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Time-restricted eating with or without a low-carbohydrate diet improved myocardial status and thyroid function in individuals with metabolic syndrome: secondary analysis of a randomized clinical trial

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Abstract

Background Obesity and metabolic syndrome (MetS) have become urgent worldwide health problems, predisposing patients to unfavorable myocardial status and thyroid dysfunction. Low-carbohydrate diet (LCD) and time-restricted eating (TRE) have been confirmed to be effective methods for weight management and improving MetS, but their effects on the myocardium and thyroid are unclear.

Methods We conducted a secondary analysis in a randomized clinical diet-induced weight-loss trial. Participants ($N=169$) diagnosed with MetS were randomized to the LCD group, the 8 h TRE group, or the combination of the LCD and TRE group for 3 months. Myocardial enzymes and thyroid function were tested before and after the intervention. Pearson's or Spearman's correlation was assessed between functions of the myocardium and thyroid and cardiometabolic parameters at baseline.

Results A total of 162 participants who began the trial were included in the intention-to-treat (ITT) analysis, and 57 participants who adhered to their assigned protocol were involved in the per-protocol (PP) analysis. Relative to baseline, lactate dehydrogenase, creatine kinase MB, hydroxybutyrate dehydrogenase, and free triiodothyronine (FT3) declined, and free thyroxine (FT4) increased after all 3 interventions (both analyses). Creatine kinase (CK) decreased only in the TRE (−18 [44] U/L, $P<0.001$) and combination (−22 [64] U/L, $P=0.003$) groups (PP analysis). Thyrotropin (−0.24 [0.83] μIU/mL, $P=0.011$) and T3 (−0.10 ± 0.04 ng/mL, $P=0.011$) decreased in the combination group (ITT analysis). T4 (0.82 ± 0.39 μg/dL, $P=0.046$), thyroglobulin antibodies (TgAb, 2 [1] %, $P=0.021$), and thyroid microsomal antibodies (TMAb, 2 [2] %, $P<0.001$) increased, while the T3/T4 ratio (−0.01 ± 0.01, $P=0.020$) decreased only in the TRE group (PP analysis). However, no significant difference between groups was observed in either analysis. At baseline, CK was positively correlated with the visceral fat area. FT3 was positively associated with triglycerides and total

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cholesterol. FT4 was negatively related to insulin and C-peptide levels. TgAb and TMAb were negatively correlated with the waist-to-hip ratio.

Conclusions TRE with or without LCD confers remarkable metabolic benefits on myocardial status and thyroid function in subjects with MetS.

Trial registration ClinicalTrials.gov, NCT04475822.

Keywords Metabolic syndrome, Low-carbohydrate diet, Time-restricted eating, Myocardial enzymes, Thyroid function

Background

Metabolic syndrome (MetS) is a cluster of concomitant conditions, including abdominal obesity, elevated blood pressure, insulin resistance (IR), and hyperglycemia, that predispose individuals to cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and mortality. Along with elevated prevalence rates of obesity [1], MetS affects more than 30% of the population worldwide [2–4]. As critical methods of lifestyle modification, multifarious dietary interventions [5], such as a low-carbohydrate diet (LCD) and time-restricted eating (TRE), are emerging and are well established to cause 5% to 7% weight loss on average. However, no dietary strategy is consistently superior to others for the MetS population.

Compared with individuals without MetS, individuals with MetS are more than twofold more likely to have myocardial infarction (MI) [6, 7], and a dose–response relationship was found between cumulative exposure to MetS components and MI [8]. As indicators of myocardial injury, myocardial enzymes are closely correlated with the risk of obesity and MetS [9, 10], and higher levels of myocardial enzymes have been observed in obese patients and MetS patients [11, 12]. Additionally, MetS is closely related to thyroid dysfunction. Thyroid hormones (THs) play vital roles in maintaining the basal metabolic rate; controlling protein, carbohydrate, and lipid metabolism; and modulating heart rate, body temperature, cardiovascular functions, and weight [13, 14]. An increasing number of studies have shown that subclinical or clinical hypothyroidism in individuals with obesity and MetS is characterized by increased thyrotropin (TSH) and triiodothyronine (T3) levels and decreased thyroxine (T4) levels [15–18], with increasing risks of metabolic disorders, such as dyslipidemia, IR, and nonalcoholic fatty liver disease [19–21]. THs levels and autoantibody titers are associated with MetS components even in euthyroid individuals [22–24].

Despite considerable evidence on the benefits of LCD and TRE for improving MetS [25, 26], whether these interventions also ameliorate myocardial status and thyroid dysfunction in individuals with MetS and which is the superior method are still unclear. Controversial results have been reported regarding THs after LCD or TRE in participants with obesity and MetS. Some studies have shown that THs are altered to varying degrees [27, 28], but some studies have failed to find any changes [29, 30]. In addition, studies on the effects of diet-induced weight loss on thyroid autoantibodies and myocardial enzymes in individuals with MetS are scarce. Furthermore, no study to date has directly compared the effects of LCD, TRE, or their combination on myocardial enzymes and thyroid function in the MetS population.

Therefore, we aimed to evaluate the effects of LCD, TRE, and their combination on the myocardium and thyroid and to determine which is the superior method. We hypothesized that all three interventions could improve thyroid function and myocardial status and that TRE with or without LCD may result in prominent improvements due to additional benefits for weight and cardiometabolic risk factors [31].

