Lifestyle intervention in obese Chinese adolescents with non-alcoholic fatty liver disease: a randomised controlled study

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KEY MESSAGE

A 16-week lifestyle intervention effectively reduced body fat and intra-hepatic triglyceride content in obese Chinese adolescents with non-alcoholic fatty liver disease.

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Introduction

The incidence of non-alcoholic fatty liver disease (NAFLD) has increased because of the growing prevalence of obesity and overweight in the paediatric population.[1] NAFLD is one of the most common forms of chronic liver disease in children.[1] Lifestyle intervention is the main management approach. Although a lifestyle modification programme involving diet restriction and physical exercise provides beneficial effects for adults with NAFLD, there is limited evidence of its efficacy in adolescents. The present study evaluated the efficacy of a lifestyle modification programme at reversing and reducing NAFLD in obese adolescents.

Participants and Methods

The study was approved by the Joint Chinese University of Hong Kong and New Territories East Cluster Clinical Research Ethics Committee. Written informed consent was obtained from the parents and/or participants. The study was conducted in compliance with the Declaration of Helsinki and International Conference on Harmonisation-Good Clinical Practice.

Post-pubertal obese Chinese adolescents aged 14 to 18 years with body mass index (BMI) ≥95th percentile of the local reference[2] and who attended the Obesity and Lipid Disorder Clinic at Prince of Wales Hospital, Hong Kong were invited to participate. Their intra-hepatic triglyceride content (IHTC) was measured at baseline and week 16 using proton magnetic resonance spectroscopy (^{1}H-MRS) with a whole-body 3-Tesla scanner (Achieva TX; Philips Healthcare, Best, the Netherlands) by a trained investigator blinded to group allocation. Fatty liver was defined as the presence of hepatic steatosis ≥5% fat content level.

Participants were randomised to the intervention (lifestyle modification programme) or control group. In the intervention group, counselling sessions were provided weekly for the first 4 months and then bi-monthly for 52 weeks. The lifestyle modification programme aims to improve knowledge, attitude, and practice regarding diet and exercise based on motivational interviewing and behavioural modification. In the control group, diet and exercise advice was provided during routine consultations at the Obesity Clinic every 4 months by attending physicians.

Anthropometrics including body height, weight, BMI, and percentage of body fat were measured at baseline, week 16, and week 68, as well as dietary records and laboratory tests.

Between-group and within-group comparisons were made at baseline, week 16, and week 68 using paired or independent *t* tests, the Chi squared test, or Fisher's exact test, as appropriate. Logistic regression was used to determine NAFLD remission at week 16 based on the ^{1}H-MRS, anthropometric, and laboratory results. Per-protocol analysis was performed among adherent participants. All statistical tests were two-sided, and a P value of <0.05 was considered statistically significant. SPSS (for Windows, version 21; IBM Corp, Armonk, NY, US) was used for all statistical analyses.

Results

A total of 79 obese adolescents aged 14 to 18 years were invited for NAFLD screening and assessed by ^{1}H-MRS between February and March 2014. Of these,

52 were diagnosed with NAFLD and randomised to the intervention (n=26) or control (n=26) group (Fig). At baseline, the two groups were well-matched in terms of demographic characteristics, clinical and laboratory data, and IHTC measurements (Table 1).

At week 16, four participants in the intervention group had withdrawn owing to poor motivation (n=2), tight schedule (n=1), or study abroad (n=1); and two participants in the control group had withdrawn owing to tight schedule (n=2). Therefore, 22 participants in the intervention group and 24 participants in the control group were included in the per-protocol analysis. The compliance rate was 85% in the intervention group and 92% in the control group. None of the participants were using weight loss agents or lipid-lowering drugs.

The between-group difference in the change of IHTC from baseline to week 16 was significant (P=0.029), and the mean reduction in the proportion of IHTC from before to after intervention was significantly greater in the intervention group than the control group (30.5% vs 7.5%, P<0.001, Table 2). Ten (19%) of the 52 participants (six in the intervention group and four in the control group) had complete remission of NAFLD at 16 weeks. The aspartate aminotransferase (AST) / alanine aminotransferase (ALT) ratio, insulin, and homeostasis model assessment (HOMA) also improved significantly, paralleling the reduction in body size in the intervention group (Table 2). Multivariate analysis showed only reduction in body fat and baseline IHTC as independent factors associated with NAFLD remission (Table 3).

