and writing - review and editing: Wang G

Availability of data and materials

All the data generated and analyzed during this study are included in our manuscript. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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None.

Conflicts of interest

Liyuan Zhou serves as a Guest Editor for the Special Issue “*Chrono-Nutrition and Metabolic Health and Dysfunction: From Mechanisms to Translational Science*” in the journal *Metabolism and Target Organ Damage*. Liyuan Zhou was not involved in any part of the editorial processing of this manuscript, including reviewer selection and decision-making. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Chao-yang Hospital affiliated with Capital Medical University (Approval No. 2021-KE-10). Written informed consent was obtained from all individual participants prior to enrollment.

Consent for publication

Not applicable.

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