Methods

Study design

The detailed protocol is reported elsewhere [31]. Briefly, we conducted a single-center, 3-month, open-label, clinical trial to investigate the effects of LCD, TRE, and their combination on body weight and cardiometabolic risk factors in patients with MetS. We conducted this secondary analysis to explore the effects of LCD, TRE, and their combination on myocardial status and thyroid function. This trial was ethically approved by the Institutional Review Board of the First Affiliated Hospital of Xi'an Jiaotong University, and all participants provided written informed consent. The original study [31] and this secondary analysis followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Participants

Participants were recruited by fliers, posters, and advertisements. Free-living men and women with MetS who met at least 3 out of 5 criteria [32] and were aged 18 to 65 years were eligible for screening. The exclusion criteria included pregnancy or lactation, night shift work, history of major diseases or related diseases, participation in other weight loss trials, consumption of a prescribed diet for special diseases or any drugs that affect appetite,

and history of bariatric surgery. The present trial was screened from July 2020 to September 2020 and was completed in January 2021.

Protocol

The detailed methods and procedures have been published previously [31]. In brief, the protocol included a run-in period before the intervention, during which participants were instructed to maintain their habitual diet and physical activity level for 2 weeks to stabilize weight. Participants in the LCD group were required to follow a reduced-carbohydrate diet (carbohydrates < 130 g/day or < 26% total energy) without time limitations. Participants in the TRE group were restrained from eating ad libitum (AL) within 8 h per day and fasted for 16 h. Participants in the combination group were instructed to restrict both carbohydrate intake and the eating window. Participants in the latter two groups voluntarily chose either early TRE (eTRE, eat from 8 AM to 4 PM and fast from 4 PM to 8 AM the next day) or late TRE (lTRE, eat from 12 to 8 PM and fast from 8 to 12 PM the next day) according to their eating habits. All participants were not allowed to change their physical activity habits or dose of medication during the trial.

Dietary guidance was carried out online through a unique and novel application called Zhihui Hao Yiyuan, which was established as a medical assistance platform. All participants were encouraged but not compulsory to write a daily dietary log. Nutrient intake was assessed every other week through an online Food Frequency Questionnaire (FFQ) which also included a 2-week recall of mealtime and days of adherence.

Outcome measurement

Specific processes and approaches to obtaining anthropometric metrics have been described elsewhere [31]. In the original study, the primary outcomes were changes in weight and body fat after 3-month interventions, and the secondary outcomes included changes in blood pressure, blood glucose, blood lipid, and uric acid. This secondary analysis reported additional outcomes including changes in myocardial enzymes and thyroid function after 3-month interventions.

Blood samples were obtained at the First Affiliated Hospital of Xi'an Jiaotong University after a whole-night fast (from 8 PM on) before and after intervention following a standard procedure of blood sample collection and stored at − 80 °C until assessment. The staff who collected and analyzed the outcomes were blinded to the participant assignments. Myocardial enzymes were tested by velocity assays using a LABOSPECT 008AS automatic biochemical analyzer. The laboratory reference ranges of lactate dehydrogenase (LDH), creatine kinase (CK), creatine kinase MB (CKMB), and hydroxybutyrate dehydrogenase (HBDH) were 120–250 U/L, 50–210 U/L, 0–24 U/L, and 72–182 U/L, respectively, using standard reagents to the nearest 1 U/L, 1 U/L, 1 U/L, and 1 U/L, respectively. THs were measured by radioimmunoassay using GC-2016 16th automatic sampling change equipment. The laboratory reference ranges of free triiodothyronine (FT3), free thyroxine (FT4), TSH, T3, and T4 were 2.91–9.08 pmol/L, 9.05–25.50 pmol/L, 0.25–5.00 μIU/mL, 0.78–2.20 ng/mL, and 4.20–13.50 μg/dL, respectively, using standard reagents to the nearest 0.01 pmol/L, 0.01 pmol/L, 0.01 μIU/mL, 0.01 ng/mL, and 0.01 μg/dL, respectively. Thyroid autoantibodies were tested by radioimmunoassay using an FM-2000 gamma immune counter, the laboratory reference ranges of thyroglobulin antibodies (TgAb) and thyroid microsomal antibodies (TMAb) were < 30% and < 20% with standard reagents to the nearest 1% and 1%, respectively.

Statistical analysis

Data from participants who started the 3-month intervention were included in this intention-to-treat (ITT) analysis. Missing data were handled by multiple imputations with the use of the Markov chain Monte Carlo method. The per-protocol (PP) analysis included participants who adhered to their assigned protocol. The data are presented as the means ± standard errors of the means (SEMs) for normally distributed variables, medians (interquartile ranges) for abnormally distributed variables, or numbers (percentages) for categorical variables. Comparisons among groups at baseline were assessed using one-way ANOVA for normally distributed variables, the Kruskal–Wallis H test for abnormally distributed variables, or the chi-square test or Fisher's exact test for categorical variables. Within-group comparisons of outcome variables were performed by paired t tests for normally distributed variables or paired Wilcoxon tests for abnormally distributed variables, and between-group comparisons of changes were performed by independent samples t tests for normally distributed variables or Mann–Whitney U tests for abnormally distributed variables. Statistical significance was considered when two-tailed $P < 0.05$. Pearson's correlation for normally distributed variables or Spearman's correlation for abnormally distributed variables was performed to investigate the correlation between functions of the myocardium and thyroid and cardiometabolic parameters at baseline. All the statistical analyses were performed using R version 4.1.3