At week 68, two participants in each group were lost to follow-up during the maintenance phase. Therefore, 20 participants in the intervention group and 22 participants in the control group were included in the per-protocol analysis. Participants who completed or did not complete assessment at week 16 or week 68 were similar in terms of baseline body size and IHTC.

After the intervention, the mean BMI z-score of the intervention group was reduced to 2.2, whereas that of the control group was non-significantly

TABLE 1. Baseline characteristics of participants with non-alcoholic fatty liver disease

Variable	Intervention (n=26)*	Control (n=26)*
Age, y	15.3±3.4	13.8±5.3
Male sex	16 (61.5)	17 (65.4)
Body weight, kg	91.1±9.8	91.1±8.0
Male	93.7±7.7	91.4±8.2
Female	87.0±11.6	90.3±7.8
Body mass index, kg/m^2	32.59±3.28	32.12±3.12
Male	32.26±3.11	31.23±2.92
Female	33.14±3.63	34.12±2.75
Body mass index z-score	2.32±0.38	2.29±0.37
Male	2.18±0.28	2.12±0.29
Female	2.54±0.42	2.68±0.22
Waist circumference, cm	103.9±9.7	103.6±7.8
Male	106.0±9.8	103.1±8.2
Female	100.5±8.8	104.7±7.1
Body fat, %	41.1±8.5	39.0±9.1
Male	38.4±7.4	34.2±5.5
Female	45.5±8.7	49.8±5.3
Alanine aminotransferase, IU/L	38.9±25.6	36.7±26.6
Aspartate aminotransferase, IU/L	22.5±7.8	23.4±9.5
Aspartate aminotransferase / alanine aminotransferase ratio	0.68±0.23	0.80±0.37
Insulin, mIU/L	27.4±16.2	27.8±23.2
Fasting glucose, mmol/L	5.0±0.4	4.9±0.5
Homeostasis model assessment	6.3±4.2	5.3±3.1
Quantitative insulin-sensitivity check index	0.50±0.07	0.52±0.12
Intra-hepatic triglyceride content, %	13.1±7.8	13.5±10.2

* Data are presented as mean±standard deviation or No. (%) of participants

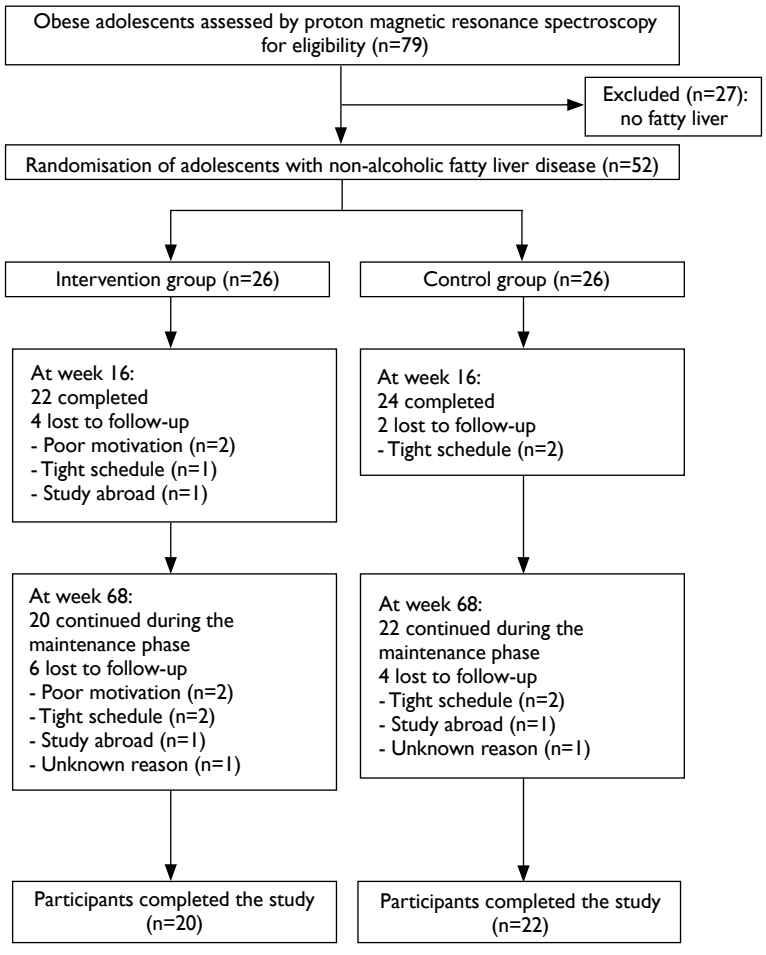

FIG. Flowchart of the study

TABLE 2. Clinical and laboratory characteristics of participants at 16 weeks and 68 weeks