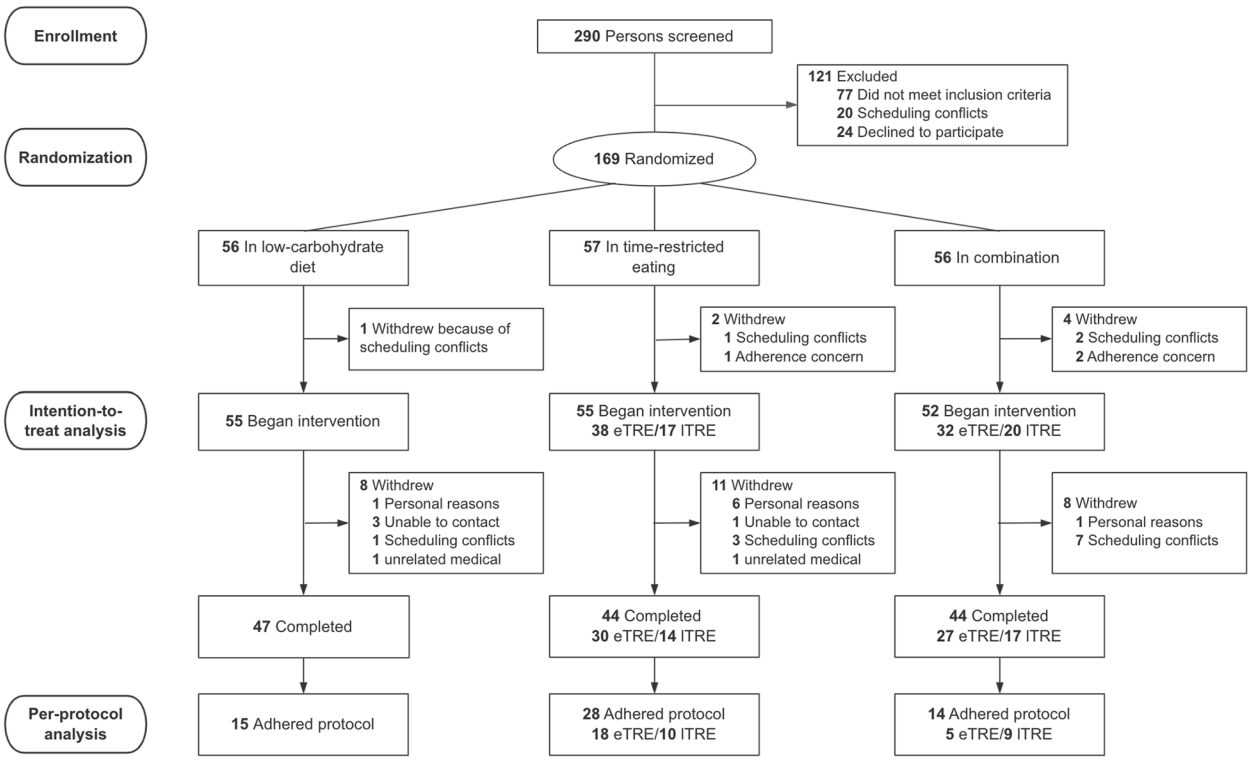

Fig. 1 Participant flow. eTRE, early time-restricted eating; lTRE, late time-restricted eating

Results

Participant characteristics

As Fig. 1 shows, 290 individuals were screened at the beginning of the study, 121 individuals were excluded because they failed to meet the study criteria ($n=77$), had scheduling conflicts ($n=20$), or declined to participate ($n=24$), and 169 individuals were randomly assigned at a 1:1:1 ratio to the LCD group ($n=56$), TRE group ($n=57$), or combination group ($n=56$). Seven participants dropped out before commencing the study, 4 of whom had scheduling conflicts and 3 of whom had adherence concerns. In total, 162 participants started the interventions (55 in the LCD group, 55 in the TRE group, and 52 in the combination group), and 135 completed the interventions (47 in the LCD group, 44 in the TRE group, and 44 in the combination group). Fifty-seven participants (15 in the LCD group, 28 in the TRE group, and 14 in the combination group) who adhered to their assigned protocol were included in the PP analysis (LCD: daily carbohydrate intake < 150 g/day on ≥ 5 days/week for 3 months; TRE: daily eating window ≤ 8 h on ≥ 5 days/week for 3 months; combination treatment: combined criteria of LCD and TRE.)

The baseline data are outlined in Table 1. The mean ± SEM average body mass index (BMI) was above 28.0 kg/m^2 in each group. The majority of participants had normal myocardial and thyroid functions; 33/162 (20.4%) had elevated myocardial enzymes, and 26/162 (16.0%) had thyroid dysfunction. Overall, the baseline characteristics were significantly equal among the three intervention arms and between those who completed the study and those who withdrew (Additional file 1: Table S1).

Only 3 participants (2 in the LCD group and 1 in the TRE group) had been diagnosed with hypothyroidism and were taking levothyroxine sodium tablets before the intervention; no other medication in addition to cardiovascular medication was taken by any of the participants. All participants maintained their medication dosage and did not change their level of physical activity during the 3-month intervention. The intake of aquatic products was decreased in the TRE group and the intake of phytocomycetes was increased in the combination group (Additional file 1: Table S3).

LCD, TRE, and their combination reduced LDH, CK, CKMB, and HBDH

All three groups exhibited equivalent reductions in LDH, CK, CKMB, and HBDH after the 3-month intervention ($P<0.01$). Moreover, there was no significant difference

Table 1 Baseline characteristics of participants

	LCD (*N* = 55)	TRE (*N* = 55)	Both (*N* = 52)	*P* value
Male, no. (%)	27 (49.1)	31 (56.4)	31 (59.6)	0.320
Age (years)	41.8 ± 1.4	42.6 ± 1.5	39.3 ± 1.3	0.252
Weight (kg)	84.5 ± 2.4	84.6 ± 2.3	85.4 ± 2.0	0.953
Body mass index (kg/m^2)	29.1 ± 0.5	29.3 ± 0.5	29.0 ± 0.5	0.924
High school education, no. (%)	52 (94.5)	49 (89.1)	46 (88.5)	0.470
Income of household, no. (%)				0.171
< ¥30,000	2 (3.6)	2 (3.6)	0 (0.0)	
¥30,000–¥100,000	11 (20.0)	12 (21.8)	18 (34.6)	
¥100,000–¥200,000	24 (43.6)	22 (40.0)	15 (28.8)	
¥200,000–¥500,000	18 (32.7)	15 (27.3)	18 (34.6)	
> ¥500,000	0 (0.0)	4 (7.3)	1 (1.9)	
Current smoker, no. (%)	14 (25.5)	16 (29.1)	18 (34.6)	0.602
Current drinker, no. (%)	14 (25.5)	17 (30.9)	12 (23.1)	0.662
Myocardial enzymes				
Lactate dehydrogenase (U/L)	200 ± 6	195 ± 4	187 ± 4	0.228
Creatine kinase (CK, U/L)	93 (86)	98 (68)	96 (68)	0.858
CKMB (U/L)	13 (4)	12 (5)	13 (4)	0.795
HBDH (U/L)	166 ± 4	162 ± 3	155 ± 3	0.319
Thyroid function				
Free T3 (FT3, pmol/L)	7.00 ± 0.10	7.02 ± 0.11	6.86 ± 0.11	0.507
Free T4 (FT4, pmol/L)	16.68 ± 0.29	16.65 ± 0.32	16.74 ± 0.33	0.977
Thyrotropin (μIU/mL)	1.37 (1.35)	1.40 (1.21)	1.54 (1.44)	0.462
Triiodothyronine (T3, ng/mL)	1.46 ± 0.03	1.48 ± 0.04	1.48 ± 0.04	0.906
Thyroxine (T4, μg/dL)	9.82 ± 0.19	9.24 ± 0.26	9.47 ± 0.22	0.179
T3/T4 ratio	0.15 ± 0.00	0.16 ± 0.00	0.16 ± 0.00	0.124
Thyroglobulin antibodies (%)	5 (2)	4 (1)	5 (1)	0.526
Thyroid microsomal antibodies (%)	4 (2)	4 (1)	4 (1)	0.223

LCD, low-carbohydrate diet; *TRE*, time-restricted eating; *Both*, combination treatment; *CKMB*, creatine kinase MB; *HBDH*, hydroxybutyrate dehydrogenase. Unless otherwise indicated, the data are presented as the mean ± standard error of the mean for normally distributed variables or the median (interquartile range) for abnormally distributed variables. Differences among treatment arms (LCD, TRE, and Both) were tested by one-way ANOVA for normally distributed variables, the Kruskal–Wallis *H* test for abnormally distributed variables, or chi-square tests for categorical variables

in the reductions in myocardial enzymes among the three groups (Fig. 2A–D and Table 2). Differently, PP analysis revealed that CK levels decreased only in the TRE (−18 [44] U/L, $P < 0.001$) and combination (−22 [64] U/L, $P = 0.003$) groups, without significant changes in the LCD (−11 [10] U/L, $P = 0.075$) group (Fig. 3B and Additional file 1: Table S4); moreover, changes in the other three myocardial enzymes were similar to those observed in the ITT analysis (Fig. 3A, C, and D and Additional file 1: Table S4). No significant difference between the eTRE and lTRE groups was observed for either the TRE or combination group (Additional file 1: Table S6).

LCD, TRE, and their combination altered FT3 and FT4, while only combination treatment reduced TSH

After 3 months, FT3 levels decreased and FT4 levels increased in all three groups (Fig. 2E and F and Table 2). Reductions in TSH (−0.24 [0.83] μIU/mL, $P = 0.011$) and T3 (−0.10 ± 0.04 ng/mL, $P = 0.011$) were observed in the combination group (Fig. 2G and H and Table 2). Only the TRE group exhibited an increase in T4 (0.70 ± 0.28 μg/dL, $P = 0.013$; Fig. 2I and Table 2). The T3/T4 ratio decreased in both the TRE (−0.01 ± 0.01, $P = 0.003$) and combination (−0.01 ± 0.00, $P = 0.012$) groups (Fig. 2J and Table 2). No significant difference in changes in THs was observed among the three groups. The results from the PP analysis differed moderately from those from the primary analysis. Relative to those at baseline, TSH and T3 levels remained unchanged in all three groups (Fig. 3G and H), and the T3/T4 ratio decreased only in the TRE (−0.01 ± 0.01, $P = 0.020$) group (Fig. 3J and Additional file 1: Table S4). The eTRE and lTRE subgroups in both the TRE and combination groups showed comparable improvements in THs (Additional file 1: Table S6).