	Baseline	Baseline to 16 weeks			Baseline to 68 weeks		
		Within-group difference	Between-group difference in change		Within-group difference	Between-group difference in change	
	Mean±SD	Mean±SD	Mean±SE	P value	Mean±SD	Mean±SE	P Value
Body weight, kg							
Control	91.1±8.0	–0.7±2.9	Reference		–0.08±7.16	Reference	
Intervention	91.1±9.8	–5.2±5.4*	–4.5±1.3	0.001	–1.60±6.49	–1.52±2.19	0.472
Body mass index, kg/m^2							
Control	32.1±3.1	–0.37±0.95	Reference		–0.69±2.15	Reference	
Intervention	32.6±3.3	–1.8±1.6*	–1.45±0.38	0.001	–0.79±2.01	–0.10±0.65	0.882
Body mass index z-score							
Control	2.3±0.4	–0.03±0.08	Reference		–0.07±0.21	Reference	
Intervention	2.3±0.4	–0.19±0.17*	–0.16±0.04	<0.001	–0.05±0.18	0.02±0.64	0.808
Waist circumference, cm							
Control	103.6±7.8	3.1±5.2*	Reference		–0.16±6.95	Reference	
Intervention	103.9±9.7	–0.6±5.0	3.71±1.51	0.018	–1.04±6.26	0.88±2.02	0.831
Body fat, %							
Control	39.0±9.1	1.0±4.2	Reference		0.86±6.27	Reference	
Intervention	41.1±8.5	–3.1±4.0*	–4.12±1.21	0.001	–3.81±6.02*	–4.67±1.88	0.017
Alanine aminotransferase, IU/L							
Control	36.7±26.6	–4.4±8.7	Reference		10.00±53.98	Reference	
Intervention	38.9±25.6	–4.10±16.5	0.30±3.86	0.610	5.41±22.63	–4.59±12.48	0.715
Aspartate aminotransferase, IU/L							
Control	23.4±9.5	–0.9±5.4	Reference		6.91±23.60	Reference	
Intervention	22.5±7.8	–0.70±5.64	0.18±1.67	0.917	7.40±11.27	0.49±5.78	0.933
Aspartate aminotransferase / alanine aminotransferase ratio							
Control	0.80±0.37	0.02±0.14	Reference		0.09±0.27	Reference	
Intervention	0.68±0.23	0.12±0.17*	0.11±0.05	0.052	0.13±0.26*	0.04±0.08	0.650
Insulin, mIU/L							
Control	27.8±23.2	–0.88±18.29	Reference		–2.43±21.88	Reference	
Intervention	27.4±16.2	–4.98±10.86*	–4.10±4.49	0.366	–0.62±10.38	3.06±5.31	0.507
Fasting glucose, mmol/L							
Control	4.9±0.5	0.12±0.29	Reference		0.07±0.31	Reference	
Intervention	5.0±0.4	–0.11±0.39	–0.23±0.12	0.039	0.03±0.47	–0.04±0.12	0.771
Homeostasis model assessment							
Control	5.3±3.1	0.8±2.70	Reference		0.32±1.92	Reference	
Intervention	6.3±4.2	–1.2±1.90*	–2.00±0.80	0.018	0.23±2.69	–0.11±0.81	0.894
Quantitative insulin-sensitivity check index							
Control	0.52±0.12	–0.04±0.11	Reference		2.23±0.32*	Reference	
Intervention	0.50±0.07	0.03±0.06	–0.01±0.03	0.043	2.28±0.31*	0.05±0.10	0.509
Intra-hepatic triglyceride content, %							
Control	13.5±10.2	–0.96±4.18	Reference		-	-	-
Intervention	13.1±7.8	–4.02±5.02*	–3.1±1.36	0.029	-	-	-
Abdominal adipose tissue, mL							
Control	16456.8±2715.5	593.7±1697.2	Reference		-	-	-
Intervention	16002.3±3709.5	–795.8±1918.1	-1389.5±533.10	0.012	-	-	-
Subcutaneous abdominal adipose tissue, mL							
Control	13640.2±2341.4	243.5±1091.7	Reference		-	-	-
Intervention	13038.7±3432.2	–727.1±1575.1*	–970.6±403.04	0.019	-	-	-
Visceral adipose tissue, mL							
Control	2816.6±786.8	350.2±1108.5	Reference		-	-	-
Intervention	2963.6±865.9	–68.8±834.9	–419.0±291.45	0.158	-	-	-