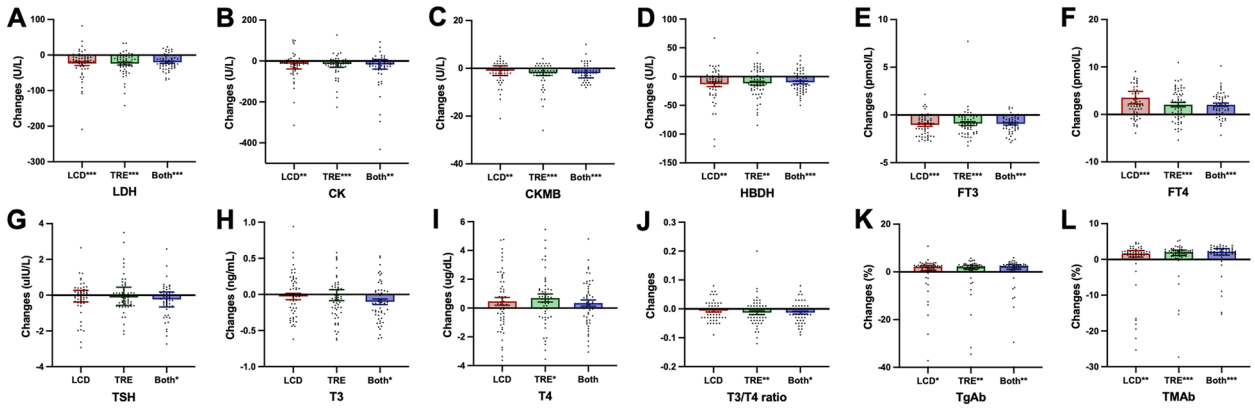

Fig. 2 Changes in myocardial enzymes and thyroid function among participants. **A**–**D** Changes in myocardial enzymes among the three groups after the low-carbohydrate diet (LCD), 8-h time-restricted eating (TRE), or combination treatment (Both). **A** Lactate dehydrogenase (LDH), **B** creatine kinase (CK), **C** creatine kinase MB (CKMB), and **D** hydroxybutyrate dehydrogenase (HBDH). **E**–**J** Changes in thyroid hormone levels among the three groups after intervention. **E** Free triiodothyronine (FT3), **F** free thyroxine (FT4), **G** thyrotropin (TSH), **H** triiodothyronine (T3), **I** thyroxine (T4), and **J** the T3/T4 ratio. **K**, **L** Changes in **K** thyroglobulin antibodies (TgAb) and **L** thyroid microsomal antibodies (TMAb) among the three interventions after 3 months. Changes from baseline are presented as the mean ± standard error of the mean for normally distributed variables or the median (interquartile range) for abnormally distributed variables. Analysis was conducted on 162 participants who began interventions (55 in the LCD group, 55 in the TRE group, and 52 in the Both group). *$P<0.05$, **$P<0.01$, ***$P<0.001$: significant differences shown on the x-axis compared with baseline (paired *t* test for normally distributed variables or paired Wilcoxon test for abnormally distributed variables)

LCD, TRE, and their combination increased TgAb and TMAb

Compared to baseline, the TgAb and TMAb levels increased in all three groups (Fig. 2K and L and Table 2). The changes in thyroid autoantibodies were not significantly different among the groups (Table 2). PP analysis revealed that TgAb (2 (1) %, $P=0.021$) and TMAb (2 (2) %, $P<0.001$) increased only in the TRE group (Fig. 3K and L and Additional file 1: Table S4). No significant difference was observed in TgAb or TMAb between the two subgroups (eTRE vs. lTRE) (Additional file 1: Table S6).

Correlation analysis

Pearson's or Spearman's correlation was assessed between functions of the myocardium and thyroid and cardiometabolic parameters at baseline (Additional file 1: Fig. S1). CK was positively correlated with visceral fat area (VFA, $r=0.213$, $P=0.013$). FT3 was positively associated with triglyceride ($r=0.237$, $P=0.006$) and total cholesterol ($r=0.223$, $P=0.009$). FT4 was negatively related to fasting insulin ($r=-0.244$, $P=0.004$) and C-peptide ($r=-0.238$, $P=0.005$). TgAb and TMAb were negatively correlated with the waist-to-hip ratio (WHR, $r=-0.237$, $P=0.006$; $r=-0.245$, $P=0.004$, respectively).

Discussion

In this study, we observed that all three distinct interventions improved myocardial status and thyroid function, while TRE with or without LCD had apparent beneficial effects on CK, TSH, T3, T4, and the T3/T4 ratio. In the preliminary analysis, eTRE and lTRE had comparable effects on the myocardium and thyroid. Correlations between the functions of the myocardium and thyroid and cardiometabolic risk factors were observed at baseline. In addition, the results of the PP analysis seemed more precise in that only adherent participants were included, which could reflect the real effects of the diverse diet without bias from higher compliance in the TRE group [31]. However, whether the changes in the intake of aquatic products and phytocomycetes indicated that the exact iodine intake changed accordingly was unclear. To our knowledge, the present study is the first to directly compare the effects of LCD and TRE on myocardial status and thyroid function, especially on thyroid autoimmunity, in subjects with MetS.

Although the majority of the patients were within the reference range at baseline, myocardial enzymes, including LDH, CK, CKMB, and HBDH, markedly decreased after all three interventions, without differences among the groups. Our findings are consistent with other studies that showed decreased LDH, CK, and HBDH after weight loss induced by bariatric surgery [33] and reduced LDH after a low-calorie diet [34]. However, the results of existing trials on changes in myocardial enzymes via LCD and TRE are sparse, and further studies are needed to investigate the effects of LCD and TRE on myocardial enzymes in individuals with MetS to verify our findings. Notably, in the PP analysis, CK decreased only in the TRE and combination groups, partially because of decreased VFA in the TRE and combination treatments but not in the LCD group [31], given that CK was positively correlated

Table 2 Changes in myocardial enzymes and thyroid function after 3 months among participants

		LCD (group A)		TRE (group B)		Both (group C)		*P* value between-group comparison		
		N = 55	*P* value	*N* = 55	*P* value	*N* = 52	*P* value	A vs. B	A vs. C	B vs. C
Myocardial enzymes										
LDH (U/L)	3 m	176 ± 4		171 ± 3		166 ± 2				
	Δ	− 24 ± 6	*< 0.001*	− 24 ± 4	*< 0.001*	− 21 ± 3	*< 0.001*	0.838	0.665	0.989
Creatine kinase (CK, U/L)	3 m	77 (65)		80 (45)		83 (48)				
	Δ	− 13 (40)	*0.002*	− 14 (32)	*< 0.001*	− 18 (47)	*0.001*	0.713	0.711	0.989
CKMB (U/L)	3 m	12 (3)		11 (3)		11 (3)				
	Δ	− 1 (4)	*0.003*	− 2 (3)	*< 0.001*	− 2 (4)	*< 0.001*	0.526	0.601	0.974
HBDH (U/L)	3 m	152 ± 3		150 ± 3		145 ± 2				
	Δ	− 13 ± 4	*0.001*	− 12 ± 3	*0.001*	− 10 ± 3	*< 0.001*	0.925	0.839	0.700
Thyroid function										
Free T3 (pmol/L)	3 m	5.95 ± 0.09		6.11 ± 0.18		5.93 ± 0.09				
	Δ	− 1.04 ± 0.15	*< 0.001*	− 0.91 ± 0.20	*< 0.001*	− 0.93 ± 0.12	*< 0.001*	0.811	0.472	0.558
Free T4 (pmol/L)	3 m	20.21 ± 1.34		18.70 ± 0.36		18.77 ± 0.33				
	Δ	3.53 ± 1.33	*< 0.001*	2.05 ± 0.46	*< 0.001*	2.03 ± 0.35	*< 0.001*	0.656	0.798	0.969
Thyrotropin (μIU/mL)	3 m	1.42 (1.11)		1.34 (1.08)		1.31 (0.99)				
	Δ	− 0.01 (0.65)	0.528	− 0.13 (1.02)	0.435	− 0.24 (0.83)	*0.011*	0.693	0.149	0.233
Triiodothyronine (T3, ng/mL)	3 m	1.43 ± 0.04		1.47 ± 0.07		1.38 ± 0.04				
	Δ	− 0.03 ± 0.04	0.511	− 0.01 ± 0.08	0.076	− 0.10 ± 0.04	*0.011*	0.457	0.220	0.451
Thyroxine (T4, μg/dL)	3 m	10.29 ± 0.28		9.94 ± 0.27		9.81 ± 0.27				
	Δ	0.46 ± 0.27	0.087	0.70 ± 0.28	*0.013*	0.34 ± 0.22	0.121	0.583	0.729	0.437
T3/T4 ratio	3 m	0.14 ± 0.01		0.15 ± 0.01		0.15 ± 0.01				
	Δ	− 0.01 ± 0.00	0.189	− 0.01 ± 0.01	*0.003*	− 0.01 ± 0.00	*0.012*	0.238	0.300	0.802
TgAb (%)	3 m	7 (2)		7 (1)		7 (2)				
	Δ	2 (2)	*0.011*	2 (2)	*0.001*	2 (2)	*0.001*	0.852	0.373	0.472
TMAb (%)	3 m	6 (2)		6 (1)		6 (2)				
	Δ	2 (2)	*0.003*	2 (2)	*< 0.001*	2 (2)	*< 0.001*	0.371	0.084	0.298

LCD low-carbohydrate diet, *TRE* time-restricted eating, *Both* combination treatment, *LDH* lactate dehydrogenase, *CKMB* creatine kinase MB, *HBDH* hydroxybutyrate dehydrogenase, *TgAb* thyroglobulin antibodies, *TMAb* thyroid microsomal antibodies. All the data are presented as the mean ± standard error of the mean for normally distributed variables or the median (interquartile range) for abnormally distributed variables. The outcome variables tested at postintervention are represented by "3 m," and the variations from baseline to 3 months are represented by "Δ" in the table. Within-group comparisons of outcome variables between baseline and follow-up were performed by paired *t* tests for normally distributed variables or paired Wilcoxon tests for abnormally distributed variables, and between-group comparisons (e.g., LCD vs. TRE, LCD vs. Both, and TRE vs. Both) of changes were tested by independent sample *t* tests for normally distributed variables or Mann–Whitney *U* tests for abnormally distributed variables. Significant *P* values are italicized

with VFA (Additional file 1: Fig. S1A). As an ATP-regenerating enzyme, CK regulates energy metabolism, affects cardiovascular hemodynamics [35], and is abundant in type II skeletal muscle fibers, which particularly contribute to IR and obesity. Accordingly, higher levels of serum CK are found in patients with obesity [11, 12]. CK is correlated with multiple MetS components, such as BMI, waist circumference, and blood pressure [9, 10, 36]. Therefore, TRE with or without LCD markedly reduced CK levels and could ameliorate unfavorable myocardial status and cardiovascular risk.