Abbreviations: SD=standard deviation; SE = standard error

* P<0.05, paired t-test within group

reduced by 0.07. Body fat was significantly lower in the intervention group than the control group (mean difference=4.6%, P=0.025, Table 2). The IHTC, quantitative insulin sensitivity check index, and high-density lipoprotein cholesterol level were improved significantly in both groups compared with baseline (Table 2). The improvement in the AST/ALT ratio from baseline to week 68 was significant in the intervention group (P=0.017). The proportion of participants with insulin resistance (HOMA >3) did not differ significantly between groups (16/20 vs 15/22, P=0.384).

TABLE 3. Factors associated with remission of non-alcoholic fatty liver disease at week 16

Factor	Univariate		Multivariate	
	Odds ratio (95% confidence interval)	P value	Adjusted odds ratio (95% confidence interval)	P value
Intervention group	1.875 (0.451-7.802)	0.388	0.392 (0.034-4.519)	0.453
Age	0.730 (0.362-1.473)	0.379		
Baseline intra-hepatic triglyceride content	0.596 (0.375-0.950)	0.029	0.431 (0.209-0.889)	0.023
Baseline body weight	0.988 (0.912-1.071)	0.771		
Change in body weight	0.704 (0.549-0.902)	0.006		
Baseline body mass index	0.852 (0.663-1.095)	0.211		
Change in body mass index	0.387 (0.200-0.749)	0.005		
Baseline body mass index z-score	0.238 (0.031-1.809)	0.165		
Change in body mass index z-score	0.000 (0.000-0.029)	0.002		
Baseline body fat	0.890 (0.801-0.990)	0.031		
Change in body fat	0.826 (0.686-0.994)	0.044	0.687 (0.483-0.975)	0.036
Baseline abdominal adipose tissue	1.000 (1.000-1.000)	0.148		
Change in abdominal adipose tissue	1.000 (0.999-1.000)	0.137		
Baseline subcutaneous abdominal adipose tissue	1.000 (1.000-1.000)	0.242		
Change in subcutaneous abdominal adipose tissue	0.999 (0.999-1.000)	0.042		
Baseline visceral adipose tissue	0.999 (0.998-1.000)	0.122		
Change in visceral adipose tissue	1.000 (0.999-1.001)	0.760		

Discussion

The 16-week lifestyle modification programme significantly reduced IHTC, body size, and subcutaneous abdominal adipose tissue. The laboratory variables, including AST/ALT ratio, insulin, and HOMA, improved significantly in the intervention group. Body fat and baseline IHTC were independent factors associated with NAFLD remission at week 16. This indicates that the effects of the programme were largely mediated by body fat reduction and baseline IHTC. Body fat reduction improved not only liver condition (AST/ALT ratio and IHTC) but also insulin resistance indices (HOMA and quantitative insulin sensitivity check index). Insulin resistance is a common finding in paediatric patients with NAFLD.[3] Weight loss in healthy adults can improve insulin sensitivity and lower the risk of diabetes conferred by insulin resistance.[4] This may partially explain the programme's beneficial effects of improving the AST/ALT ratio, insulin levels, and HOMA. Baseline IHTC was associated with remission of NAFLD in both groups.

There are limitations to our study. The nature of the study did not allow blinding of study participants. Liver biopsy was not performed to evaluate the presence of necrosis and inflammation. Nonetheless, ^{1}H-MRS enables an accurate assessment of IHTC,[5] and the technicians were blinded to the grouping. Further studies are required to determine the long-term prognoses of development of fibrosis, mortality, and quality of life and their modification by weight reduction.

Conclusion

Childhood obesity has significant medical and socio-economic impacts on society. NAFLD is an important obesity-related complication. The 16-week lifestyle modification programme effectively reduced body fat and IHTC in obese Chinese adolescents with NAFLD.

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