Studies on the effects of LCD and TRE on THs have yielded inconsistent results. As the most sensitive and significant serum biomarker of thyroid function, TSH decreased only in the combination group according to the ITT analysis and showed a decreasing trend but was insignificant in the combination group according to the PP analysis, which is consistent with the findings of several trials that failed to detect any significant changes in TSH after LCD or TRE intervention [26–28]. Nevertheless, studies on the effects of LCD combined with TRE on TSH are scarce, and further larger-scale trials are needed to investigate whether TRE combined with LCD could induce a reduction in TSH levels. Notably, TRE with or without LCD led to a significant reduction in the T3/T4 ratio (an index of deiodinase activity), indicating that the reduction in (F)T3 and increase in (F)T4 may be signals of decreased deiodinase activity and peripheral

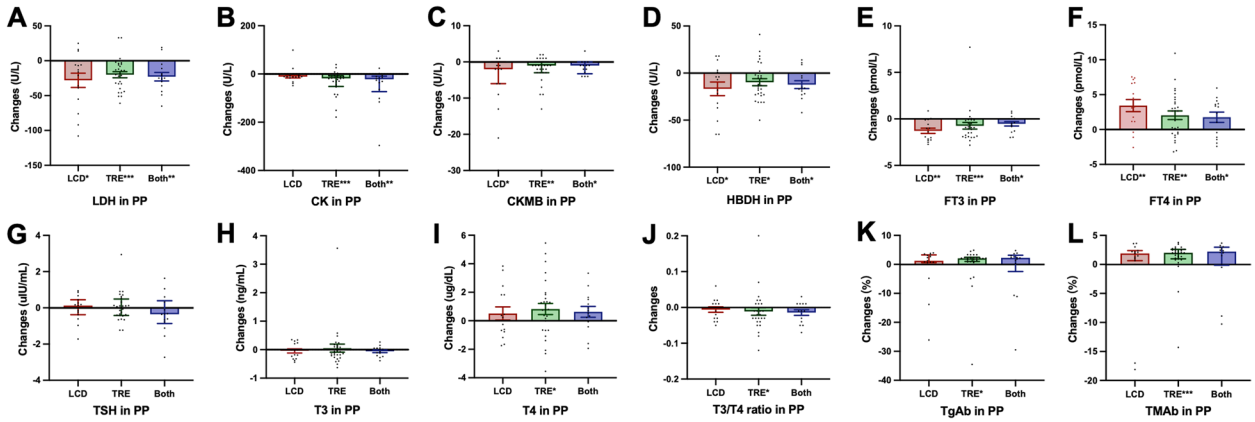

Fig. 3 Changes in myocardial enzymes and thyroid function according to the PP analysis. **A**–**D** Changes in myocardial enzymes among the three groups in the per-protocol (PP) analysis after the low-carbohydrate diet (LCD), 8-h time-restricted eating (TRE), or combination treatment (Both) interventions. **A** Lactate dehydrogenase (LDH), **B** creatine kinase (CK), **C** creatine kinase MB (CKMB), and **D** hydroxybutyrate dehydrogenase (HBDH). **E**–**J** Changes in thyroid hormone levels among the three groups according to the PP analysis after intervention. **E** Free triiodothyronine (FT3), **F** free thyroxine (FT4), **G** thyrotropin (TSH), **H** triiodothyronine (T3), **I** thyroxine (T4), and **J** the T3/T4 ratio. **K**, **L** Changes in **K** thyroglobulin antibodies (TgAb) and **L** thyroid microsomal antibodies (TMAb) in the PP analysis among the three interventions after 3 months. Changes from baseline are presented as the mean ± standard error of the mean for normally distributed variables or the median (interquartile range) for abnormally distributed variables. Analysis was conducted on 57 adherent participants (15 in the LCD group, 28 in the TRE group, and 14 in the Both group). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$: significant differences shown on the *x*-axis compared with baseline (paired *t* test for normally distributed variables or paired Wilcoxon test for abnormally distributed variables)

conversion from T4 to T3. Another explanation for the observed trends toward (F)T3 and (F)T4 is decreased ATP-dependent uptake of T4 into T3-producing tissues, including the liver [37]. (F)T3 activates thermogenesis and induces an increase in energy expenditure and oxygen consumption. Therefore, a reduction in (F)T3 may represent strong self-protection to save energy and decrease resting energy expenditure in response to energy deficits induced by carb restriction or fasting. Our findings of changes in FT3 and FT4 were consistent with the findings of other trials after LCD (15% carbohydrate) [27] or gastric banding [38]. However, our findings were at odds with several trials that showed no significant changes in FT3 or FT4 after LCD [29] or TRE [30]. These differences might be partially attributed to differences in the scales and durations of the study, thyroid function at baseline, or extent of weight loss. Overall, in this study, we found that all three interventions improved FT3 and FT4 levels, while only TRE with or without LCD significantly improved T3, T4, and the T3/T4 ratio.

Consistent with previous findings [39, 40], we also observed that THs were closely associated with the lipid profile and insulin sensitivity (Additional file 1: Fig. S1B and S1C), which are not only MetS components but also risk factors for multiple chronic diseases, revealing the mechanism of correlation between thyroid dysfunction and chronic endocrine disorders. Recently, several TH analogs or thyromimetics have been developed to modulate lipid and glucose levels based on the possibility that THs control multiple signaling pathways involved in related metabolism [41–43].

Our results showed that TgAb and TMAb levels increased after all three interventions in the ITT analysis but increased only in the TRE group after the PP analysis. For participants with negative baseline thyroid autoantibodies, TgAb and TMAb levels increased after all three interventions in both the ITT and PP analyses (Additional file 1: Fig. S2). Elevated thyroid autoantibodies are common not only in patients with autoimmune thyroid disease but also in individuals without evident thyroid dysfunction. The percentage of patients with a positive serum TgAb concentration is estimated to be 12.6% in the Chinese general population [44]. Negative correlations have been observed between TgAb levels and BMI [45], prevalence of impaired fasting glucose, hypertriglyceridemia, and metabolic dysfunction-associated fatty liver disease [23, 46]. We found that TgAb and TMAb levels were negatively correlated with the WHR (Additional file 1: Fig. S1D), which was recently identified as a stronger adiposity surrogate associated with mortality than BMI [47]. However, several studies have reported a correlation between positivity or higher titers of TgAb and MetS components [48–50]. These inconsistencies might be partly due to altered thyroid function and differences in the specificity and sensitivity of the antibody detection methods. To date, no study has investigated the effects of LCD or TRE on thyroid autoimmunity, and whether

increased thyroid autoantibody levels, even within the normal range, adversely impair thyroid function is unclear. Further studies are warranted to elucidate the effects of LCD and TRE on thyroid autoimmunity and explore the underlying mechanism involved.

Following circadian rhythms, eTRE was previously suggested to be superior to lTRE [51]. We observed that eTRE and lTRE improved myocardial enzymes and thyroid function comparably, which indicated that people could choose freely following preferences. Indeed, studies comparing the effects of eTRE and lTRE on the myocardium and thyroid are scarce. Zhang et al. reported that TSH levels were significantly lower in the eTRE group than in the lTRE group after 4 but not 8 weeks [52]. Although our early or late TRE method involves self-selection but not randomization, the outcomes could still be used to tentatively explore the effects of eTRE and lTRE on the myocardium and thyroid. Further randomized controlled trials with longer durations and larger scales are needed to verify our findings.

This analysis has several limitations. First, the lack of an AL control group limits the exploration of the effects of TRE alone and LCD alone, although we conducted a comparison between pre- and postintervention data. Second, in line with the findings of other TRE trials [51, 53, 54], participants in the TRE group spontaneously reduced their daily carbohydrate intake by approximately 4.6%, and the exact daily iodine intake of all participants was obscure. Third, to enhance adherence, eTRE and lTRE were not randomized but rather self-selected, which impaired the reliability of the analytical results to some extent. Further randomized trials are warranted to compare the effects of eTRE and lTRE on the thyroid and myocardium. Moreover, a limited number of participants in the LCD and combination groups were included in the PP analysis, and further larger-scale and strict follow-up trials are warranted to verify our findings. Finally, thyroid antibodies are influenced by multiple factors, and the results vary depending on the testing methods used; additional trials are needed to verify our results.

Conclusions

Taken together, LCD, TRE, and their combination all improved functions of the myocardium and thyroid even though the majority were within the reference range at baseline, and TRE with or without LCD conferred substantial benefits regarding CK, TSH, T3, T4, and the T3/T4 ratio, suggesting that TRE with or without LCD can serve as effective dietary strategy for ameliorating the myocardial status and thyroid function in patients with MetS.

Abbreviations

MetS	Metabolic syndrome
LCD	Low-carbohydrate diet
TRE	Time-restricted eating
LDH	Lactate dehydrogenase
CK	Creatine kinase
CKMB	Creatine kinase MB
HBDH	Hydroxybutyrate dehydrogenase
THs	Thyroid hormones
FT3	Free triiodothyronine
FT4	Free thyroxine
TSH	Thyrotropin
TgAb	Thyroglobulin antibodies
TMAb	Thyroid microsomal antibodies

Supplementary Information

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Additional file 1: Fig. S1. Correlations between myocardial and thyroid functions and cardiometabolic risk factors at baseline. Fig. S2. Changes in TgAb and TMAb after 3 months in participants with negative baseline thyroid autoimmunity. Table S1. Baseline characteristics of all, completed, and dropout participants. Table S2. Baseline characteristics of adherent participants. Table S3. Intake of food containing high iodine among completed participants. Table S4. Changes in myocardial enzymes and thyroid function after 3-month intervention among adherent participants. Table S5. Baseline characteristics of the early TRE and late TRE subgroups. Table S6. Changes in myocardial enzymes and thyroid function after 3-month intervention between early TRE and late TRE subgroups.

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Authors' contributions

YZ and MH conducted the clinical trial, analyzed the data, and wrote the manuscript. BS designed the research and revised the manuscript. ML1, XZ, and XL assisted with the data analysis. JW, QL, JY, MZ, ZC, ML2, YW, JS, WQ, and HG assisted with the conduction of the clinical trial. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files. All data reported in this paper and any additional information required to reanalyze the data reported in this paper will be shared by the lead contact upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of the First Affiliated Hospital of Xi'an Jiaotong University (XJTU1AF2020LSK-003). Participants provided written informed consent and received no compensation.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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